Association between respiratory function and bone mineral density in Japanese men

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Abstract

The aim of this cross-sectional study was to investigate the association between respiratory function and bone mineral density (BMD). The study included 146 male subjects, aged 60.0 ± 11.5 years (mean ± standard deviation) who underwent spirometric lung function and BMD tests at a medical check-up. Forced vital capacity (FVC), %FVC, forced expiratory volume in 1 second (FEV_1), FEV_1% predicted, and FEV_1/FVC were measured in respiratory function tests. BMD was measured in the non-dominant radius by dual-energy X-ray absorptiometry. In multiple linear regression analyses that included age, BMI, pack-years, alcohol intake, and physical activity as covariates, FVC was positively associated with BMD and negatively associated with age and BMI, %FVC was positively associated with BMD and negatively associated with BMI, and FEV_1 was positively associated with BMD and negatively associated with age, BMI and pack-years. Respiratory function is positively associated with BMD.

Keywords: bone mineral density, lung function tests, respiratory function, spirometry

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. Osteoporosis is diagnosed by measuring the bone mineral density (BMD), and the most popular method of measuring BMD is dual-energy X-ray absorptiometry (DXA) [2]. Low BMD is a strong risk factor for fracture [3,4].

Recent scientific evidence has shown that osteoporosis is common in patients with chronic obstructive pulmonary disease (COPD) [5 ～ 9]. Osteoporosis might develop in patients with COPD due to a number of factors, including age, limited physical activity, low body mass index (BMI), smoking, hypogonadism, malnutrition, use of corticosteroids [7, 8], and systemic inflammation [9]. Kado et al reported that the age-adjusted relative risk for pulmonary mortality was higher in women who had vertebral fractures than in those who did not (relative risk, 2.0; 95% confidence interval, 1.4–2.9) [10]. In addition, Moayyeri et al suggested that, in the general community, middle-aged and older people with low respiratory function are at increased risk of osteoporosis and hip fracture [11]. COPD appears to be associated with low BMD [12].

The association of osteoporosis with COPD is well established, but the relationship between respiratory function and BMD has not been thoroughly explored. Two studies in British women and men suggest that respiratory function is associated with BMD [13, 14], but no study has exclusively studied this association in Japanese patients. Better understanding of the association between respiratory function and BMD would help identify patients who would benefit from BMD monitoring and lead to more effective osteoporosis prevention and the improvement of public health. The aim of this cross-sectional study was to investigate the association between respiratory function and BMD in Japanese men.

Methods

Subjects

The study included 146 male subjects who underwent a comprehensive health screening that included a physical examination, spirometry, chest X-ray, and blood tests. All subjects were seen between April 2008 and March 2009 at the Japanese Red Cross Kumamoto Health Care Center, Kumamoto, Japan. The participants included workers and residents of a rural area of Kumamoto, Japan. Employees in Japan generally undergo annual check-ups at their workplace or at designated clinics. The health check-up programs involve physical examination, laboratory data collection, and

Table 1. Characteristics of the subjects among 146 men

Age (years)	60.0 ± 11.5
Height (cm)	166.3 ± 5.9
Weight (kg)	64.3 ± 9.1
BMI (kg/m^2)	23.2 ± 3.0
Albumin (g/dL)	4.5 ± 0.3
CRP (mg/L)	0.13 ± 0.30
BMD (g/m^2)	0.516 ± 0.075
FVC (mL)	3728.0 ± 674.9
%FVC (%)	106.2 ± 14.5
FEV_1 (mL)	2910.0 ± 593.6
FEV_1 % predicted	92.1 ± 13.1
FEV_1/FVC (%)	78.0 ± 6.8
Smoking history (%)	
Never smokers	39.0
Former smokers	35.6
Current smokers	25.4
Pack-years	19.7 ± 24.5
Alcohol intake (%)	
Non-drinkers	26.0
1–2 days/week	10.3
3–4 days/week	17.1
5–6 days/week	11.0
Everyday drinkers	35.6
Regular physical activity (%)	46.1

Values are the mean ± SD.
Abbreviations : BMI = body mass index,
CRP = C-reactive protein,
BMD = bone mineral density,
FVC = Forced expiratory vital capacity,
FEV_1 = Forced expiratory volume in one second,
Pack-years = (number of cigarettes smoked per day × number of years smoked)/20.

