Distribution of Bone Mineral Content Is Associated with Body Weight and Exercise Capacity in Patients with Chronic Obstructive Pulmonary Disease

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Key Words

Bone mineral content · Chronic obstructive pulmonary disease · Body mass index · Exercise capacity

Abstract

Background: Although low bone mineral density is highly prevalent in patients with chronic obstructive pulmonary disease (COPD), the distribution of the reduced bone mass has not been fully elucidated. **Objectives:** To determine regional bone mass loss in patients with COPD and investigate whether the change in distribution may be associated with body weight loss and functional capacity. **Methods:** Body mass index (BMI) was assessed, and height squared indices were derived for the bone mineral content index (BMCI) of the arms, legs and trunk by dual-energy X-ray absorptiometry in 45 male patients with COPD and 12 age- and sex-matched control subjects. Pulmonary function tests were performed, and maximal oxygen uptake ($\dot{V}O_2\text{max}$) was measured. **Results:** The BMCI was lower in the total bone, legs and trunk of patients with COPD than in control subjects, although the BMCI in the arms was similar between the groups. BMI correlated significantly with the BMCI in all 3 segments. Bone mineral content (BMC) in the trunk, expressed as a percentage of total BMC (BMC trunk/total BMC), correlated significantly

with BMI. The BMCI in the trunk was closely related with $\dot{V}O_2\text{max}$ but not with airflow limitation. **Conclusions:** There was a regional difference in BMC reduction, but a predominant reduction of bone mass in the trunk was not associated with the severity of airflow limitation but rather with body weight loss and exercise intolerance. These data suggest that body weight loss and exercise intolerance are important risk factors for vertebral fracture in patients with COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a usually progressive airflow limitation that is not fully reversible [1]. COPD has been recognized as a systemic disease with extrapulmonary manifestations such as cachexia, skeletal muscle wasting, cardiovascular disease, metabolic syndrome and depression [2]. Moreover, patients with COPD are at a higher risk of developing osteoporosis than are healthy subjects [3]. Osteoporotic fractures remarkably reduce quality of life and are associated with mortality [4]. In addition, pulmonary function impairment caused by vertebral fractures is an important problem in patients with COPD [5].

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural changes in bone tissue that increases an individual's susceptibility to fractures [6]. The World Health Organization definition of osteoporosis is based on BMD measurements [7]. Dual-energy X-ray absorptiometry (DXA) is the gold standard for taking these measurements [8]. Osteopenia is defined as a BMD that is 1–2.5 standard deviations (SDs) below the mean for young adults (i.e. the T score), while osteoporosis is defined as a BMD >2.5 SDs below the mean for young adults [7]. Many studies have demonstrated lower BMD in patients with COPD [9–12].

Multiple sites can be used to measure BMD by DXA. The sites most frequently used are the hip, lumbar spine, forearm and whole body. The International Society for Clinical Densitometry advocates measurement of BMD of the lumbar spine and the hip and to base the diagnosis of osteoporosis on the lowest T score of the measured locations [13]. Indeed, a higher prevalence of osteoporosis was found using local (hip and lumbar spine) compared to whole-body DXA scanning in patients with clinically stable COPD [14]. Accordingly, we hypothesize that nutritional status, airflow limitation and exercise capacity would have different effects on bone mass in each subregion, including the arms, legs and trunk.

Our objectives were to determine the distribution of reductions in bone mineral content (BMC) as a measurement of bone mass and investigate whether the BMC distribution is associated with body weight loss and maximal exercise capacity.

Materials and Methods

Subjects

We enrolled 45 male outpatients with COPD diagnosed according to the definition of the Global Initiative for Chronic Obstructive Lung Disease [1] and 12 age-matched male control subjects. Female patients were not included in this study because of their remarkable differences from male patients with regard to the prevalence of osteoporosis and bone metabolism. In addition, subjects were excluded from the study if they were receiving oral corticosteroid therapy or had known heart disease, malignancy, cor pulmonale or any other inflammatory or metabolic condition. All subjects gave written, informed consent, and the study had local research ethics committee approval.

