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ORIGINAL RESEARCH

Low bone mineral density in COPD patients with osteoporosis is related to low daily physical activity and high COPD assessment test scores

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Abstract: COPD patients have an increased prevalence of osteoporosis (OP) compared with healthy people. Physical inactivity in COPD patients is a crucial risk factor for OP; the COPD assessment test (CAT) is the newest assessment tool for the health status and daily activities of COPD patients. This study investigated the relationship among daily physical activity (DPA), CAT scores, and bone mineral density (BMD) in COPD patients with or without OP. This study included 30 participants. Ambulatory DPA was measured using actigraphy and oxygen saturation by using a pulse oximeter. BMD was measured using dual-energy X-ray absorptiometry. OP was defined as a T-score (standard deviations from a young, sex-specific reference mean BMD) less than or equal to −2.5 SD for the lumbar spine, total hip, and femoral neck. We quantified oxygen desaturation during DPA by using a desaturation index and recorded all DPA, except during sleep. COPD patients with OP had lower DPA and higher CAT scores than those of patients without OP. DPA was significantly positively correlated with (lumbar spine, total hip, and femoral neck) BMD ($r=0.399$, 0.602, 0.438, respectively, all $P<0.05$) and T-score ($r=0.471$, 0.531, 0.459, respectively, all $P<0.05$), whereas CAT scores were significantly negatively correlated with (total hip and femoral neck) BMD ($r=-0.412$, -0.552, respectively, $P<0.05$) and (lumbar spine, total hip, and femoral neck) T-score ($r=-0.389$, -0.429, -0.543, respectively, $P<0.05$). Low femoral neck BMD in COPD patients was related to high CAT scores. Our results show no significant difference in desaturation index, low SpO_2, and inflammatory markers (IL-6, TNF-α, IL-8/CXCL8, CRP, and 8-isoprostane) between the two groups. Chest physicians should be aware that COPD patients with OP have low DPA and high CAT scores.

Keywords: chronic obstructive pulmonary disease, osteoporosis, daily physical activity, COPD assessment test, bone mineral density

Introduction

COPD pathology involves both the lungs and extra-pulmonary abnormalities, such as skeletal muscle wasting, cachexia, diabetes, and anemia.[1] COPD is also characterized by low-grade systemic inflammation caused by circulating inflammatory mediators, such as IL-6, TNF-α, IL-8/CXCL8, and CRP, and leukocytes are increased or activated in stable disease conditions.[2,3] Lee et al[4] found that intracellular oxidative stress was increased in patients with severe COPD. Moreover, sedentary behavior is believed to be crucial to the development of skeletal muscle weakness in COPD patients. Physical activity in daily life is known to be reduced because of multifactorial causes and worsened prognosis in COPD patients. As the disease progresses, COPD patients have an increased prevalence of osteoporosis (OP) compared with healthy people.[5,6] Low bone mineral density (BMD) leading to OP is common in COPD patients.[7] OP is a systemic skeletal disease characterized by low BMD caused by microarchitectural changes in the bone.

These changes lead to an increased susceptibility to fractures.[8] A strong association exists between COPD and OP because of common risk factors such as age, low body mass index (BMI), history of smoking, systemic inflammation, systemic corticosteroid use, and inactivity.[9] Large variations have been found in the physical activity levels of COPD patients.[10,11] Katajisto et al observed high levels of physical inactivity and increased patient perception of dyspnea in COPD patients.[12]

The COPD assessment test (CAT) is the newest assessment tool for the health status and daily activities of COPD patients.[13] Validation studies have shown that it has properties similar to those of St George's Respiratory Questionnaire.[12,13] This instrument has been noted for its ease of use[14] and contains eight items including cough, phlegm, chest tightness, breathlessness walking up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy.[15] This study investigated the relationship among daily physical activity (DPA), CAT scores, and BMD in COPD patients with or without OP.

Methods

Study design and patients

We recruited COPD patients from the pulmonary outpatient unit of a medical center. COPD diagnosis was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[16] COPD patients with a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <70% of the predicted value were eligible to participate in this study. Those who had acute infection or exacerbation and used systemic (oral) corticosteroids were excluded. Thirty patients were eligible and consented to participate in this study. All participants were ambulatory, in stable conditions, and undergoing standard pharmacological treatment. The study protocol was approved by the Ethics Committee of the Chang-Gung Memorial Hospital (100-2225A3), and all participants provided informed written consent before being enrolled.