interview questionnaires. Data on medical history and lifestyle information were collected by means of questionnaire analyses conducted through interviews by a public health nurse. A physician examined all of the participants. All data were prospectively recorded and entered into an electronic database. Subjects with physician-diagnosed asthma or a history of asthma were excluded from the study. Asthma was considered present if diagnosed by a physician. Subjects were also excluded if they had physician-diagnosed bronchiectasis or bronchitis. Subjects who had undergone pneumoconiosis screening were excluded. Subjects who had a history of physician-diagnosed osteoporosis was also excluded. Of the 18,539 participants who had initially enrolled during this period only 180 had undergone BMD measurements. Of these 180 men, 157 had undergone respiratory measurements. The following exclusion criteria were applied: 1) a history of physician-diagnosed respiratory disease; and 2) a history of physician-diagnosed fracture and osteoporosis. Of the 157 men, 6 had history of physician-diagnosed respiratory disease and 5 had history of physician-diagnosed fracture and osteoporosis. There were no patients taking medications known to influence respiratory function or bone or calcium metabolism. Finally, we analyzed 146 men in this study. Our research protocol was approved by the Human Ethics Committee of Kumamoto University. Informed consent was obtained from all subjects in oral format prior to the health check-up.

Measurements

After an overnight fast, blood samples were obtained for the measurement of serum levels of routine medical check-up markers such as C-reactive protein (CRP) and albumin. CRP levels were measured using a high-sensitivity latex assay. Albumin levels were measured using the bromocresol purple method (Aqua-auto Kainos ALB Test Kit, Kainos Co. Ltd., Tokyo, Japan). Body mass index (BMI) was calculated as weight (kg) divided by the height (meters) squared.

Questionnaires

Lifestyle information such as smoking history, alcohol intake, and physical activity was obtained through an interview questionnaire [15]. Detailed smoking history was used to define individuals as ‘‘never smokers’’ (those who denied past and current smoking), ‘‘former smokers’’ (those who reported smoking before the examination but denied current smoking at examination), or ‘‘current smokers’’ (those who reported smoking at least one cigarette per day). Pack-years (packs of cigarettes per day multiplied by smoking years) was used as the smoking index. The frequency of alcohol drinking was divided into five categories: ‘‘non-drinkers,’’ ‘‘once or twice a week,’’ ‘‘three or four times a week,’’ ‘‘five or six times a week,’’ and ‘‘everyday drinkers.’’ Physical activity was divided into 2

Table 2. Correlation between age, BMI, albumin, CRP, BMD, FVC, %FVC, FEV_1, FEV_1% predicted, and FEV_1/FVC

		BMI (kg/m^2)	Albumin (g/dL)	CRP (mg/L)	BMD (g/m^2)	FVC (mL)	%FVC (%)	FEV_1 (mL)	FEV_1 % predicted	FEV_1/FVC (%)
Age (year)	*r*	0.036	−0.345	0.111	−0.229	−0.590	−0.240	−0.634	−0.022	−0.274
	p	0.664	<0.001	0.212	<0.05	<0.001	<0.05	<0.001	0.793	<0.05
BMI (kg/m^2)	*r*	—	−0.020	0.045	0.242	−0.192	−0.210	−0.146	−0.160	0.042
	p	—	0.807	0.613	<0.05	<0.05	<0.05	0.078	0.054	0.617
Albumin (g/dL)	*r*	—	—	−0.069	0.129	0.132	−0.017	0.195	−0.019	0.200
	p	—	—	0.44	0.119	0.111	0.842	<0.05	0.820	<0.05
CRP (mg/L)	*r*	—	—	—	−0.069	−0.146	−0.157	−0.208	−0.265	−0.260
	p	—	—	—	0.438	0.100	0.077	<0.05	<0.05	<0.05
BMD (g/m^2)	*r*	—	—	—	—	0.230	0.168	0.230	0.093	0.071
	p	—	—	—	—	<0.05	<0.05	<0.05	0.265	0.393
FVC (mL)	*r*	—	—	—	—	—	0.902	0.918	0.62	0.112
	p	—	—	—	—	—	<0.001	<0.001	<0.001	0.177
%FVC (%)	*r*	—	—	—	—	—	—	0.778	0.792	−0.011
	p	—	—	—	—	—	—	<0.001	<0.001	0.896
FEV_1 (mL)	*r*	—	—	—	—	—	—	—	0.717	0.490
	p	—	—	—	—	—	—	—	<0.001	<0.001
FEV_1 % predicted	*r*	—	—	—	—	—	—	—	—	0.462
	p	—	—	—	—	—	—	—	—	<0.001

Pearson correlation coefficient (*r*)

Abbreviations : BMI = body mass index, CRP = C-reactive protein, BMD = bone mineral density,

FVC = Forced expiratory vital capacity, FEV_1 = Forced expiratory volume in one second.

categories: ‘‘regular physical activity’’ (defined as physical activity performed regularly, at least twice per week for at least 30 min per session throughout the year) and ‘‘physical inactivity’’ (defined as engaging inirregular physical activity or engaging in no form of physical activity at all).

