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ORIGINAL RESEARCH

Vitamin D Status and Longitudinal Changes in Body Composition in Patients with Chronic Obstructive Pulmonary Disease – A Prospective Observational Study

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Background: Alterations in body weight and composition are common in patients with chronic obstructive pulmonary disease (COPD) and are independent predictors for morbidity and mortality. Low vitamin D status is also more prevalent in patients with COPD compared to controls and has been related to lower lung function, muscle atrophy and impaired musculoskeletal function. This study aimed to evaluate the association between vitamin D levels and status with body composition (BC), as well as with its changes over time.

Patients and Methods: Patients with COPD and controls without COPD, participating in the Individualized COPD Evaluation in relation to Ageing (ICE-Age) study, a prospective observational study, were included. Plasma 25-hydroxyvitamin D (25(OH)D) was measured at baseline and BC was measured by dual-energy X-ray absorptiometry scan, at baseline and after two years of follow-up. Multiple linear regression analyses were performed to assess the relationships between 25(OH)D (nmol/l) and longitudinal changes in BMI, fat-free mass index (FFMI), fat mas index (FMI) and bone mineral density (BMD).

Results: A total of 192 patients with COPD (57% males, mean ± SD age, 62 ± 7, FEV1, 49 ± 16% predicted) and 199 controls (45% males, mean ± SD age 61 ± 7) were included in this study. Vitamin D levels were significantly lower in patients with COPD (64 ± 26 nmol/L, 95% CI 60–68 nmol/L versus 75 ± 25 nmol/L, 95% CI 72–79 nmol/L) compared to controls. Both patients and controls presented a significant decline in FFMI and T-score hip, but vitamin D level or status did not determine differences in BC or changes in BC over time in either COPD or controls.

Conclusion: Vitamin D status was not associated with BC or longitudinal changes in BC. However, vitamin D insufficiency and low BMD were more prevalent in patients with COPD compared to controls.

Keywords: chronic obstructive pulmonary disease, body composition, vitamin D, longitudinal changes, fat-free mass, bone mineral density

Introduction

Although primarily a disease of the lungs, chronic obstructive pulmonary disease (COPD) is commonly characterized by extrapulmonary manifestations, including malnutrition, sarcopenia, and osteoporosis.[1–5] Indeed, low body mass index (BMI) and low fat-free mass index (FFMI) are independent predictors for morbidity and mortality in patients with COPD.[6–8] Low fat-free mass (FFM) has also been associated with lower exercise capacity and lower quality of life.[9–11]

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In addition, reduced bone mineral density (BMD), in patients with COPD, is related with the severity of the disease.[12,13] Low BMD have also been associated with low FFM and low BMI.[1,3,14]

Vitamin D is important for bone health and the regulation of calcium and phosphate metabolism.[15] In the general population, low vitamin D levels have been associated with the development of various diseases[15] and altered body composition, ie higher BMI,[16] higher fat mass (FM) percentage[17] and lower BMD.[18] Low levels of 25-hydroxyvitamin D (25(OH)D) contribute to muscle protein breakdown[19] and have been recognized in the pathophysiology of sarcopenia in elderly people.[20]

In patients with COPD, a higher prevalence of vitamin D deficiency and insufficiency have been shown compared to controls.[21,22] Limited sunlight exposure caused by reduced outdoor activity, common use of glucocorticoids, smoke-induced skin aging, and insufficient dietary intake are factors that likely contribute.[4,21,22] Also, in patients with COPD, low vitamin D status has been related to lower lung function and higher exacerbation frequency,[21,23] but also muscle atrophy[24] and impaired musculoskeletal function.[24,25]

There is limited knowledge however on longitudinal changes in body composition in relation to vitamin D status in patients with COPD. Only two previous studies[26,27] investigated the change of various COPD-related outcomes in relation to vitamin D status. However, no associations between 25(OH)D and longitudinal change in FFMI, over the course of six months[26] and three years,[27] respectively, were found.

Taken together, both low vitamin D status and altered body composition are associated with several adverse COPD-related outcomes. However, the association between vitamin D status and longitudinal changes in body composition have only partially been investigated. Thus, it is of interest to further explore whether vitamin D status is a factor related with alterations in body composition in patients with COPD. We therefore aimed to evaluate the association between vitamin D levels and status with body composition, as well as body composition changes over time, in well-characterized patients with COPD compared to controls.

