Distribution of bone mineral content is associated with body weight and exercise capacity in patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: Although low bone mineral density (BMD) 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 the regional bone mass loss 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 ($\dot{V}O_2max$) 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 $\dot{V}O_2max$, 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 of vertebral fracture in patients with COPD. (248 wards)

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 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][10][11][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 (GOLD)[1] and 12 age-matched male control subjects. Female patients were not included in this study because of their remarkable differences from male patients in 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 one second (FEV_1), residual volume (RV) and total lung capacity (TLC) were measured by a pulmonary function instrument using computer processing (FUDAC 70; Fukuda Denshi, Tokyo, Japan) and the FEV_1/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/height squared. BMC and fat-free mass (FFM) were measured by DXA using a total body scanner (Lunar DPX; Lunar Radiation Corp., Madison, WI, USA). BMC and FFM in the subregions, including the trunk, arms, and legs can be determined separately or together as a whole body. Height squared indices were derived for BMC (BMCI) and fat-free mass index (FFMI) of the arms, legs, and trunk. BMC in each subregion expressed as a percentage of total BMC, 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, CA, USA). Minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) were measured by the breath-by-breath method. Arterial oxygen saturation was also monitored by a pulse oximeter (BSM-8500; Nihon Kohden, Tokyo, Japan).

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 among static lung function, body composition measurements and $\dot{V}O_2max$ 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 yr). BMI was significantly lower in the patient group than in the controls (18.5±2.6 vs. 22.3±1.9 kg/m^2, $p<0.0001$). There was no difference in smoking status between the two groups. FEV_1 % predicted, FEV_1/FVC ratio and VC % predicted 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 %, 84.5±21.3 vs. 95.7±2.0 %, $p<0.0001$).

Body composition analysis

The BMCI and FFMI values of the patients and the control subjects for both the total and the subregions are shown in Table 2. Total BMCI and FFMI values of the patients were significantly lower than those of the controls ($p<0.01$ and $p<0.01$, respectively). BMCI in the legs and trunk were significantly reduced in the patients compared with the control subjects ($p<0.05$ and $p<0.05$, respectively). However, there

was no significant difference in arm BMCI between the two groups (Figure 1). In contrast, the FFMI in the arms and trunk was significantly lower in the patients than in the control subjects ($p<0.05$ and $p<0.005$, respectively) 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 (Figure 2), whereas BMC arms/total BMC and BMC legs/total BMC did not correlate with BMI.

Correlation between BMC and functional capacity

Total and each subregion BMCI did not correlate with FEV_1% predicted. In addition, the distribution of BMC did not correlate with FEV_1% predicted (Table 3). Total BMCI did not correlate with other pulmonary function parameters, including % RV, PaO_2 and $PaCO_2$ but did correlate %DLco ($r=0.339$, $p<0.05$) (data not shown). Total and subregion BMCI correlated significantly with $\dot{V}O_2max$ (Table 3). BMC trunk/ total BMC correlated significantly with $\dot{V}O_2max$ ($p=0.0099$), while BMC arms/total BMC and BMC legs/total BMC did not correlate with $\dot{V}O_2max$.

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 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 for 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)20)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[22)23)24)25)]. 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, predominantly consist of cancellous bone which exerts 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 is also an important risk factor of bone fractures in patients with COPD. Microarchitectural changes can be assessed by histomorphometric analysis or micro-computed tomographic analysis of bone biopsy samples[26)], 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[27)]. In patients with COPD, these markers can be significant predictors of fractures independent of BMD, but we did not determine 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)28)]. 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 GOLD stage and/or a lower FEV_1 have been shown to be correlated with

osteoporosis and/or a low BMD[20)29)30)]. Moreover, a significant correlation between FEV_1 and BMD in subjects without COPD[31)32)] has been reported. On the other hand, several studies have demonstrated no significant relationship between $\%FEV_1$ and BMD in patients with COPD[10)25)28)33)]. 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 subregional BMCI and $\%FEV_1$. However, BMCI was significantly correlated with %DLco in accordance with other studies[34)35)].