Procedures and measurements

Each participant was personally interviewed to collect demographic, lifestyle (dietary and exercise patterns; use of coffee, tobacco, alcohol, and other drugs; and occupation), and disease-related data. The CAT was administered, and the weight and height of patients were measured according to standard methods. Body weight was measured to the nearest 0.1 kg with participants standing barefoot and wearing light indoor clothing, and height was measured to the nearest 0.1 cm. BMI was calculated according to the formula: weight (kg)/height^2 (m^2). Body fat (%) was measured using

bioelectrical impedance analysis (BF-800 Body Fat Monitor, TANITA, Tokyo, Japan). Fat-free mass (FFM) was calculated by subtracting body weight from fat mass. Fat-free mass index (FFMI) was calculated according to the formula: FFM (kg)/height^2 (m^2).[2,17] Serum samples were obtained and were stored at −80°C for laboratory measurements.

Pulmonary function parameters were assessed using the Vitalograph Spirotac V™. FEV_1 and FVC were measured, and FEV_1/FVC was calculated.

Oxygen saturation was measured during DPA. We monitored oxygenation by using an oximeter (WristOx; Nonin Medical, Inc., MN, USA), and daily activity was assessed using a MicroMini-Motionlogger® actigraph.[18] Patients underwent ambulatory recordings, producing 24-hour continuous data, and daily card records were maintained. DPA refers to the total activity amount subtracted from sleep time. We used a desaturation index (DSI) or % time for oxygen saturation, which was <90% during the recording.[19]

Lumbar spine, total hip, and femoral neck BMDs were assessed using dual-energy X-ray bone densitometry to identify OP risk. BMD was categorized according to the World Health Organization (WHO) criteria.[20] Normal BMD was considered to be within 1 standard deviation (SD) of the average reference value for healthy young adults (T-score). OP was defined as a T-score less than or equal to −2.5 SD for the lumbar spine and the total hip in any variable.

We used enzyme-linked immunosorbent assays to determine the serum levels of TNF-α, IL-6, CRP (R&D Systems, Inc., Minneapolis, MN, USA), and 8-isoprostane (MyBioSource, San Diego, CA, USA) according to manufacturer instructions.

Statistical analyses

The results were statistically analyzed using SPSS for Windows 19.0 (SPSS Inc., Chicago, IL, USA) and Prism 5. Descriptive data are expressed as mean ± SD or percentage. Continuous variables were compared using Student's t-test, and categorical variables were compared between the two groups by using the chi-square test. Pearson's correlation was used to evaluate the strength of the relationship among BMD, age, anthropometric indicators, actigraphy activity, and CAT scores. Multiple linear regression analysis was used to determine the independent factors associated with BMD (g/cm^2) at the lumbar spine, total hip, and femoral neck sites. We collected the demographic data of COPD patients. Subsequently, we used a simple linear regression model to identify potential significant factors and then use multivariate analysis to confirm the independent variables. In these methods, the variables selected were age, disease severity (FEV_1, % predicted), BMI,

FFMI, CAT scores, and DPA. Statistical significance for all evaluations was set at $P<0.05$.

Results

Descriptive statistics are listed in Table 1. The mean age was similar between COPD patients without and with OP (71.7±9.1 vs 70.2±9.0 years, $P>0.05$). Most participants without and with OP had a history of smoking (11/11 and 18/19, respectively); anthropometric indicators, including BMI and FFMI, were significantly higher in patients without OP than that of those with OP (27.7±4.2 vs 23.5±3.9 kg/m²; 19.3±2.3 vs 17.4±2.1 kg/m², all $P<0.01$). CAT scores were significantly different between those without and with OP (5.0±3.8 vs 8.1±5.8, $P<0.05$). No significant differences were observed in pulmonary function, including FEV_1, FVC, and FEV_1/FVC, between the groups ($P>0.05$). BMDs at the lumbar spine, total hip, and femoral neck sites were significantly different between patients without and with OP (1.05±0.05 vs 0.86±0.04, $P<0.05$; 0.95±0.04 vs 0.73±0.03, $P<0.001$; 0.82±0.04 vs 0.62±0.02, $P<0.001$).