Materials and Methods

Study Design and Population

Data are derived from the Individualized COPD Evaluation in relation to Ageing (ICE-Age) study (registered on www.controlled-trails.com with identifier ISRCTN86049077). The ICE-Age study was a prospective observational study with two years of follow-up performed in a tertiary care pulmonary rehabilitation center (CIRO, Horn, The Netherlands), from December 2010 to August 2016. Inclusion and exclusion criteria, as well as the enrolment process, have previously been described.[28] In summary, clinically stable (absence of respiratory tract infection or exacerbation of the disease for <4 weeks before study entry) patients diagnosed with moderate-to-severe COPD, age 45–75 years were recruited on referral to pulmonary rehabilitation. Healthy smoking and non-smoking, controls, comparable in age and sex were recruited from the same region. Exclusion criteria for both patients and controls were any kind of carcinogenic pathology <5 y before study participation, chronic use of oral corticosteroids >10mg/day and investigator's uncertainty about the willingness or ability of the participant to comply with the protocol requirements. All included patients used long-acting beta agonists or long-acting muscarinic antagonists, 66% used short-acting beta agonists, short-acting muscarinic antagonists, or a combination thereof, 21% used inhaled corticosteroids. Exclusion criteria in the present study were no measure of plasma 25(OH)D or no available baseline dual-energy X-ray absorptiometry (DEXA) scan measurements for fat-free mass (FFM).

Assessments

Demographic and anthropometric data include age, sex, smoking status, number of pack years smoked, body weight, height, DEXA scan measurements, lung function tests, blood tests, self-reported comorbidities, and medications. Body composition measurements and lung function tests were performed at baseline and repeated after two years of follow-up. Patients with COPD performed six-minute walk test (6MWT) and answered COPD-related questionnaires at baseline. Number of exacerbations and hospitalizations due to COPD, in the previous 12 months was recorded at baseline. An exacerbation was defined as an acute need to use a course of oral glucocorticoids or antibiotics and/or hospitalization due to acute respiratory worsening.[29] After baseline assessments, patients with COPD underwent an 8-week pulmonary rehabilitation program.

Plasma 25(OH)D was assayed by radioimmunoassay (Immunodiagnostic systems, Boldon, UK) at the Central Diagnostic Laboratory of Maastricht. Plasma 25(OH)D was categorized as <25 nmol/L), 25–49 nmol/L and ≥50 nmol/L as suggested by the Institute of Medicine.[30] There is a growing agreement that plasma or serum 25(OH)D above 50 nmol/L corresponds to sufficient levels, and that less than 25–30 nmol/L indicates deficiency.[30–32] Therefore, when dichotomized, 25(OH)D <50 nmol/L is referred to as vitamin D insufficiency and ≥50 nmol/L is referred to as sufficient.[31]

Body weight and height were used to calculate BMI (kg/m^2). BMI was categorized as: underweight <18.5 kg/m^2, normal weight 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, and obesity >30 kg/m^2, according to the World Health Organization (WHO) definition.[33] Body composition, including lean, fat and bone mass was assessed by DEXA scan (Lunar Prodigy system; GE Healthcare, Madison, WI, USA). FFM was calculated as the sum of lean mass and bone mineral content. FM was calculated as the difference between body weight and FFM. Fat mass index (FMI) and FFMI was calculated by dividing FM and FFM in kg by height, from visit one, in meters squared (kg/m^2). BMD was measured at the proximal femur (hip) and at the lumbar spine (L2-L4) and recorded as g/cm^2 and as T-score hip and T-score lumbar spine. Participants with a T-score between <-1 and >-2.5 at either hip or lumbar spine were classified as having osteopenia and participants with a T-score of −2.5 or less, as having osteoporosis, as defined by WHO.[34]

Post-bronchodilator lung function tests were performed to assess forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) and its ratio (FEV1/FVC), using a standardized spirometer method (Masterlab®, Jaeger, Germany), following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[35] FEV1 and FVC are presented as percentages of reference values.[36] Patients were classified according to the most recent GOLD criteria.[37] In patients with COPD, the 6MWT was performed according to the ATS guidelines.[38] Questionnaires, including modified Medical Research Council (mMRC) dyspnoea scale[39] and St George Respiratory Questionnaire (SGRQ)[40] were used to assess the level of functional disability due to breathlessness in daily activity and disease-related quality of life respectively. Higher scores indicating more limitations.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$ for all comparisons. Figures were created using GraphPad Prism 8.3.5 (GraphPad Software, La Jolla, CA, USA).

Continuous variables were checked for normal distribution using graphical plots. Descriptive statistics for continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables, otherwise median and first and third quartiles are shown. Comparison between two groups were done with independent samples *t*-test or the non-parametric Mann–Whitney *U*-test. Comparison within groups were done with either paired samples *t*-test for mean values or related samples Wilcoxon sign rank test for median values. Chi-squared test was used to compare categorical variables.

Longitudinal changes in BMI, FFMI, FMI, T-score hip, and T-score lumbar spine, were calculated by subtracting the data at two years of follow-up from baseline data.

Multiple linear regression analyses were performed to assess the relationships between 25(OH)D (nmol/l) and longitudinal changes in BMI, FFMI, FMI, T-score hip, and T-score lumbar spine. The minimal adjusted model included sex and group. The fully adjusted model included additionally age, smoking status and the baseline value of the dependent variable being analyzed. Thereafter, the interaction term (25(OH)D ≥50 nmol/L/<50 nmol/L x group (control/COPD) was included. Residuals were tested for normality using graphical plots. Included covariates were justified based on previous research and clinical relevance.