Reduced physical activity due to impaired pulmonary function may cause osteoporosis[36)]. Patients with COPD have been shown to be physically inactive compared with age-matched healthy subjects[37)]. Although an association between physical activity and BMD in healthy women has been demonstrated[38)39)], the effect of exercise capacity on BMD has not been fully elucidated in patients with COPD. A significant relationship between osteoporosis and 6-min walk distance was reported in patients with COPD[25)]. In a longitudinal study, the change of total BMC was shown to be significantly correlated with 12-min walk distance[40)]. In the present study, a significant relationship between BMCI and maximal oxygen uptake 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[41)] and systemic inflammation and results in higher serum levels of interlekin-6 and tumor necrosis factor-α[42)43)] which can contribute to osteoporosis[44)]. These findings suggest that active patients with higher $\dot{V}O_2$max levels may have lower levels of these cytokines, resulting in preserved bone

mass. In addition, $\dot{V}O_2$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 $\dot{V}O_2$max than in those with lower $\dot{V}O_2$max.

Moreover, we demonstrated that BMC trunk/total BMC correlated significantly with $\dot{V}O_2$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 $\dot{V}O_2$max can be made. 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[45]. 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 evaluate in the present study. Kyphosis due to vertebral fractures may reduce pulmonary function and ventilatory capacity[46]. In the present study, BMC trunk/BMC total was significantly correlated with maximal voluntary ventilation, which is a significant determinant of $\dot{V}O_2$max[47] (data not shown). This may partly explain the significant relationship between BMC trunk/BMC total and $\dot{V}O_2$max.

Our study has several limitations. First, we did not determine pulmonary function parameters, except for spirometric data and $\dot{V}O_2$ max in the controls. Accordingly, it is unknown whether BMCI is significantly correlated with %DLco and $\dot{V}O_2$ max in both

patients with COPD and in control subjects. Second, despite evidence of statistical significance, a direct cause-effect relationship between $\dot{V}O_2$ max and BMC trunk/BMC total could not be established. An interventional study is required that includes exercise training and/or anti-osteoporotic medication. Third, 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 suggest that weight loss and exercise intolerance are important risk factors of vertebral fractures in patients with COPD.

Conflict of interest

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

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Table 1 Patients characteristics

Characteristics	COPD
No	45
Age, yr	70 ± 6
BMI, kg/m²	18.5 ± 2.6
Smoking status (current/ex, %)	12/88
Stage (GOLD), n	
I	5
II	11
III	17
IV	12
FEV_1%pred.	45.4 ± 22.5
FEV_1/FVC, %	41.4 ± 12.2
VC, %pred.	84.5 ± 21.3
RV/TLC, %	57.8 ± 10.0
DLco, %pred	42.8 ± 23.5
PaO_2, mmHg	72.2 ± 8.4
$PaCO_2$, mmHg	44.1 ± 5.0
VO_2max	593.4± 273.1
VEmax	31.7± 10.8
ΔSpO_2	6.4± 5.1

Values are mean ± SD.
BMI=body mass index; GOLD=Global Initiative for Chronic Obstructive Lung disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; VC=vital capacity; RV=residual volume; TLC=total lung capacity; DLco=diffusing capacity for carbon monoxide; $\dot{V}O_2$max=maximum oxygen uptake; $\dot{V}E$max=maximum minute ventilation; ΔSpO2: a difference in SpO_2 between before and after exercise testing.

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

	BMCI (kg/m²)		FFMI (kg/m²)	
	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 mean ± SD.
BMCI=bone mineral content (kg) / height (m)²; FFMI=fat-free mass (kg) / height (m)²
**p<0.01, *p<0.05 for the difference in BMCI between controls and COPD.
#p<0.05, ##p<0.01, § p<0.005 for the difference in FFMI between controls and COPD.

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

	BMI		$\%FEV_1$		$\dot{V}O_2max$	
	r	p value	r	p value	r	p value
BMCI(total)	0.496	0.0004	0.176	0.2502	0.414	0.0048
BMCI(arms)	0.465	0.0011	0.105	0.4958	0.344	0.0217
BMCI(legs)	0.466	0.0011	0.157	0.3063	0.467	0.0012
BMCI(trunk)	0.542	0.0001	0.243	0.1087	0.453	0.0018
BMC arm / total BMC	0.002	0.9916	-0.199	0.4367	-0.104	0.5043
BMC leg / 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