Pulmonary Function Tests

All patients underwent pulmonary function testing. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), residual volume (RV) and total lung capacity were measured by a pulmonary function instrument using computer processing (FUDAC 70, Fukuda Denshi, Tokyo, Japan), and the

FEV₁/FVC ratio was calculated. Lung volumes were determined by the helium gas dilution method, and diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath method. The values obtained were expressed as a percentage of the predicted values [15]. Arterial blood samples obtained in room air were analyzed by a standard blood gas analyzer (ABL800, Radiometer Corp., Copenhagen, Denmark).

Body Mass Index and Body Composition Analysis

Body mass index (BMI) was calculated as weight divided by height squared. BMC and fat-free mass (FFM) were measured by DXA using a total-body scanner (Lunar DPX, Lunar Radiation Corp., Madison, Wisc., USA). BMC and FFM in the subregions, including the trunk, arms and legs, can be determined separately or together as the whole body. Height squared indices were derived for BMC (BMCI) and FFM (FFMI) of the arms, legs and trunk. BMC in each subregion, expressed as a percentage of total BMC, i.e. BMC arms/total BMC, BMC legs/total BMC and BMC trunk/total BMC, was defined as the BMC distribution.

Exercise Performance

All patients underwent maximal exercise tests on a cycle ergometer (STB-1350, Nihon Kohden, Tokyo, Japan). After 1 min of unloaded pedaling, the workload was increased by 10 W every minute in a ramp protocol until exhaustion. Gas exchange was monitored during the exercise test with a computerized metabolic cart (Vmax 229, SensorMedics Corp., Yorba Linda, Calif., USA). Minute ventilation, oxygen uptake (V̇O₂) and carbon dioxide output were measured by the breath-by-breath method. Arterial oxygen saturation was also monitored by a pulse oximeter (BSM-8500, Nihon Kohden).

Statistical Analysis

Values are expressed as means ± SD. The differences among measured parameters in the two groups were determined by unpaired Student's *t* tests. Pearson's correlation coefficients between static lung function, body composition measurements and maximal V̇O₂ (V̇O₂max) were calculated. Differences of *p* < 0.05 were considered statistically significant.

Results

Anthropometric and Pulmonary Function Data

The study was conducted from November 2011 to December 2012. Patient characteristics are summarized in table 1. There was no difference in age between the control and patient groups (71 ± 6 vs. 70 ± 6 years). BMI was significantly lower in the patient group than in the controls (18.5 ± 2.6 vs. 22.3 ± 1.9; *p* < 0.0001). There was no difference in smoking status between the two groups. FEV₁% predicted, FEV₁/FVC ratio and %VC were significantly lower in the patient group than in the control group (45.4 ± 22.5 vs. 93.0 ± 3.9%, 41.4 ± 12.2 vs. 84.0 ± 2.3% and 84.5 ± 21.3 vs. 95.7 ± 2.0%, respectively; *p* < 0.0001).

Table 1. Characteristics of COPD patients

Number	45
Age, years	70±6
BMI, kg/m ²	18.5±2.6
Current smokers/ex-smokers, %	12/88
GOLD stage, n	
I	5
II	11
III	17
IV	12
FEV ₁ , % predicted	45.4±22.5
FEV ₁ /FVC, %	41.4±12.2
VC, % predicted	84.5±21.3
RV/TLC, %	57.8±10.0
DLCO, % predicted	42.8±23.5
PaO ₂ , mm Hg	72.2±8.4
PaCO ₂ , mm Hg	44.1±5.0
$\dot{V}O_2$ max	593.4±273.1
$\dot{V}E_{max}$	31.7±10.8
ΔSpO_2	6.4±5.1

Values are means ± SD. GOLD = Global Initiative for Chronic Obstructive Lung Disease; VC = vital capacity; RV = residual volume; TLC = total lung capacity; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; $\dot{V}E_{max}$ = maximum minute ventilation; ΔSpO_2 = difference in oxygen saturation as measured by pulse oximetry between before and after exercise testing.