Figure 1A shows that COPD patients with OP had significantly lower DPA ($P=0.0193$) than that of those without OP; however, no significant differences were observed in DSI and low SpO_2 ($P=0.1330$ and 0.8946) between the

two groups. Figure 1B indicates that TNF-α (1.35±0.33 vs 1.10±0.12, $P>0.05$), IL-6 (1.77±0.34 vs 1.55±0.26, $P>0.05$), CRP (3.72±1.55 vs 5.49±1.63, $P>0.05$), and 8-isoprostane (12.25±1.08 vs 13.04±1.06, $P>0.05$) were not significantly different between COPD patients without and with OP.

Table 2 lists the Pearson's correlation coefficients of BMD, anthropometric indicators, actigraphy activity, and CAT scores in COPD patients. Age and disease severity (FEV_1%) were not significantly correlated with BMD (all $P>0.05$). Anthropometric indicators (BMI and FFMI) were all significantly correlated with BMD at the lumbar spine, total hip, and femoral neck sites (r=0.701, 0.761, and 0.643; 0.666, 0.719, and 0.628, respectively, all $P<0.01$). CAT scores were significantly negatively correlated with total hip and femoral neck BMD (r=–0.412, $P<0.05$; r=–0.552, $P<0.01$, respectively). DPA was significantly correlated with BMD at the lumbar spine, total hip, and femoral neck sites (r=0.399, 0.602, and 0.438, respectively, all $P<0.05$). DSI and low SpO_2 were not significantly correlated with lumbar spine, total hip, and femoral neck BMD (all $P>0.05$).

Figure 2A shows that DPA was significantly correlated with lumbar spine, total hip, and femoral neck T-scores (r=0.471, $P=0.010$; r=0.531, $P=0.003$; r=0.459, $P=0.012$, respectively). Figure 2B indicates that CAT scores were significantly negatively correlated with lumbar spine, total hip, and femoral neck T-scores (r=–0.389, $P=0.037$; r=–0.429, $P=0.010$; r=–0.543, $P=0.002$, respectively).

Table 3 shows the multiple linear regression analysis of BMD in COPD patients. Although age, FEV_1%, BMI, FFMI, CAT scores, and DPA were subjected to multivariate stepwise linear regression analysis, only BMI and CAT scores were independent factors for BMD. Low BMI was associated with low total hip BMD (β=0.744, $P=0.050$). A high CAT score was associated with low femoral neck BMD (β=–0.384, $P=0.021$).

Discussion

This study revealed two main findings in COPD patients with OP: 1) low DPA and high CAT scores and 2) a relationship between femoral neck BMD and CAT scores.

Lower DPA in COPD patients with OP than in those without OP

This study found that COPD patients with OP had significantly lower DPA than that of those without OP. Physical inactivity is a crucial risk factor for OP, and previous studies have suggested that exercise can prevent bone loss.[21,22] The etiology of reduced DPA in COPD patients is multifactorial;[23,24] sedentary lifestyles, severe COPD, higher dyspnea severity, worse leg muscle function, and long-term oxygen therapy use

Table 1 Characteristics of the patients with COPD

Variables	Without OP (n=11)	OP (n=19)	P-value
Age	71.7±9.1	70.2±9.0	0.9370
Sex (n)			
Male	10	18	0.6855
Female	1	1	
Smoke status (n)			
Never smoke	0	1	0.4603
Smoking	0	0	
Ex-smoking	11	18	
BMI, kg/m²	27.7±4.2	23.5±3.9	0.0104
FFMI, kg/m²	19.3±2.3	17.4±2.1	0.0328
CAT	5.0±3.8	8.1±5.8	0.0424
Pulmonary function test			
FEV_1[a], %	42.6±15.8	44.3±14.2	0.758
FVC, %	67.0±14.5	64.1±14.0	0.5944
FEV_1/FVC, %	50.6±10.5	49.2±12.1	0.7540
Bone mineral density			
Lumbar spine, g/cm²	1.05±0.05	0.86±0.04	0.0481
Total hip, g/cm²	0.95±0.04	0.73±0.03	<0.0001
Femoral neck, g/cm²	0.82±0.04	0.62±0.02	<0.0001

