

# Vitamin D Deficiency and Radiological Findings in Adult Non-Cystic Fibrosis Bronchiectasis

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## Abstract

**OBJECTIVES:** Vitamin D may play an important role in immunity and its deficiency has been related to increased respiratory infections. The aim of this study was to detect the prevalence of vitamin D deficiency and to investigate the relationship between radiological and clinical effects on adult bronchiectasis (BR) patients.

**MATERIALS AND METHODS:** A total of 130 patients with BR and 73 healthy individuals (control group) were enrolled in this study. Radiological severity was assessed using Modified Reiff Score.

**RESULTS:** The mean age of patients was 41.9±9.1 years (range, 18–85). The mean 25-hydroxyvitamin D (25(OH)D) level was 14.7±9.6 ng/mL in BR patients and 19.8±6.9 ng/mL in the control group (p=0.001). Moreover, 95 (73.1%) adult BR patients were categorized as vitamin D deficient. Patients in the vitamin D deficiency group had significantly higher Modified Medical Research Council scores than those in the group without vitamin D deficiency (p=0.036). The mean modified Reiff score was higher in the vitamin D deficient group than the without vitamin D deficiency group (6.9±3.8 vs 4.9± 2.7, p=0.001). Additionally, the vitamin D deficient group had lower forced vital capacity% predicted value (p=0.02). This model showed that Reiff score (OR, 1.285[1.039–1.590]; p=0.021) was independently related to vitamin D deficiency.

**CONCLUSION:** We found that vitamin D deficiency is commonly seen in adult BR patients in a stable period. Moreover, it might be related to severe radiological findings on chest computed tomography and worse lung functions.

**KEYWORDS:** Bronchiectasis, bronchiectasis severity index, radiology, reiff score, vitamin D deficiency

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## INTRODUCTION

Vitamin D (25-hydroxyvitamin D (25(OH)D)) is a fat-soluble steroid synthesized in the skin from 7-dehydrocholesterol (as a hormone) or ingested with food (as a vitamin). Vitamin D plays a primary functional role throughout the body, especially in the musculoskeletal system. It also plays an important role in directly regulating the immune system and inducing the secretion of antimicrobial proteins against pathogens, including *Pseudomonas aeruginosa* [1, 2].

Recent studies have shown that vitamin D deficiency in patients with chronic respiratory diseases, such as chronic obstructive lung disease (COPD), asthma, and cystic fibrosis, is highly prevalent and associated with recurrent infection, disease severity, and declining lung function [3-5]. Non-cystic fibrosis bronchiectasis (BR) is a chronic respiratory disease characterized by destruction and dilatation of the medium-sized airways, cough, abnormal sputum production, and recurrent infections. BR patients have a vicious cycle of chronic bronchial infections, inflammation, impaired mucociliary clearance, and structural lung damage, especially in the lower airways [6]. Some studies have shown that vitamin D has an anti-inflammatory effect that reduces cytokines and chemokines secretion that promote tissue destruction [7, 8]. Low 25-hydroxyvitamin D (25(OH)D) levels were detected in adult non-cystic fibrosis BR patients [4]. However, a recent study reported that 25(OH)D levels were higher in the BR group than in the adult population [9].

To our knowledge, limited studies have investigated the prevalence of vitamin D deficiency in adult bronchiectasis patients. This study aimed to assess the prevalence of vitamin D deficiency and to investigate its association with radiological and clinical effects in adult BR patients.

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## MATERIALS AND METHODS

This case-control study investigated patients who had been diagnosed with bronchiectasis by high-resolution computed tomography (HRCT) of the chest between December 15, 2016, and December 15, 2017. All BR patients were clinically stable for at least four weeks before their enrollment in the study. Demographic parameters, clinical data (respiratory symptoms, duration of illness, etc.), pulmonary function tests, HRCT findings, complete blood count, and sputum culture results were recorded. Sputum samples were considered acceptable if they had less than ten squamous cells and more than 25 leukocytes per low-power microscopic field [10]. The study was approved by the Local Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval no: 2016/66). Each participant signed an informed consent form.