Ethics

All participants in the ICE-Age study provided written informed consent prior to study participation. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and was approved by the local ethics review board of the Maastricht University Medical Centre (Maastricht, The Netherlands, MEC 10-3-033) and the Swedish Ethical Review Authority (registration number: 2023-07359-01). In addition, the study analyses were approved by the board of directors of CIRO (Horn, The Netherlands).

Results

Patient Characteristics

A total of 192 patients with COPD and 199 participants without COPD (controls) were included in this study, Figure 1. Thirty-five participants did not return for outcome assessments. Reasons for no follow-up include participants no longer wanted to participate, participants not being available for follow-up or participant died during the study. In total 84% (n=162) patients with COPD and 98% (n=194) controls repeated the measurements.

The participants baseline characteristics are presented in Table 1. Patients with COPD had on average moderate-to-severe COPD and almost half of them had frequent exacerbations. They were on average highly symptomatic with reduced quality of life. There were more men than women in the COPD group and the mean age was slightly higher compared to the control group. Patients with COPD were more frequent ex-smokers and had a significantly higher number of pack years smoked. There was a larger proportion of non-smokers in the control group. Baseline BMI, FFMI and FMI were comparable between patients and controls. Majority of participants had either overweight or obesity, but obesity was more prevalent in patients with COPD, 27% (n=52) compared to 16% (n=32) in controls. Five percent of patients with COPD had a BMI less than 18.5, whereas none of the controls were underweight. Osteopenia and osteoporosis were significantly more prevalent in patients with COPD, as were self-reported cardiac disease, gastro-intestinal disease, and use of calcium-vitamin D supplements.

Vitamin D Status

Mean plasma 25(OH)D level in the total cohort was 70 ± 27 nmol/L, ranging from 13 to 152 nmol/L. Vitamin D levels were significantly lower in patients with COPD (64 ± 26 nmol/L, 95% CI 60–68 nmol/L versus 75 ± 25 nmol/L, 95% CI 72–79 nmol/L) compared to controls. Overall, only 3% of participants had 25(OH)D <25 nmol/L. As presented in Figure 2, in total, 34% (n=65) of patients with COPD had vitamin D insufficiency, compared to 16% (n=31) among the controls. The mean 25(OH)D, after excluding participants with vitamin D supplementation, was still significantly lower

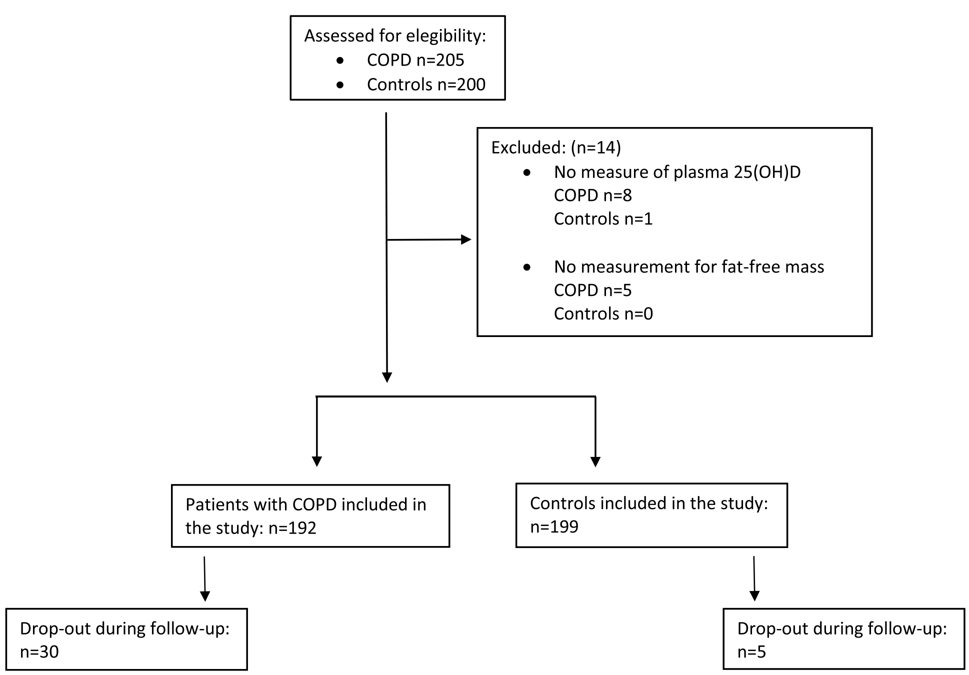

Figure 1 Flow chart of participants included in the study.