Notes: Values are expressed as the mean ± SD unless otherwise indicated; [a]the prevalence on without OP group was 10% in stage GOLD I and II, 20% in stage GOLD III, and 6.7% in stage GOLD IV; prevalence of OP group was 23.3% in stage GOLD I and II, 30% in stage GOLD III, and 10% in stage GOLD IV; control vs COPD.
Abbreviations: BMI, body mass index; FFMI, fat-free mass index; CAT, COPD assessment test; FEV_1, forced expiratory volume in the 1 second; FVC, forced vital capacity; OP, osteoporosis; SD, standard deviation.
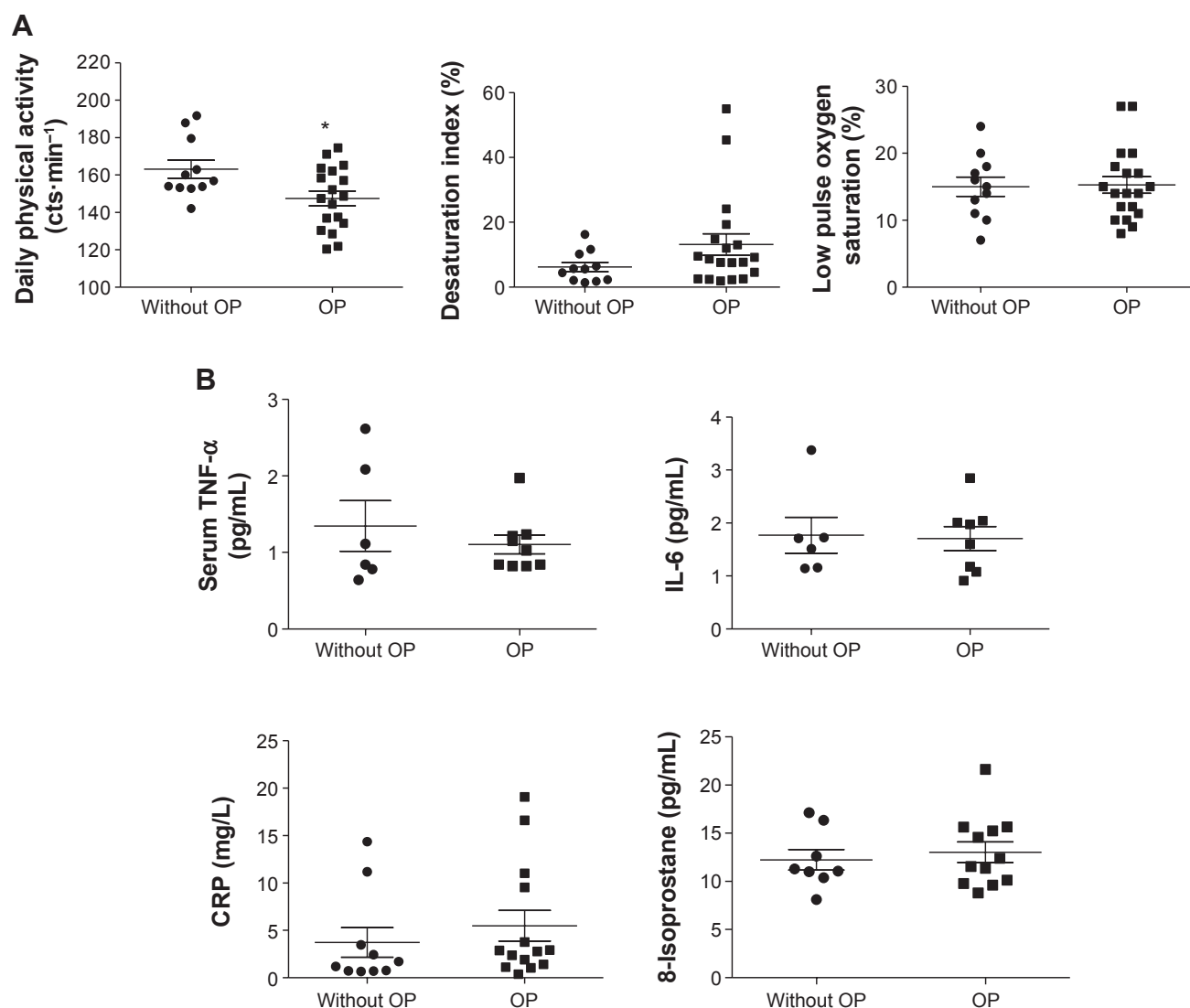
A