**Case group:** A total of 130 adult BR patients between 18 and 85 years, who were previously diagnosed with BR, were included in the study. Exclusion criteria were age <18 years, cystic fibrosis (CF; patients previously diagnosed according to the CF guideline), interstitial lung disease, allergic bronchopulmonary aspergillosis, active tuberculosis, supplementation of vitamin D prior to or during the study, non-stable bronchiectasis, and the use of antibiotics for at least four weeks prior to the study [11].

**Control group:** Seventy-three age-matched, gender-matched, and body mass index (BMI)-matched healthy individuals with no history of the disease, and no supplementary use of vitamin D before or during the study, were recruited from the community.

The radiological severity of BR was assessed using the modified Reiff score, which evaluates the number of lobes involved (the lingula was considered as a separate lobe; tubular BR = 1, varicose BR = 2, and cystic BR = 3 points). The minimum score is 1 and the maximum score is 18 [12]. The Bronchiectasis Severity Index (BSI) was applied to determine disease severity. The nine parameters of BSI are age, BMI, forced expiratory volume in 1 second (FEV<sub>1</sub>)% predicted, hospitalization with severe exacerbation in the past 2 years, number of exacerbations in the previous year, the Modified Medical Research Council (mMRC) dyspnea scale score, *Pseudomonas* colonization, colonization of other

organisms, and radiological severity ( $\geq 3$  lobes involved or cystic bronchiectasis). These scores classify patients into mild (0-4 points), moderate (5-8 points), and severe (9+ points) groups and identify patients at risk of future mortality, hospitalization, and exacerbation [13]. The bronchiectasis etiology and comorbidity index was used to assess any comorbidity that carried an independent prognostic value relating to exacerbation and *Pseudomonas aeruginosa* infection [14].

The major circulating form of vitamin D is 25(OH)D and is the best indicator of overall vitamin D status. The blood samples for 25(OH)D were taken between 8:00 to 10:00 a.m. Vitamin D level was measured by liquid chromatography tandem mass spectroscopy, which is accepted as the gold standard technique for estimating 25(OH)D status. Assessment of vitamin D levels, as recommended by the Turkish Endocrinology and Metabolism Association, was as follows: <20 ng/mL (50 nmol/L)=deficiency, 20-30 ng/mL (50-70 nmol/L)=insufficient, and  $\geq 30$  ng/mL=sufficient [15, 16].

### Statistical Analyses

Statistical analyses were carried out using the IBM Statistical Package for the Social Sciences package version 20 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics of mean and standard deviation were used for continuous variables. Values were presented as median and interquartile range for continuous non-parametric data, and as frequencies and percentages for categorical data. Comparisons between two groups were performed using the unpaired t-test, Mann-Whitney U test, or Chi-squared test, depending on the data distribution. For multivariate analysis, the possible factors identified with univariate analyses were further entered into a logistic regression analysis to determine the independent predictors of vitamin D deficiency. The Hosmer-Lemeshow goodness-of-fit statistics was used to assess model fit. Statistical significance was set at  $p < 0.05$ .

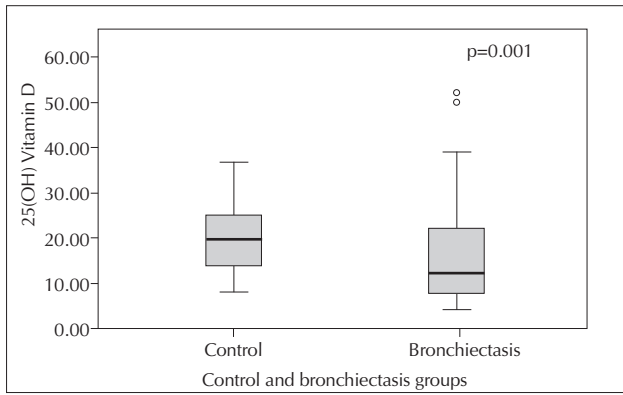
Although adequate epidemiological studies related to vitamin D deficiency in adult BR patients are lacking, the sample size was calculated using the prevalence rate of 0.93 for vitamin D deficiency in adult Turkish population with 95% confidence level and 5% confidence interval. For this study, we calculated that a sample size of 101 patients was required [17].