Table 1 Baseline Characteristics of the Participants

Variables	COPD n=192	Controls n=199	p-value
Male n (%)	109 (57)	89 (45)	0.02[a]
Age, years mean (SD)	62 ± 7	61 ± 7	0.03[b]
Smoking status			
Former smoker n (%)	162 (84)	114 (57)	
Current smoker n (%)	27 (14)	26 (13)	
Non-smoker n (%)	3 (2)	59 (30)	
Number of pack years smoked	43 (31–59)	7 (0–20)	<0.001[c]
Vitamin D level			
Plasma 25(OH)D nmol/L	64 ± 26	75 ± 25	<0.001[b]
Body Composition			
BMI (kg/m^2)	26.6 ± 5	26.9 ± 3.4	0.51[b]
BMI <18.5 n (%)	10 (5)	0 (0)	
BMI 18.5–24.9 n (%)	60 (31)	60 (30)	
BMI 25–29.9 n (%)	70 (36)	107 (54)	
BMI <30 n (%)	52 (27)	32 (16)	
FFMI (kg/m^2)	17.6 ± 2.6	17.9 ± 2.3	0.19[b]
FMI (kg/m^2)	9.0 ± 3.7	8.9 ± 2.9	0.89[b]
BMD hip (g/cm^2)	0.84 (0.77–0.92)	0.94 (0.85–1.04)	<0.001[c]
BMD lumbar spine (g/cm^2)	1.10 (0.95–1.22)	1.20 (1.05–1.3)	<0.001[c]
T-score hip	−1.5 (−2.1 – −0.9)	−0.7 (−1.3–0.1)	<0.001[c]
T-score lumbar spine	−1 (−1.7–0.1)	0 (−1.2–1.1)	<0.001[c]
Lung function			
FEV1% predicted	49 ± 16	119 ± 15	<0.001[b]
FVC % predicted	98 ± 21	124 ± 16	<0.001[b]
FEV1/FVC ratio	41 ± 11	79 ± 4	<0.001[b]
Self-reported medications			
Calcium- vitamin D supplements n (%)	28 (15)	3 (2)	<0.001[a]
Comorbidities			
Osteopenia, n (%)	104 (54)	77 (39)	0.002[a]
Osteoporosis, n (%)	39 (21)	14 (7)	<0.001[a]
Self-reported Diabetes mellitus, n (%)	13 (7)	6 (3)	0.08[a]
Self-reported Hypertension, n (%)	43 (22)	42 (21)	0.80[a]
Self-reported Cardiac disease, n (%)	39 (20)	9 (5)	<0.001[a]
Self-reported Gastrointestinal disease, n (%)	20 (10)	9 (5)	0.026[a]
≥ **2 exacerbations in the previous year**	86 (45)	-	
≥ **1 hospital admission in the previous year**	60 (31)	-	
6MWT, m	465 ± 113	-	
Questionnaires			
mMRC, score	3 ± 1	-	
SGRQ, Total score	54.8 ±16.7	-	

Notes: Data are presented as mean ± SD or median (quartiles 1 and 3), unless otherwise stated. [a]Pearson Chi-squared test. [b]Independent samples *t*-test. [c]Independent samples Mann Whitney *U*-test.

Abbreviations: COPD, chronic obstructive pulmonary disease; 25(OH)D, 25-hydroxyvitamin D; BMI, Body mass index; FFM, fat-free mass; FM, fat mass; FFMI, Fat-free mass index; FMI, Fat-mass index; BMD, Bone mineral density; FEV1% predicted, forced expiratory volume in the first second in percent of predicted value; FVC % predicted, forced vital capacity in percent of predicted value; 6MWT, Six-minute walk test; mMRC, Modified Medical Research Council; SGRQ, St George Respiratory Questionnaire.

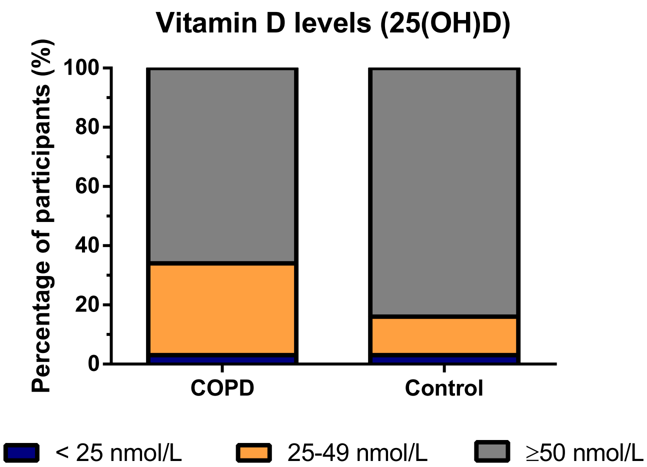

Figure 2 Vitamin D levels in patients with COPD and controls.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; COPD, Chronic obstructive pulmonary disease.

in patients with COPD (62 ± 25 nmol/L versus 75 ± 25 nmol/L, $p<0.001$) compared to controls. Considering both patients and controls as a combined group, it is noteworthy that 25(OH)D levels were initially significantly lower in men (67 ± 27 nmol/L) compared to women (73 ± 26 nmol/L) ($p=0.03$). However, after excluding participants with vitamin D supplementation, this difference was no longer significant ($p=0.13$).