B

Figure 1 Comparison between OP and without OP.
Notes: (**A**) Daily physical activity, desaturation index, and low pulse oxygen saturation in COPD patients without and with OP; (**B**) serum TNF-α, IL-6, CRP, and 8-isoprostane levels in COPD patients without and with OP; *$P<0.05$; circles, without OP; squares, OP.
Abbreviations: OP, osteoporosis; cts·min^{-1}, counts per minute.

Table 2 Pearson's correlation coefficients (r) of the bone mineral density, actigraphy activity, and CAT in the patients with COPD (n=30)

Indicators	BMD		
	Lumbar spine	Total hip	Femoral neck
Age, years	0.011	0.028	0.123
BMI, kg/m²	0.701**	0.761**	0.643**
FFMI, kg/m²	0.666**	0.719**	0.628**
CAT, score	−0.147	−0.412*	−0.552**
FEV₁, %	0.331	0.190	0.100
DPA, cts·min⁻¹	0.399*	0.602**	0.438*
DSI, %	0.000	−0.099	−0.150
Low SpO₂ (%)	0.103	−0.032	−0.085

Notes: *$P<0.05$; **$P<0.01$.
Abbreviations: BMI, body mass index; FFMI, fat-free mass index; BMD, bone mineral density; FEV₁, forced expiratory volume in the 1 second; DPA, daily physical activity; DSI, desaturation index; CAT, COPD assessment test; cts·min⁻¹, counts per minute.

were independently associated with lower physical activity.[21] These patients may experience dyspnea during exertion, which can lead to a vicious cycle of inactivity, deconditioning, and further increased dyspnea on exertion.[12,25] Each of these outcomes, including disability, deconditioning, and low physical activity, has been associated with low BMD and increased fracture risk.[26] Our results are further supported by the finding that most of the COPD patients with OP demonstrated lower DPA than did those without OP.