## RESULTS

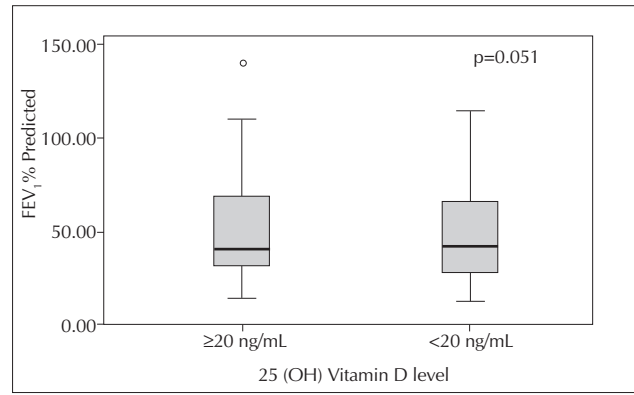
One hundred and thirty patients with BR were enrolled in the study. Their mean age was  $41.9 \pm 9.1$  years (range, 18-85), and 66 patients (50.8%) were women. Baseline characteristics of both the patient and control groups are shown in Table 1. Only 29.2% of the BR patients had comorbidities such as COPD (20[15.4%]), hypertension (17[13.1%]), gastro-esophageal reflux (10[7.7%]), asthma (6[4.6%]), diabetes (6[4.6%]), and coronary arterial disease (4[3.1%]). The mean 25(OH)D level in the BR patient group was  $14.7 \pm 9.6$  ng/mL, and  $19.8 \pm 6.9$  ng/mL in the control group ( $p = 0.001$ ) (Figure 1). Using the Turkish Endocrinology and Metabolism Association definitions for serum 25(OH)D concentrations, 95 (73.1%) adult BR patients were categorized as vitamin D deficient (<20 ng/mL). Vitamin D deficiency was present in 40 (54.8%) participants of the control group. Vitamin D insufficiency was present in 27 (20.8%)

### MAIN POINTS

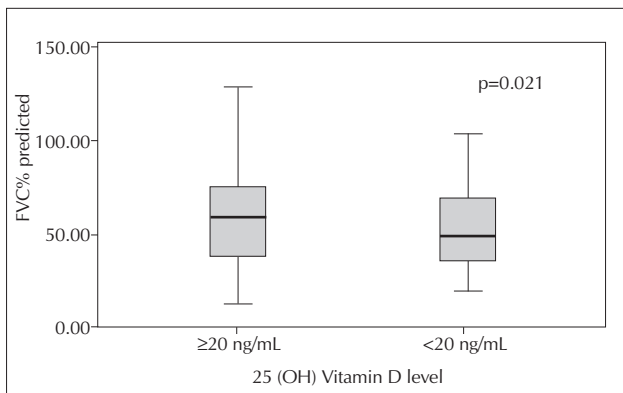
- This study is the first to investigate the influence of vitamin D deficiency on the radiological severity of bronchiectasis.
- Vitamin D deficiency was detected in 73.1% of adult bronchiectasis patients.
- Our findings show that adult bronchiectasis patients in the vitamin D deficiency group had significantly higher modified Reiff scores that reflect radiological severity of bronchiectasis.
- Additionally, the vitamin D deficient group had lower forced vital capacity % predicted value.