Baseline characteristics by vitamin D status for patients with COPD and controls are presented in Table 2. Vitamin D insufficient patients with COPD had significantly lower FEV1% predicted (46 ± 16 vs 51 ± 16, $p=0.03$) and a larger proportion had experienced at least one hospital admission due to COPD in the previous year, as compared to the vitamin D-sufficient patients (42% vs 26%, $p=0.03$). Furthermore, they walked a shorter distance on the 6MWT (438 ± 106 vs 481 ± 114, $p=0.03$) and had reduced quality of life, according to the SGRQ total score (59 ± 17 vs 53 ± 16, $p=0.02$), compared to vitamin D sufficient patients. There were no significant differences in exacerbation frequency, or mMRC score.

Table 2 Baseline Characteristics by Vitamin D Status

Variables	COPD Vitamin D Insufficiency	COPD Vitamin D Sufficiency	p-value	Controls Vitamin D Insufficiency	Controls Vitamin D Sufficiency	p-value
	n=65	n=127		n=31	n=168	
Male n (%)	40 (62)	69 (54)	0.34[a]	14 (45)	75 (45)	0.96[a]
Age, years	61 ± 8	63 ± 7	0.32[b]	62 ± 7	61 ± 7	0.48[b]
Current smoker n (%)	13 (20)	14 (11)	0.09[a]	3 (10)	23 (14)	0.54[a]
Body composition						
BMI (kg/m^2)	26.3 ± 4.9	26.7 ± 5	0.61[b]	27.7 ± 3.5	26.7 ± 3.4	0.13[b]
BMI <18.5 n (5) n (%)	3 (5)	7 (6)		0 (0)	0 (0)	
BMI 18.5–24.9 n (%)	22 (34)	38 (30)		7 (23)	53 (32)	
BMI 25–29.9 n (%)	24 (37)	46 (36)		16 (52)	91 (54)	
BMI >30 n (%)	16 (25)	36 (28)		8 (26)	24 (14)	
FFMI (kg/m^2)	17.5 ± 2.3	17.7 ± 2.7	0.55[b]	18.3 ± 2.3	17.9 ± 2.3	0.38[b]
FMI (kg/m^2)	8.9 ± 3.7	9 ± 3.7	0.78[b]	9.5 ± 3.2	8.9 ± 2.9	0.27[b]
T-score hip	−1.5 (−2.1 – −1)	−1.5 (−2.1 – −0.8)	0.33[c]	−1.0 (−1.5–0)	−0.7 (−1.3–0.2)	0.29[c]
T-score lumbar spine	−1.1 (−1.9–0)	−1 (−1.7–0.1)	0.47[c]	−0.2 (−1.3–0.6)	0.1 (−1.2–1.1)	0.26[c]

(*Continued*)

Table 2 (Continued).

Variables	COPD Vitamin D Insufficiency	COPD Vitamin D Sufficiency	p-value	Controls Vitamin D Insufficiency	Controls Vitamin D Sufficiency	p-value
	n=65	n=127		n=31	n=168	
Lung function						
FEV1% predicted	46 ± 16	51 ± 16	0.03[b]	118 ± 16	119 ± 15	0.60[c]
FVC % predicted	95 ± 19	100 ± 22	0.10[b]	121 ± 18	125 ± 16	0.19[b]
FEV1/FVC ratio, %	39 ± 12	42 ± 11	0.15[b]	80 ± 5	78 ± 5	0.14[b]
Comorbidities						
Osteopenia n (%)	38 (58)	66 (52)	0.39[a]	16 (52)	61 (36)	0.11[a]
Osteoporosis n (%)	15 (23)	24 (19)	0.50[a]	2 (6)	12 (7)	0.89[a]
Self-reported Gastrointestinal disease	8 (12)	12 (9)	0.54[a]	1 (3)	8 (5)	0.71[a]
≥ 2 exacerbations in the previous year n (%)	29 (45)	57 (45)	0.94[a]	-	-	
≥ 1 hospital admission in the previous year n (%)	27 (42)	33 (26)	0.03[a]			
6MWT, m	438 ± 106	481 ± 114	0.03[b]	-	-	
Questionnaires						
mMRC, grade	3 ± 1	3 ± 1	0.15[b]	-	-	
SGRQ, Total score	59 ± 17.4	52.6 ± 15.9	0.02[b]	-	-	

Notes: Data are presented as median (quartiles 1 and 3) or mean ±SD unless otherwise stated. Vitamin D insufficiency = 25-hydroxyvitamin D <50 nmol/L and Vitamin D sufficiency = 25-hydroxyvitamin D ≥50 nmol/L. [a]Pearson Chi Squared test. [b]Independent samples *t*-test. [c]Independent samples Mann Whitney *U*-test.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FFMI, fat-free mass index; FMI, fat-mass index; FEV1% predicted, Forced expiratory volume in the first second in percent of predicted value; FVC % predicted, Forced vital capacity in percent of predicted value; 6MWT, Six-minute walk test; mMRC, Modified Medical research Council dyspnoea scale; SGRQ, St George Respiratory Questionnaire.