BMD at different sites and OP in COPD patients

COPD and OP share common risk factors, and the relationship among these conditions is complicated. Men with
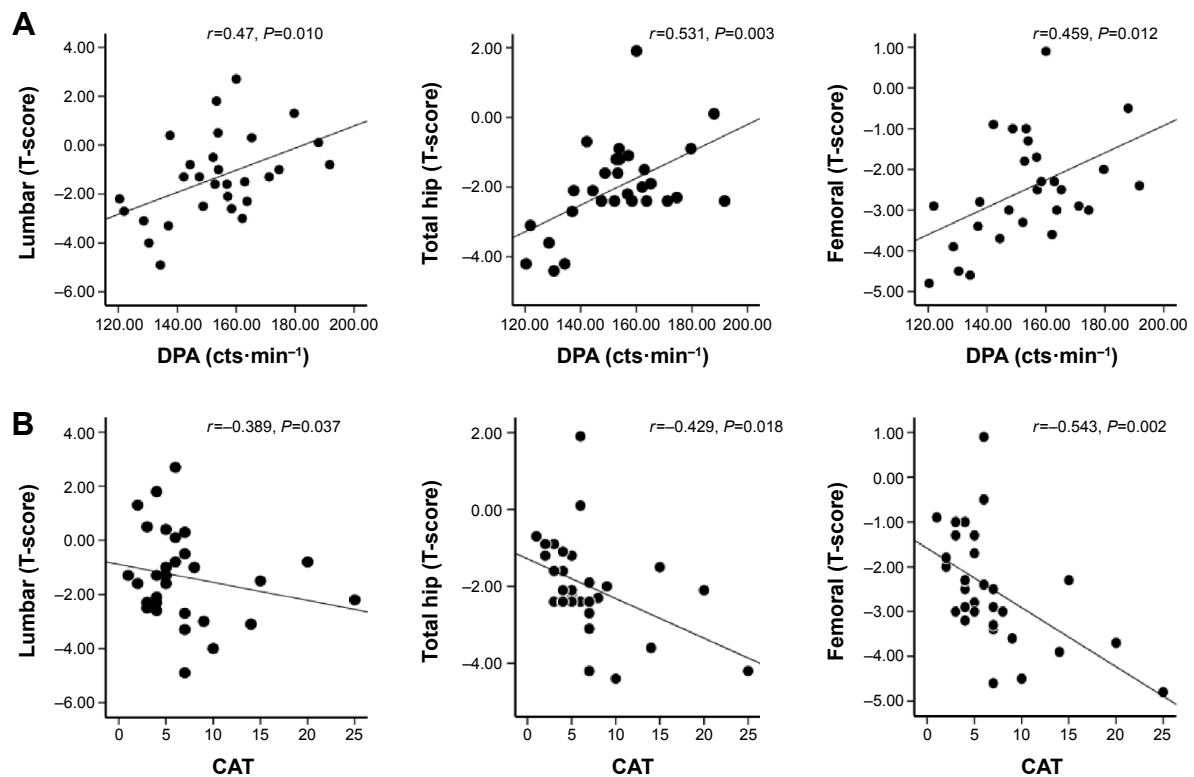
Figure 2 Pearson's correlation scores of CAT and DPA assessments.
Notes: Correlation of (**A**) lumbar spine, total hip, and femoral neck T-scores and DPA, and (**B**) lumbar spine, total hip, and femoral neck T-scores and CAT scores in COPD patients.
Abbreviations: CAT, COPD assessment test; DPA, daily physical activity; cts·min⁻¹, counts per minute.

COPD or asthma had lower total hip, femoral neck, and spine BMD compared with healthy controls after adjustment for age, clinic site, BMI, and smoking.[27] In 2011, Duckers et al enrolled 30 clinically stable male ex-smokers with COPD and 15 age-matched ex-smoker controls. Their results demonstrated that hip BMD was lower in COPD patients; however, lumbar spine[28] measurements were not different. This finding may reflect physical deconditioning or different bone compositions. After adjustment age, sex and FEV_1 (%) matched COPD patients with and without OP, our study determined that BMDs at the lumbar spine, total hip, and femoral neck sites were lower in COPD patients with OP.

We also observed that patients with OP had lower DPA than that of those without OP. The Cochrane database confirmed that aerobics, weight-bearing, and resistance exercises are effective for improving BMD of the spine in postmenopausal women, and walking improves the BMD of the hip.[29] Our study found that DPA was significantly positively correlated with lumbar spine, total hip, and femoral neck BMD (weight-bearing sites). Although a correlation between DPA and BMD was not confirmed in multivariate analysis, the result that might be due to under power, the relation could not be completely excluded in the present study. It is worth testing this with a larger number with adequate power and, more

Table 3 Linear regression analysis of bone mineral density in the patients with COPD (N=30)

Variables	Lumbar spine BMD			Total hip BMD			Femoral neck BMD		
	β	t	P-value	β	t	P-value	β	t	P-value
Age, years	−0.050	−0.310	0.759	−0.006	−0.044	0.966	0.131	0.878	0.396
FEV_1, %	0.121	0.734	0.471	−0.074	−0.539	0.596	−0.177	−1.166	0.259
BMI, kg/m²	0.595	1.379	0.182	0.744	2.083	0.050	0.327	0.823	0.420
FFMI, kg/m²	0.100	0.222	0.826	−0.153	−0.409	0.688	0.247	0.595	0.558
CAT score	0.116	0.689	0.498	−0.121	−0.872	0.393	−0.384	−2.486	0.021
DPA, cts·min⁻¹	0.059	0.299	0.768	0.191	1.168	0.256	−0.058	−0.320	0.752

Notes: Lumbar spine BMD: adjust R^2=0.360, F=3.247, P=0.017. Total hip BMD: adjust R^2=0.561, F=6.112, P=0.001. Femoral neck BMD: adjust R^2=0.457, F=4.366, P=0.004.
Abbreviations: BMD, bone mineral density; FEV_1, forced expiratory volume in 1 second; BMI, body mass index; FFMI, fat-free mass index; CAT, COPD assessment test; DPA, daily physical activity.

importantly the causative effect. This result is likely supported by the previous finding on the association of reduced physical activity with bone loss in elderly COPD patients. We not only suggest exercise training but also encourage physical activity in COPD patients.