Table 2. BMCI and FFMI of subregions in COPD patients and controls

	BMCI, kg/m ²		FFMI, kg/m ²	
	controls (n = 12)	COPD (n = 45)	controls (n = 12)	COPD (n = 45)
Total	0.92±0.17	0.79±0.14**	17.0±1.6	15.2±1.7 ⁺⁺
Arms	0.13±0.03	0.11±0.02	1.69±0.30	1.43±0.35 ⁺
Legs	0.33±0.06	0.29±0.05*	5.53±0.84	5.14±0.80
Trunk	0.26±0.06	0.21±0.06*	8.15±0.68	7.21±0.75 ⁺⁺⁺

Values are means ± SD. * $p < 0.05$, ** $p < 0.01$: difference in BMCI compared to controls. ⁺ $p < 0.05$, ⁺⁺ $p < 0.01$, ⁺⁺⁺ $p < 0.005$: difference in FFMI compared to controls.

Body Composition Analysis

The BMCI and FFMI values of the patients and control subjects for both the total and subregions are shown in table 2. Total BMCI and FFMI values of the patients were significantly lower than those of the controls ($p < 0.01$ for both). BMCI in the legs and trunk was significantly re-

Fig. 1. BMCI in the arms, legs and trunk in patients with COPD. Values are means ± SD of 45 patients with COPD and 12 controls.

duced in the patients compared with the control subjects ($p < 0.05$ for both). However, there was no significant difference in arm BMCI between the two groups (fig. 1). In contrast, the FFMI in the arms and trunk was significantly lower in the patients than in the control subjects ($p < 0.05$ for both), and there was no significant difference in FFM in the legs between the two groups. In addition, there was a significant relationship between total BMCI and total FFMI in patients with COPD ($r = 0.418$, $p < 0.005$).

Correlations between BMC and BMI in Patients with COPD

Total and subregion BMCI correlated significantly with BMI (table 3). BMC trunk/total BMC correlated significantly with BMI (fig. 2), whereas BMC arms/total BMC and BMC legs/total BMC did not correlate with BMI.

Correlation between BMC and Functional Capacity

Total BMCI and BMCI for each subregion did not correlate with FEV₁ % predicted, and nor did the distribution of BMC (table 3). Total BMCI did not correlate with other pulmonary function parameters, including %RV, arterial oxygen tension and arterial carbon dioxide tension, but did correlate with %DLCO ($r = 0.339$, $p < 0.05$; data not shown). Total and subregion BMCI correlated significantly with $\dot{V}O_2$ max (table 3). BMC trunk/total BMC correlated significantly with $\dot{V}O_2$ max ($p = 0.0099$), while BMC arms/total BMC and BMC legs/total BMC did not correlate with $\dot{V}O_2$ max.

Table 3. Relationship between BMI and functional capacity and BMC in subregions or distribution of BMC

	BMI, kg/m ²		%FEV ₁		$\dot{V}O_2$ max	
	r	p value	r	p value	r	p value
BMCi						
Total	0.496	0.0004	0.176	0.2502	0.414	0.0048
Arms	0.465	0.0011	0.105	0.4958	0.344	0.0217
Legs	0.466	0.0011	0.157	0.3063	0.467	0.0012
Trunk	0.542	0.0001	0.243	0.1087	0.453	0.0018
BMC arms/total BMC	0.002	0.9916	−0.199	0.4367	−0.104	0.5043
BMC legs/total BMC	−0.054	0.7282	−0.082	0.5961	0.120	0.4399
BMC trunk/total BMC	0.401	0.0059	0.284	0.0584	0.382	0.0099

r = Pearson's correlation coefficient.

Fig. 2. Relationship between BMI and BMC trunk/total BMC.