Vitamin D Status and Body Composition

None of the body composition variables differed significantly by vitamin D status within the patient group, nor within the control group (Table 2).

Vitamin D Status and Changes in Body Composition Over Time

Changes in body composition over two years are presented in Table 3. Both patients with COPD and controls maintained a stable BMI over time but had a significant decline in FFMI (mean ± SD kg/m^2, −0.4 ± 0.8 vs −0.1 ± 0.5 respectively) and increase in FMI (mean ± SD kg/m^2 +0.4 ± 1.6 and +0.3 ± 1.3 respectively). The decline in FFMI was significantly greater for patients with COPD compared to controls (Independent samples Mann Whitney *U*-test, p<0.001). Furthermore, a significant decline in BMD, measured at the proximal femur, expressed as change in T-score hip, was seen in both patients and controls (median −0.1 (−0.5–0.2) and −0.1 (−0.4–0.1) respectively), but no significant difference between the groups (Independent samples Mann Whitney *U*-test p=0.84). T-score lumbar spine remained stable over time.

Table 3 Changes in Body Composition Over Two Years

	COPD Baseline	COPD Year 2	p-value	Control Baseline	Control Year 2	p-value
BMI, kg/m^2	26.6 ± 5.0	27.0 ± 5.3	0.62[a]	26.9 ± 3.4	27.0 ± 3.6	0.13[a]
FFMI, kg/m^2	17.7 ± 2.6	17.3 ± 2.5	<0.001[a]	17.9 ± 2.3	17.8 ± 2.2	0.002[a]
FMI, kg/m^2	9.1 ± 3.6	9.5 ± 3.7	0.002[a]	8.9 ± 2.9	9.2 ± 3	0.006[a]
T-score hip	−1.4 (−2.1–0.9)	−1.7 (−2.2 – −1.1)	<0.001[b]	−0.7 (−1.4–0.1)	−0.9 (−1.6–0.2)	<0.001[b]
T-score lumbar spine	−1.0 (−1.7–0.3)	−0.9 (−2.1–0.2)	0.81[b]	0 (−1.3–1.1)	0 (−1.4–1.2)	0.98[b]

Notes: Data are presented as mean ± SD or median (quartiles 1 and 3). [a]Paired samples *t*-test. [b]Related samples Wilcoxon sign rank test.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, Body mass index; FFMI, Fat-free mass index; FMI, Fat-mass index.

Multiple linear regression analyses for the whole group (COPD and controls combined) showed a significant relationship between 25(OH)D and change in T-score hip over two years in the model adjusted for sex (female vs male) and group (control vs COPD), but not in the fully adjusted model additionally adjusted for age, smoking status (former or non-smoker vs current smoker) and baseline value of T-score hip. In the fully adjusted model, sex, group, and baseline value of T-score hip were significant predictors of change in T-score hip. No significant relationship between 25 (OH)D and change in BMI, FFMI, FMI or T-score lumbar spine over two years was seen neither in the minimal adjusted models nor in the fully adjusted models, Table 4 and S-Tables 1–5 in the online supplement. The interaction term (25 (OH)D ≥50 nmol/l/<50 nmol/L x group (control/COPD) was statistically significant in the model testing the relationship between 25(OH)D and change in BMI (Unstandardized B-coefficient 0.629, Standard error 0.319, p= 0.049). Due to the significant interaction, stratified analyses were performed. The stratified analyses for patients with COPD and controls showed no statistically significant relationship between any of the included covariates and longitudinal change in BMI (S-Table 6a and b, in the online supplement).

Longitudinal changes in body composition did not differ significantly by vitamin D status, neither within the patient group, nor within the control group (Figure 3).

Discussion

The main finding of the present study is that vitamin D insufficiency is more prevalent in patients with COPD compared to controls, but vitamin D status was not related to body composition. Neither was vitamin D level or status associated with changes in body composition over 2 years in either patients with COPD or controls.

Our results add to previous studies showing that lower vitamin D levels are more common in patients with COPD compared to controls.[21,22] The prevalence of vitamin D deficiency in patients with COPD, varies between studies, as does the cut-off values used to define deficiency and insufficiency. Both higher, lower, and similar prevalence have been reported.[23,41,42] In the SPIROMICS study, Burkes et al reported that about one in five patients with COPD had vitamin D deficiency,[23] whereas the prevalence in a British study reported a prevalence as high as 61.5%.[41] We have previously

Table 4 Multiple Linear Regression Analyses to Assess the Relationship Between 25(OH)D (Nmol/l) and Longitudinal Changes in Body Composition

Dependent Variable	Model 1		Model 2	
	B (SE)	p-value	B (SE)	p-value
Δ BMI[a]* n=356	−0.002 (0.003)	0.53	−0.003 (0.003)	0.47
Δ FFMI[b]*,[c]* n=353	0.002 (0.001)	0.25	0.001 (0.001)	0.34
Δ FMI[d]* n=353	−0.003 (0.003)	0.33	−0.004 (0.003)	0.25
Δ T-score hip[e]* n=345	−0.003 (0.001)	0.01	−0.001 (0.001)	0.19
Δ T-score lumbar spine[f]*,[g]* n=351	−0.002 (0.001)	0.15	−0.001 (0.001)	0.21