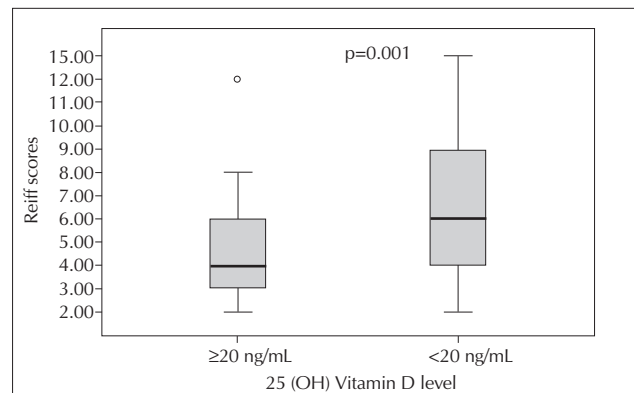
**Figure 1.** The mean level of 25(OH)vitamin D in the control and bronchiectasis groups



**Figure 2.** Association between 25(OH) vitamin D level and FEV<sub>1</sub>% predicted values



**Figure 3.** Association between 25(OH)vitamin D level and FVC% predicted values



**Figure 4.** Association between 25(OH)vitamin D level and Reiff scores in bronchiectasis patients

**Table 1.** Baseline characteristics of the study population

	Case Group (n=130)	Control Group (n=73)	p
Age, years	41.9±9.1	45.5±16.7	0.062
Female/Male	66/64	39/34	0.666
BMI*, kg/m <sup>2</sup>	25.7±2.7	25.4±5.4	0.764
25(OH)vitamin D**	14.7±9.6	19.8±6.9	0.001
<b>Vitamin D level*** (ng/mL)</b>			0.016
Normal	8 (6.2)	6 (8.2)	
Insufficiency	27 (20.8)	27 (37)	
Deficiency	95 (73.1)	40 (54.8)	

\*BMI: body-mass index; \*\*25(OH)vitamin D: 25-hydroxy vitamin D (ng/mL). \*\*\*number (%)

adult BR patients and 27 (37%) participants in the control group. There was a statistically significant difference between the two groups ( $p=0.016$ ). Although blood samples were taken between December 15, 2016, and December 15, 2017, there was no significant difference in serum 25(OH)D levels vs. season between the BR and control groups ( $p=0.421$ ).

Sputum samples were taken from 95 (73.1%) patients; 35 (26.9%) patients could not give sputum samples in a stable

period. Some patients (48, 36.9%) had negative sputum culture results. The most frequently isolated microorganism was *Pseudomonas aeruginosa* (27, 20.8%) in a stable period of BR patients. The BR patient group was divided into two sub-groups according to vitamin D deficiency, i.e., 25(OH)D levels  $<20$  ng/mL and  $\geq 20$  ng/mL. The baseline characteristics, clinical symptoms, and radiological and clinical severity of the patients are summarized in Table 2. No significant difference was found between the two sub-groups for age, gender, smoking history, BMI, comorbidity, respiratory symptoms, BSI, and colonization of *Pseudomonas* or other microorganisms in the sputum ( $p>0.05$ ). FEV<sub>1</sub>% predicted value was lower in those BR patients with vitamin D deficiency ( $p=0.051$ ) (Figure 2). However, this relationship was not statistically significant. Patients in the vitamin D deficiency group had significantly higher mMRC scores than those in the group without vitamin D deficiency ( $p=0.036$ ) (Table 2). Moreover, the forced vital capacity% (FVC%) predicted value was lower in the vitamin D deficient group than without vitamin D deficiency group ( $p=0.02$ ) (Figure 3) and the mean modified Reiff score was higher in the vitamin D deficient group ( $6.9\pm 3.8$  vs.  $4.9\pm 2.7$ ,  $p=0.001$ ) (Table 2) (Figure 4).

The first stepwise multivariate model for vitamin D was generated using the following variables: age, gender, BSI, FEV<sub>1</sub>% predicted, and FVC% predicted. This model showed that none of these variables were independently correlated to vitamin D deficiency. When the Reiff score was added to the

**Table 2.** Assessment of the clinical and radiological factors in all BR groups, and in the 25(OH)D vitamin deficient and sufficient groups