Discussion

In the present study, we found that BMCI was lower in the whole body, legs and trunk in patients with COPD than in control subjects, although BMCI in the arms was similar between the groups. In addition, BMCI in each subregion correlated significantly with BMI, while only the ratio of trunk BMC to total BMC correlated significantly with BMI. We also demonstrated that BMCI was not significantly correlated with the severity of airflow limitation but was correlated with maximal exercise performance.

Multiple sites, including the hip, lumbar spine, forearm and whole body, can be used to measure BMD by DXA, and significant differences among various skeletal

sites have been found in patients with osteoporosis [16]. A recent study demonstrated that BMD of the hip and lumbar spine may be more sensitive than whole-body BMD for the diagnosis of osteoporosis in patients with COPD [14]. However, BMD of the upper extremities was not evaluated in that study.

We found that BMCI in the arms of patients with COPD was comparable to that of control subjects, while BMCI was lower in the whole body, legs and trunk in patients with COPD. Although the mechanism of BMC preservation in the arms is unclear, a possible explanation may be mechanical stresses on the bones in the arms in daily life. The metabolic and ventilatory requirements as well as dyspnea during unsupported arm exercise are greater in patients with COPD than in healthy subjects [17]. However, the arms are recruited for many activities of daily living such as lifting, bathing and dressing in patients with COPD as well as healthy subjects, whereas patients with COPD tend to refrain from walking and standing in daily life [18].

Previous studies have demonstrated that a lower BMD is associated with low BMI [11, 19–21]. However, a relationship between regional change in BMC and BMI has not been examined. Our data demonstrated that BMCI in each subregion correlated significantly with BMI as well as total BMCI. In particular, BMCI in the trunk was closely related with BMI compared with that in the arms and legs. With regard to the distribution of BMC reduction, BMC trunk/total BMC correlated significantly with BMI, while BMC arms/total BMC and BMC legs/total BMC did not. A high prevalence of vertebral fracture in patients with COPD has been documented [3, 22–24]. The risk of vertebral fractures is related to disease severity [23, 24] and systemic corticosteroid use [22, 23]. Our

data suggest that body weight loss leads to a disproportional decrease in BMC in the trunk and raises the possibility that vertebral fractures may be common in underweight patients with COPD. It is known that the bones in the trunk, including the vertebrae and ribs, consist predominantly of cancellous bone, which has enhanced bone metabolism. Thus, BMC in the trunk may be more susceptible to malnutrition than that in the extremities.

The deterioration of the microarchitecture and bone remodeling are also important risk factors for bone fractures in patients with COPD. Microarchitectural changes can be assessed by histomorphometric analysis or micro-computed tomographic analysis of bone biopsy samples [25], which are too invasive to be considered in a routine clinical setting. Therefore, these analyses were not performed in the present study. Bone turnover markers represent bone remodeling and are commonly used as independent predictors of fracture risk [26]. In patients with COPD, these markers can be significant predictors of fractures independent of BMD, but we did not determine them in the present study.

Several studies have reported a strong correlation between the prevalence of osteoporosis and reduced FFM in patients with COPD [23, 24, 27]. In line with these studies, a significant correlation between total BMCI and total FFMI was found in our study, while the distribution of BMC differed from that of FFMI.

A higher Global Initiative for Chronic Obstructive Lung Disease stage and/or a lower FEV₁ have been shown to be correlated with osteoporosis and/or a low BMD [20, 28, 29]. Moreover, a significant correlation between FEV₁ and BMD in subjects without COPD [30, 31] has been reported. On the other hand, several studies have demonstrated no significant relationship between %FEV₁ and BMD in patients with COPD [3, 10, 27, 32]. These relationships between pulmonary function parameters and BMD are complex and not yet clear. In the present study, we found no significant relationship between total or sub-regional BMCI and %FEV₁. However, BMCI was significantly correlated with %DLCO in accordance with other studies [33, 34].