Notes: Model 1, adjusted for sex (female vs male) and group (control vs COPD). Model 2, adjusted for sex (female vs male), group (control vs COPD) age, smoking status (former or non-smoker vs current smoker) and baseline value of the dependent body composition variable being analysed. *p<0.05. [a]Model 2, Age B −0.029 (0.013). [b]Model 1, Gender: B −0.221 (0.068), Group: B −0.239 (0.069). [c]Model 2, Group: B −0.265 (0.070), Baseline value of FFMI: B-0.059 (0.022). [d]Model 2, Baseline value of FMI: B −0.067 (0.025). [e]Model 2, Gender: B 0.131 (0.052), Group: B −0.209 (0.054), Baseline value of T-score hip: B −0.233 (0.025). [f]Model 1, Gender: B 0.173 (0.053). [g]Model 2, Gender: B 0.178 (0.056). Statistical significance was set at p < 0.05.

Abbreviations: Δ, change over two years in the dependent variable analysed; B, unstandardized B-coefficient; SE, standard error; 25(OH)D, 25-Hydroxyvitamin D; COPD, chronic obstructive pulmonary disease; BMI, Body mass index, FFMI, Fat-free mass index; FMI, Fat-mass index.

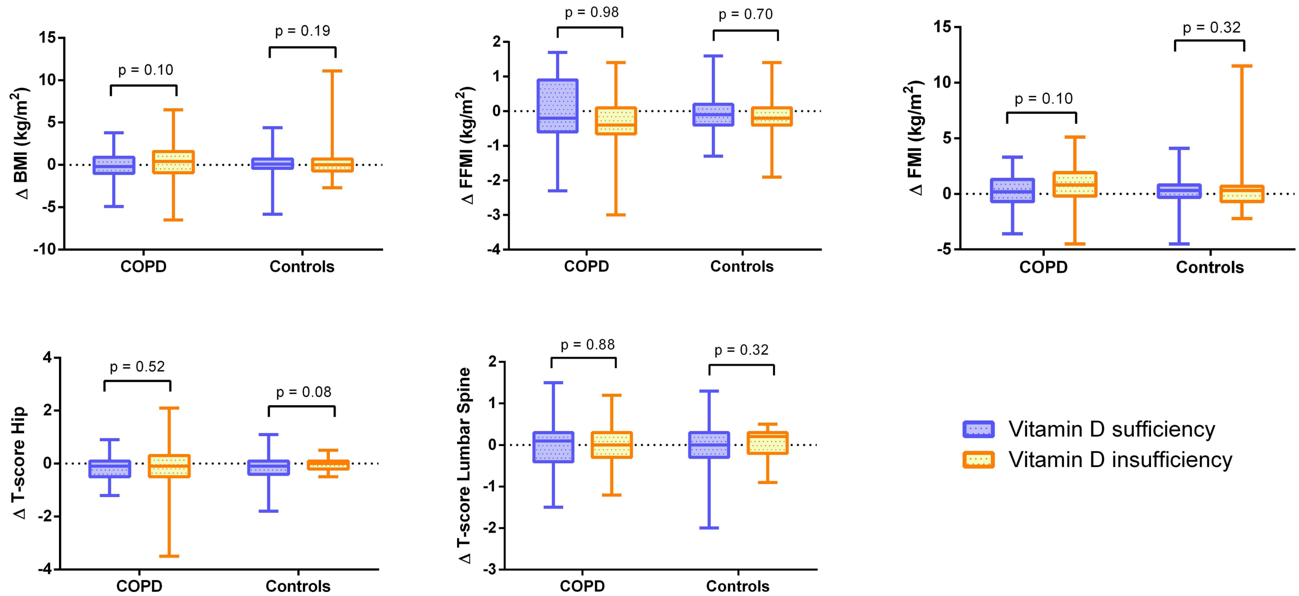

Figure 3 Changes in Body composition over two years by vitamin D status.

Notes: Δ BMI = BMI year 2 – BMI at baseline. Δ FFMI = FFMI year 2 – FFMI at baseline. Δ FMI = FMI at year 2 – FMI at baseline. Δ T-score hip = T-score hip at year 2 - T-score hip at baseline. Δ T-score lumbar spine = T-score lumbar spine at year 2 - T-score lumbar spine at baseline.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FFMI, Fat-free mass index; FMI, Fat-mass index.

reported that 33% of patients from a Swedish COPD cohort had vitamin D insufficiency by using 25(OH)D <50 nmol/L as cut-off value.[42] In agreement with several previous studies, the current study also showed a higher prevalence of vitamin D insufficiency (25(OH)D <50 nmol/l) in more severe COPD (GOLD stage 3 and 4).[21,23,25,27] A recent Swedish observational cohort study including 667 patients with COPD showed no direct association with FEV1% predicted and vitamin D level, although patients with vitamin D insufficiency had more often very severe lung function impairment (GOLD grade 4).[42]