Items	All BR Patients (n=130)	25(OH) D vitamin ≥20 ng/mL (n=35)	25(OH) D vitamin <20 ng/mL (n=95)	p
Age, years	41.9±9.1	48.1±16.5	44.7±16.8	0.804
Female/Male,	66/64	19/16	47/48	0.566
BMI, kg/m <sup>2</sup>	25.7±2.7	26.6±5.5	25.1±5.4	0.794
<b>Smoking history</b>				
Non-smoker	80 (61.5)	20 (57.1)	60 (63.2)	0.099
Smoker	23 (17.7)	6 (17.1)	17 (17.9)	
Ex-smoker	27 (20.8)	9 (25.7)	18 (18.9)	
Smoking, pack-year	26.5±16.5	29.7±17.6	25.5±16.4	0.421
Comorbidity	39 (30)	12 (34.3)	27 (28.4)	0.514
Dyspnea	112 (88.5)	26 (74.3)	86 (90.5)	0.217
Cough	106 (81.5)	25 (71.4)	81 (85.3)	0.199
Sputum	83 (63.8)	21 (60)	62 (65.3)	0.535
Hemoptysis	17 (13.1)	5 (14.3)	12 (12.6)	0.771
mMRC	2.3±1.2	1.9±1.1	2.4±1.2	0.036
Duration of diagnosis, years	9.5±7.1	9.1±6.3	9.6±7.3	0.629
BSI	6.9±4.6	6.4±4.8	7.1±4.6	0.926
FEV <sub>1</sub> % predicted	47.8±23.7	54.4±26.3	45.4±22.2	0.051
FVC% predicted	56.0±11.8	62.4±23.1	53.6±21.0	0.021
FEV <sub>1</sub> /FVC	66.3±14.5	65.5±13.7	66.5±14.9	0.678
Modified Reiff score, median (IQR)	6.0(3–9)	4.0 (3–6)	6 (4–9)	0.015
Hemoglobin, g/dL	13.5±1.6	13.6±1.6	1.4±1.5	0.758
Hematocrit, %	41.3±5.5	40.8±7.5	41.5±4.6	0.202
Number of exacerbations in the previous year	85 (65.4)	20 (57.1)	65 (68.4)	0.299
Previous hospital admission*	31 (23.8)	7 (20)	24 (25.3)	0.645
Sputum culture positivity**	47/95 (49.5%)	13/23 (56.5%)	34/72 (47.2%)	0.535
<i>P. aeruginosa</i> colonization, n (%)	27 (28.4)	9 (%39.1)	18 (%25)	0.169

Data are represented as mean±standard deviation or n (%). BMI: body mass index; mMRC: Modified Medical Research Council dyspnea scale; BSI: Bronchiectasis Severity Index; IQR: Inter quartile range; \*Hospitalization with a severe exacerbation in the past 2 years; \*\*Sputum culture in stable period. Sputum culture was performed for 95 BR patients and 48 (50.5%) patients had negative sputum culture results.

model, only Reiff score (OR 1.285 [1.039--1.590], p=0.021) was a significant predictor of vitamin D deficiency (Table 3). However, pulmonary function tests results (values of FEV<sub>1</sub>% predicted and FVC% predicted) did not indicate an increased risk of vitamin D deficiency.

**Table 3.** Logistic regression analysis for the association between vitamin D deficiency and related factors

Vitamin D	Odds ratio (95% CI)	p
Age	1.010 (0.975–1.049)	0.538
Gender (Male)	1.087 (0.307–3.897)	0.960
<b>BSI-mild</b>		0.179
BSI-moderate	0.626 (0.158–2.476)	0.504
BSI-severe	0.223 (0.044–1.144)	0.072
FEV <sub>1</sub> % predicted	1.003 (0.864–1.164)	0.926
FVC% predicted	0.963 (0.845–1.097)	0.600
<b>mMRC</b>		0.365
mMRC (1)	0.452 (0.081–2.521)	0.081
mMRC (2)	7.395 (0.782–69.947)	0.252
mMRC (3)	3.434 (0.416–28.373)	0.252
Modified Reiff Score	1.285 (1.039–1.590)	<b>0.021</b>

BSI: Bronchiectasis Severity Index; FEV<sub>1</sub>: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: Modified Medical Research Council Dyspnea Scale