Health status and OP in COPD patients

The CAT has been recommended for assessing the effect of COPD on the health status and daily activities.[13] In 2015, Sundh et al[30] found several comorbid conditions in COPD patients; in particular, OP was associated with health-related quality of life, as reflected by CAT scores and EuroQol-5 dimension results. In 2014, Watanabe et al[31] demonstrated an association between CAT scores and bone loss. We determined that CAT scores were significantly negatively correlated with BMD and DPA. For example, we revealed a relationship between femoral neck BMD and CAT scores but not DPA.

Approximately 35%–60% of patients with moderate-to-severe COPD have low BMIs or evidence of weight loss.[32] Previous studies have found that low BMI and FFMI are significantly correlated with OP and BMD.[25,33,34] One study suggested that weight loss is a major contributor to decreased BMD in patients with advanced COPD.[31] In 2010, Coin et al found that BMIs <25 kg/m^2 in COPD patients may indicate OP.[35] Our study determined that COPD patients with OP had significantly lower BMI (23.5±3.9 kg/m^2) and FFMI (17.4±2.1 kg/m^2) than of those without OP.

Inflammation in COPD also leads to a protein catabolic state. FFM is significantly decreased in these patients.[36] COPD patients appear to be under a state of continuous systemic inflammation, as suggested by the high levels of CRP, oxidative stress, and other (pro-) inflammatory mediators. Systemic inflammation is associated with OP; a recent study determined that IL-6 is also involved in the regulation of bone turnover and OP development.[37] A study assessing the association between systemic inflammation and insulin resistance showed increased insulin resistance in COPD patients compared with healthy people; TNF-α is a well-known stimulator of osteoclastic bone resorption and is involved in postmenopausal OP.[38] The most crucial factor in this inflammatory process is smoking. Smoking directly induces systemic damage by lowering the pH of bone tissue, resulting in absorption of bone salts;[39] however, it also has indirect systemic effects by the induction of an inflammatory response in the lungs with the production of systemic inflammatory mediators with effects on bone.[40] Our results showed no significant differences in all inflammatory markers between the two groups (Figure 2A); these results may be because of ex-smoking in our patients.

A previous study found that low BMD was related to the severity of COPD.[30] In 2007, Vrieze et al[25] observed that the prevalence of OP was 0% at the GOLD II stage, 9.6% at the GOLD III stage, and 17.9% at the GOLD IV stage. At the GOLD IV stage, 75% of the patients had low BMD. Jørgensen et al[41] found that 68% of 62 COPD patients with a mean FEV$_1$ of 33% had osteopenia or OP. Our study determined that BMD was not significantly correlated with FEV$_1$ (%). This may be because the prevalence of OP was only 10% at the GOLD IV stage.

Limitations

This study has some limitations. First, this study had a small sample size and used CAT scores to retrospectively estimate power (43%); although power was low, the CAT scores were still significantly different between the two groups (Table 1). Overall, the scores should be investigated further. Second, the study sample was drawn from one hospital. No control group was used for comparison or to analyze the severity of the effects. Third, the present study involved only 24-hour ambulatory actigraphy and oximetry. The applicability of these results to longer periods of actigraphy and oximetry requires further investigation. Fourth, most patients referred to this center were male; hence, we could not assess the effect of sex. Finally, this study could have benefited from using one device to simultaneously record oxygenation and DPA.

Conclusion

Our study determined that low DPA and high CAT scores were significantly correlated with low BMD and OP, especially between femoral neck BMD and high CAT scores in COPD patients. Future studies are necessary to longitudinally assess determinants of OP in COPD patients.

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Disclosure

The authors declare that they have not had any financial compensation and report no conflict of interest in this work.

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