Reduced physical activity due to impaired pulmonary function may cause osteoporosis [35]. Patients with COPD have been shown to be physically inactive compared with age-matched healthy subjects [36]. Although an association between physical activity and BMD in healthy women has been demonstrated [37, 38], the effect of exercise capacity on BMD has not been fully elucidated in patients with COPD. A significant relationship be-

tween osteoporosis and 6-min walk distance was reported in patients with COPD [3]. In a longitudinal study, the change in total BMC was shown to be significantly correlated with 12-min walk distance [39]. In the present study, a significant relationship between BMCI and $\dot{V}O_2\text{max}$ was demonstrated. This result indicated that the reduction of bone mass was related to exercise intolerance, not to the severity of airflow limitation.

Furthermore, systemic inflammation has been considered a major cause of osteoporosis in COPD. Several studies have demonstrated that physical inactivity deteriorates exercise-induced oxygen desaturation [40] and systemic inflammation and results in higher serum levels of interleukin-6 and tumor necrosis factor- α [41, 42], which can contribute to osteoporosis [43]. These findings suggest that active patients with higher $\dot{V}O_2\text{max}$ levels may have lower levels of these cytokines, resulting in preserved bone mass. In addition, $\dot{V}O_2\text{max}$ is known to be determined by circulatory and ventilatory capacity and exercise muscle performance. We hypothesize that oxygen delivery to bone tissue may be better in patients with higher $\dot{V}O_2\text{max}$ than in those with lower $\dot{V}O_2\text{max}$.

Moreover, we demonstrated that BMC trunk/total BMC correlated significantly with $\dot{V}O_2\text{max}$, while BMC arms/total BMC and BMC legs/total BMC did not. Although the precise mechanism is unclear, several possible explanations for the significant relationship between BMC trunk/total BMC and $\dot{V}O_2\text{max}$ can be offered. The effects of cytokines on bone metabolism may differ between the extremities and the vertebrae. The relationship between cytokine production by peripheral blood mononuclear cells and the rate of annual change in BMD has shown significant differences in the lumbar spine and the femoral neck, possibly reflecting differences in the proportion of trabecular and cortical bone at these sites [44]. Accordingly, we speculate that inactive patients with systemic inflammation may have lower BMD in the lumbar spine than in the extremities.

Decreased BMC in the trunk is a risk factor for vertebral fractures, which were not evaluated in the present study. Kyphosis due to vertebral fractures may reduce pulmonary function and ventilatory capacity [45]. In the present study, BMC trunk/BMC total was significantly correlated with maximal voluntary ventilation, which is a significant determinant of $\dot{V}O_2\text{max}$ [46] (data not shown). This may partly explain the significant relationship between BMC trunk/BMC total and $\dot{V}O_2\text{max}$.

Our study has several limitations. Firstly, we did not determine pulmonary function parameters, except for spirometric data and $\dot{V}O_2\text{max}$ in the controls. Accord-

ingly, it is unknown whether BMCI is significantly correlated with %DLCO and $\dot{V}O_2\text{max}$ in both patients with COPD and control subjects. Secondly, despite evidence of statistical significance, a direct cause-effect relationship between $\dot{V}O_2\text{max}$ and BMC trunk/BMC total could not be established. An interventional study is required that includes exercise training and/or antiosteoporotic medication. Thirdly, our study included a small number of patients with COPD and control subjects. Therefore, a future study with a larger number of subjects is required to validate our findings.

In conclusion, the current study demonstrated a regional difference in BMC reduction in patients with COPD and that BMC reduction is not associated with the severity of airflow limitation but rather with body weight loss and exercise intolerance. Body weight loss and exercise intolerance are more closely related to BMC reduction in the trunk than in the extremities. These data sug-

gest that weight loss and exercise intolerance are important risk factors for vertebral fractures in patients with COPD.

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All authors acknowledge that there are no conflicts of interest involving any companies/organizations whose products or services may have influenced this study.

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