## DISCUSSION

To our knowledge, this is the only study to assess the role of vitamin D deficiency in Turkish adult BR patients. We found that the prevalence of vitamin D deficiency and insufficiency was high among adult BR patients during a stable period. Furthermore, vitamin D deficiency was associated with pulmonary function tests, especially FVC% predicted values. This study is also the first to investigate the influence of vitamin D deficiency on the radiological severity of BR. Our findings show that adult BR patients with vitamin D deficiency had a higher mMRC and modified Reiff scores as compared with the vitamin D non-deficient BR patients.

Epidemiological studies suggest that in many countries vitamin D deficiency is prevalent throughout all age groups, as well as in healthy subjects [15]. In the National Health and Nutrition Examination Survey 2005 to 2006, 41.6% of the adult participants had vitamin D deficiency [18]. Vitamin D deficiency is a common problem in Turkey, especially in women, and the elderly [19, 20]. Some studies reported that the vitamin D concentrations ranged between 16.9±13.09 [18] to 21.0±20.7 ng/mL among the Turkish populations [21]. In our study, we found similar mean 25(OH)D concentrations in the healthy control group, but the adult BR patients had lower mean 25(OH)D concentrations as compared with previously reported values.

Previous studies have investigated the impact of vitamin D on asthma, chronic obstructive pulmonary diseases (COPD), and tuberculosis [22]. One study reported that the prevalence of vitamin D insufficiency was 76% and its deficiency was 23% in adult CF patients [23]. Chalmers's et al. [4] investigated 402 adult BR patients and reported that 50% of the BR patients were vitamin D deficient, and 43% were insufficient. In a recent study on advanced COPD patients, the prevalence of vitamin D deficiency was between 33% and 77% [24]. Monadi et al. showed that serum 25(OH)D

levels may be related to low FEV<sub>1</sub> in patients with COPD [25]. Another study reported a greater decline in FEV<sub>1</sub>% predicted during a three-year follow-up period in a vitamin D deficient adult BR group as compared with a sufficient group [4]. Data from the 3<sup>rd</sup> National Health and Nutrition Examinations Survey (n=14,091) reported that vitamin D levels were related to FEV<sub>1</sub> and FVC [26]. Salas et al. [27] showed that vitamin D sufficiency was associated with a reduction in the total number of asthma exacerbations. In a recent study, serum vitamin D levels correlated with low FEV<sub>1</sub> and FEV<sub>1</sub>% predicted in adult asthma patients. Moreover, lower vitamin D levels have been linked with uncontrolled asthma [28]. Limited studies have investigated the correlation between pulmonary function tests and vitamin D level in adult BR. Chalmers et al. [4] showed that the median FEV<sub>1</sub>% predicted value was 68% in a vitamin D deficient group and that this result was lower than that in vitamin D insufficient/sufficient non-CF BR patients (median FEV<sub>1</sub>% predicted value, 68% vs. 74.2% vs. 72.2%, respectively; p=0.02). They also reported that FEV<sub>1</sub> decline was higher in the vitamin D deficient group than in vitamin D insufficient/sufficient non-CF BR patients [4]. However, in a recent study from New Zealand, no significant correlation between vitamin D level and FEV<sub>1</sub> or FVC was detected in 32 adult BR patients [9]. In our study, a decline in FVC% predicted value was associated with lower 25(OH)D concentrations in adult BR patients. However, there was no relationship between the decrease in the FEV<sub>1</sub>% predicted value and vitamin D deficiency.

Chalmers et al. [4] investigated the relationship between vitamin D deficiency, chronic colonization, and disease severity in 402 adult BR patients. Chronic bacterial colonization, especially with *Pseudomonas aeruginosa* was more frequent in the vitamin D deficient group. They also reported that these patients had more frequent exacerbations and worse health-related quality of life. In our study group, 95 patients provided sputum samples for culture. There were no significant differences in *Pseudomonas aeruginosa* colonization between the vitamin D deficient and sufficient groups. However, compared with other reports, the difference observed in our study may be due to the numbers of cases.