Although both patients with COPD and controls presented a decline in FFMI and an increase in FMI over the study period of two years in the present study, no association between vitamin D status and change in BMI, FFMI or FMI was seen. Our results regarding FFMI are in line with other studies with a longitudinal design.[26,27] Neither Carson et al[26] with a six-month follow-up time, nor Persson et al[27] with a three-year follow-up time found a significant association between 25(OH)D and change in FFMI. Both patients and controls presented a significant decline in BMD at proximal femur, expressed as T-score hip, but the change was not associated with vitamin D status. BMD at lumbar spine remained stable. In contrast to our result, a large (n=3698) study by Zhu et al[43] with middle-aged participants from the Busselton Healthy Ageing Study, who investigated longitudinal stability of 25(OH)D and relations with changes in BMD over six years, found a significant association between a greater decline in vitamin D status and a larger reduction in BMD, total hip, and femur neck. However, in line with our result, previous studies in elderly participants and post-menopausal women have reported a greater longitudinal decline in BMD at the femoral neck compared to at the lumbar spine.[44,45] Age, BMI and baseline BMD at the femoral neck have been found to be predictive for longitudinal change in T-score hip, in both men and women.[45] The longitudinal stability in BMD at lumbar spine has been ascribed to age-related accumulation of mineralized artefacts.[44]

In the present study, vitamin D status was not associated with the various body composition compartments studied in patients with COPD or in controls. Comparable to our results, Graumam et al[1] found no association between vitamin D status and low BMD in patients with COPD. Førli et al have previously found an association between vitamin D deficiency and reduced T-score femur neck in underweight patients with advanced pulmonary disease.[46] Other cross-sectional studies have found an association between low vitamin D status and altered body composition, both in patients with COPD[41] and healthy adult individuals.[47] Jolliffe et al found that patients with COPD and low vitamin D status had a significantly higher BMI.[41] One reason for the difference with the present study might be the substantial lower mean 25(OH)D (45 ± 25 nmol/L compared to 62 ± 25 nmol/L) in our COPD cohort, after excluding participants with vitamin D containing supplements. In the Rotterdam study, a large population-based prospective study, including participants aged 55 years or older, it was found that low vitamin D levels (25(OH)D <50 nmol/L) was associated with higher fat mass percent, but not with lean mass.[17] In non-obese healthy individuals, 25(OH)D levels <50 nmol/L has been associated with greater BMI and waist circumference.[47] The association between low vitamin D status and obesity is well known and may be due to volumetric dilution.[48]

The current study found that both underweight and obesity were more prevalent in patients with COPD compared to controls. However, although we also noted a general lower vitamin D level in patients with COPD, this was not associated with changes in body composition. The use of vitamin D supplementation on various adverse COPD-related outcomes have yielded conflicting results. Some studies found that vitamin D supplementation reduced exacerbation frequency in vitamin D deficient patients[49] whereas a more recent study found no such association.[50] In general, the effect of vitamin D supplementation is largely dependent on the baseline vitamin D level. No effect on BMD or overall health benefits has been found in supplementation of individuals with 25(OH)D levels >50 nmol/L.[51] Considering the small number of participants with vitamin D deficiency in our cohort, it is likely that the effect on body composition is insufficiently studied.

Strengths and Limitations

Strengths of the present study include the broad characterization of a representative cohort of patients with COPD with whole-body DEXA scan measurement for the assessment of body composition, remeasurement at two years follow-up and the inclusion of a control group.

There are also some limitations. Firstly, the two-year follow-up period was defined by protocol based on the original hypothesis related to markers of ageing, particularly changes in telomere length over time.[28] Although a two-year follow-up period is appropriate to evaluate changes over time in body composition,[52] a longer follow-up time, with repeated measures of body composition variables might have rendered a different result. Secondly, we only have one measurement for 25(OH)D at baseline and no information about season for blood sampling, a factor that can affect vitamin D levels.[16,53] Thirdly, due to the low prevalence of vitamin D deficiency (25(OH)D <25 nmol/L) in our cohort, we may have been underpowered to detect associations between the lowest serum concentrations of 25(OH)D and altered body composition and/or its changes over time. Furthermore, patients with COPD underwent an 8-week pulmonary rehabilitation program that previously have shown to increase FFM,[54] but it is unlikely that this affected the two-year follow-up.

Conclusion

In conclusion, the present study demonstrates that vitamin D insufficiency and low BMD are more prevalent in patients with COPD compared to controls, but vitamin D level or status was not associated with body composition or longitudinal changes in body composition. Nevertheless, vitamin D insufficiency was related to other adverse COPD-related outcomes such as lower FEV1% predicted and reduced exercise capacity. To improve health outcomes and prevent further disease burden, we recommend that both vitamin D status and body composition are routinely assessed in patients with COPD.

Disclosure

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