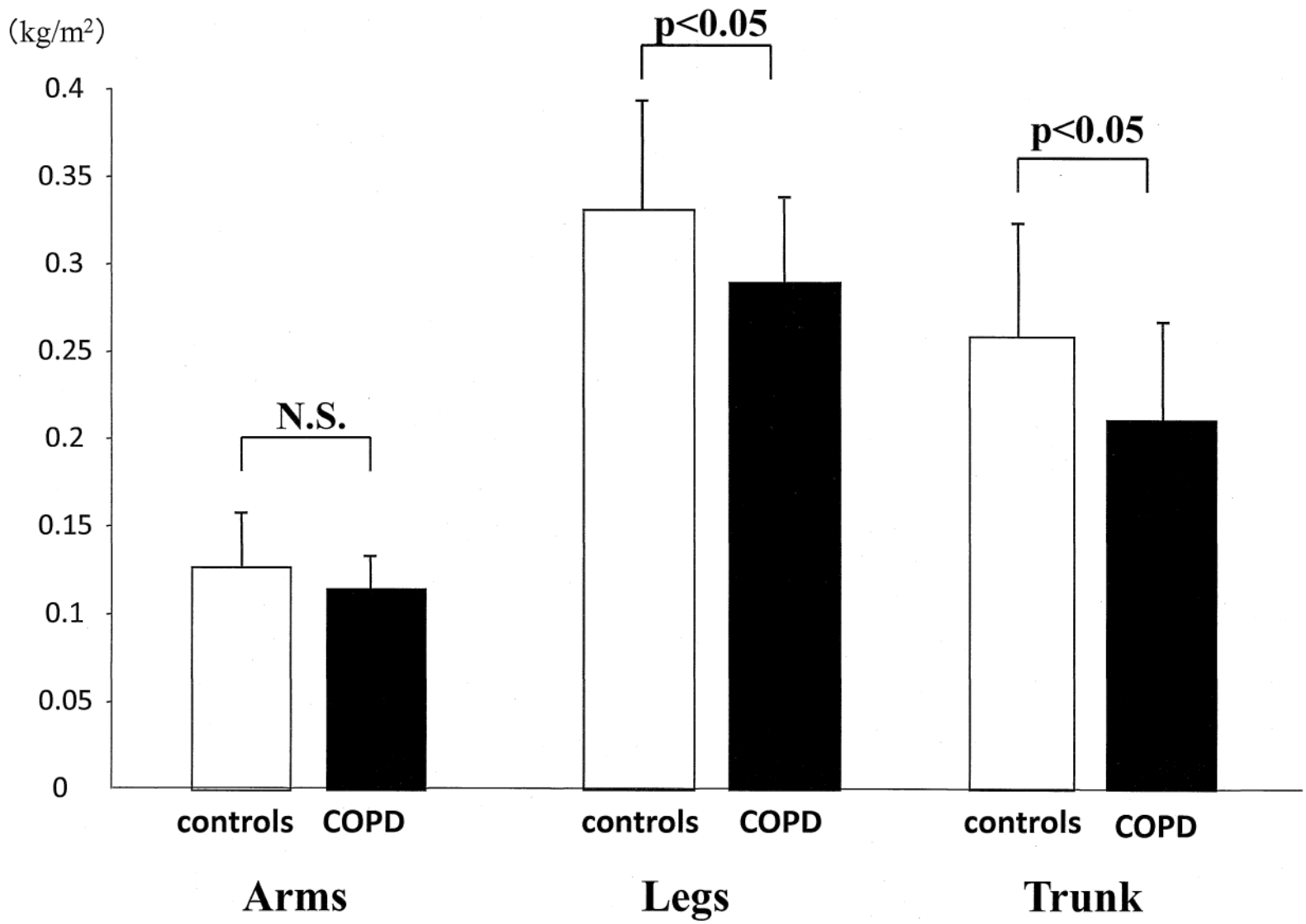
r: Pearson's correlation coefficients

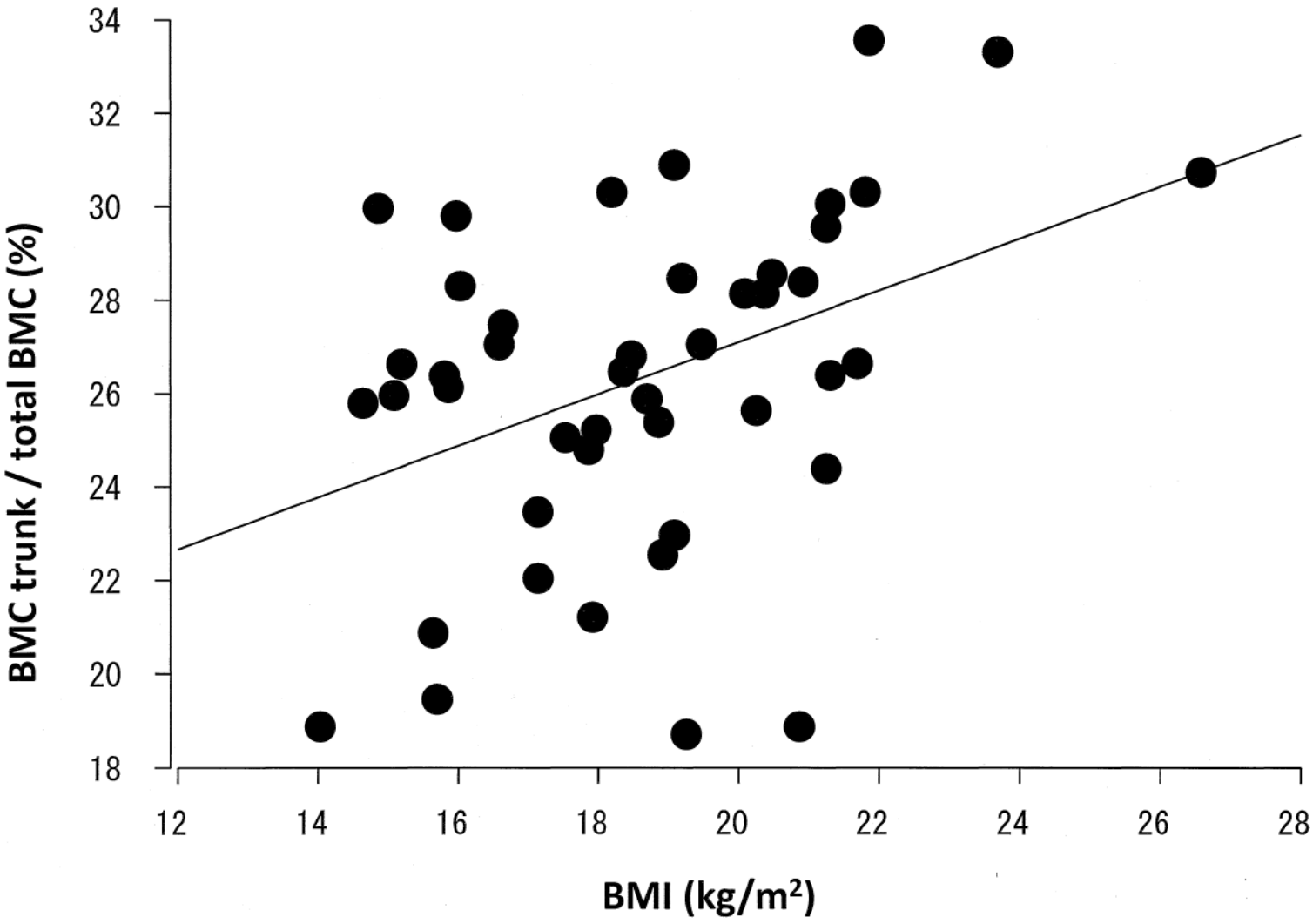
BMC=bone mineral content; BMCI=bone mineral content (kg) / height $(m)^2$; BMI=body mass index; FEV_1=forced expiratory volume in one second; $\dot{V}O_2max$=maximum oxygen uptake

Figure legends

Figure 1. BMCI in the arms, legs, and trunk in patients with COPD. BMC=bone mineral content, BMCI=bone mineral content index (kg/m^2). Values are mean $\pm$ SD of 45 patients with COPD and 12 controls.

Figure 2. Relationship between BMI and BMC trunk/total BMC. BMI= body mass index, BMC trunk=bone mineral content in the trunk, total BMC= bone mineral content in whole body.


(kg/m²)
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
p<0.05
p<0.05
N.S.
controls
COPD
controls
COPD
controls
COPD
Arms
Legs
Trunk


BMC trunk / total BMC (%)
34
32
30
28
26
24
22
20
18
12
14
16
18
20
22
24
26
28
BMI (kg/m²)