A randomized controlled trial was conducted to assess the clinical effect of a single high-dose vitamin D administration in patients with CF hospitalized for exacerbation [29]. The one-year survival, hospital-free days, and antibiotic therapy-free days were increased in the vitamin D group.

In a recent study, 32 adult BR patients had higher 25(OH) vitamin D level than the general adult population of New Zealand [9]. They also investigated vitamin D<sub>3</sub> supplementation, the time to first exacerbation, and exacerbation frequency. Although the sample size was limited, there was no association between vitamin D levels and exacerbation [9]. In this study, we evaluated the relationship between vitamin D deficiency and exacerbation of BR in the previous year, as well as the hospitalization in the previous two years. We did not detect any association between vitamin D deficiency and previous exacerbation or hospitalization of BR patients.

Obesity is a risk factor for vitamin D deficiency because the latter is a fat-soluble vitamin that is stored in adipose tissue. In obese individuals, adipose tissue reduces the release of vitamin D from the skin into the circulation [30]. Some studies have noted lower serum vitamin D levels in obese individuals, while other studies have reported vitamin D deficiency related to acute coronary syndrome, hypertension, and hyperlipidemia [18, 31, 32]. In the current study, we did not find an association among BMI, comorbidity, and vitamin D deficiency.

The mechanisms underlying the role of vitamin D in the pathogenesis of bronchiectasis are unclear. Vitamin D may affect immunity via the induction of local pro-inflammatory microenvironment, and by its anti-infective and anti-inflammatory properties in the airways. Therefore, vitamin D deficiency might be involved in the etiopathogenesis of impaired mucociliary activity, chronic colonization, and recurrent infection of airways, namely the “vicious circle hypothesis” [33]. Our results show that vitamin D deficient adult BR patients have high modified Reiff scores indicating that these patients have more severe radiological findings compared with vitamin D non-deficient BR patients. Moreover, the mMRC scores were found to be increased in BR patients with vitamin D deficiency. Patients with severe disease and more symptoms may have decreased physical activity and tend to spend less time for outdoor activities, which in turn may lead to reduced vitamin D production. Low vitamin D level is a known factor for impaired immunity, which can contribute to the development of recurrent infections in the lung, and consequently, BR. However, it is difficult to explain the association between vitamin D deficiency and the development of BR in adults, as the vitamin D level measured at one time point does not reflect the overall level throughout the year.

In this study, we would like to emphasize that vitamin D insufficiency/deficiency can be detected in chronic respiratory diseases such as BR. Although the role of vitamin D in the pathogenesis of BR is unclear, it may affect clinical and radiological parameters of BR patients. It is therefore important to identify vitamin D insufficiency/deficiency in BR patients, and proper treatment should be given to these patients. In addition, clinicians may advise prolonged sun exposure and increased physical activity to BR patients.

#### Study Limitations

There are some limitations to this study. First, the study was conducted in a single center. Second, some factors that may affect serum vitamin D levels, such as dietary patterns, dressing style, and sun exposure, could not be evaluated.

In conclusion, this study showed that serum vitamin D levels in bronchiectasis patients were less than those in healthy controls. We found that vitamin D deficiency was common in adult bronchiectasis patients in a stable period and it might be related to severe radiological findings on chest computed tomography and poor lung functions.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval no: 2016/66).

**Informed Consent:** Written informed consent was obtained from each participant who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - E.Y.N., L.K., M.A.U.; Design - E.Y.N., L.K., B.Y., M.A.U.; Supervision - G.Ç., M.A.U.; Resource - E.Y.N., D.B., B.Y.; Materials - E.Y.N., L.K., D.B.; Data Collection and/or Processing - E.Y.N., D.B.; Analysis and/or Interpretation - E.Y.N., M.A.U., D.B.; Literature Search - E.Y.N., L.K., B.Y.; Writing - E.Y.N., L.K., M.A.U.; Critical Reviews - G.Ç., M.A.U.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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