Measurement of bone mineral density (BMD)

BMD was measured at the distal 1/3 radius site on the non-dominant side using dual energy X-ray absorptiometry (DTX200; Osteometer Meditech A/S, USA) according to the manufacturer’s protocol (precision error <1.0% CV in vivo). Quality control was carried out in accordance with the manufacturer’s instructions. The BMD of the distal 1/3 radius site has been determined to be highly predictive of fracture risk [16].

Lung function tests

Lung function tests were performed using an electric spirometer (DISCOM-21 FX CHEST MI, Tokyo, Japan) connected to a computer for analysis of data, as described previously [15]. Forced vital capacity (FVC), %FVC, forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC were measured as respiratory function tests. Maneuvers were performed according to GOLD recommendations [5] under the supervision of a certified pulmonary technologist. No reversibility test was performed.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 18 software. Results are presented as the mean ± standard deviation (SD) and categorical variables are expressed as frequencies. Correlations between age, BMI, albumin, CRP, BMD, FVC, %FVC, FEV_1, FEV_1% predicted, and FEV_1/FVC as continuous variables were examined using Pearson correlation coefficients. Multiple linear regression analysis was performed to detect variables with an independent influence on respiratory function (FVC, %FVC and FEV_1). To examine multi-collinearity of the regression model, we determined the variance inflation factor. A variance inflation factor exceeding 10 indicated that collinearity was problematic. Age, BMI, BMD, pack-years, and alcohol intake, and physical activity were selected from subjects scoring less than 10.0 for the variance inflation factor, i.e., weight and height were excluded. Statistical significance was defined as $p < 0.05$.

Table 3. Multiple linear regression analysis on variables associated with FVC

	Coefficient	Standard error	t	*p*
Age (year)	−30.53	4.42	−6.91	<0.001
BMI (kg/m^2)	−47.79	16.14	−2.96	<0.05
BMD (g/m^2)	1399.91	653.07	2.14	<0.05
Pack-years	−2.31	1.98	−1.16	0.247
Alcohol intake[a]	−8.43	29.54	−0.29	0.776
Physical activity[b]	−3.59	95.66	−0.04	0.970

Maltiple linear regression analysis, adjusted R^2=0.37.
Abbreviations : FVC = Forced expiratory vital capacity,
BMD = bone mineral density, BMI = body mass index.
[a] Alcohol intake was rated as 0 (Non-drinkers), 1 (1–2 days/week), 2 (3–4 days/week), 3 (5–6 days/week), or 4 (Everyday drinkers).
[b] Physical activity was rated as 0 (Physical inactivity) and 1 (Regular physical activity).

Table 4. Multiple linear regression analysis on variables associated with %FVC

	Coefficient	Standard error	t	*p*
Age (year)	−0.19	0.11	−1.69	0.090
BMI (kg/m^2)	−1.18	0.41	−2.87	<0.05
BMD (g/m^2)	34.19	16.72	2.05	<0.05
Pack-years	−0.07	0.05	−1.31	0.192
Alcohol intake[a]	−0.25	0.76	−0.33	0.741
Physical activity[b]	0.14	2.45	0.06	0.953

Maltiple linear regression analysis, adjusted R^2=0.10.
Abbreviations : FVC = Forced expiratory vital capacity,
BMD = bone mineral density, BMI = body mass index.
[a] Alcohol intake was rated as 0 (Non-drinkers), 1 (1–2 days/week), 2 (3–4 days/week), 3 (5–6 days/week), or 4 (Everyday drinkers).
[b] Physical activity was rated as 0 (Physical inactivity) and 1 (Regular physical activity).

Table 5. Multiple linear regression analysis on variables associated with FEV_1

	Coefficient	Standard error	t	*p*
Age (year)	−28.48	3.69	−7.72	<0.001
BMI (kg/m^2)	−29.79	13.46	−2.21	<0.05
BMD (g/m^2)	1079.74	544.70	1.98	<0.05
Pack-years	−4.33	1.66	−2.61	<0.05
Alcohol intake[a]	−13.04	24.63	−0.53	0.597
Physical activity[b]	−4.09	79.79	−0.05	0.959

Maltiple linear regression analysis, adjusted R^2=0.44.
Abbreviations : FVC = Forced expiratory vital capacity,
BMD = bone mineral density, BMI = body mass index.
[a] Alcohol intake was rated as 0 (Non-drinkers), 1 (1–2 days/week), 2 (3–4 days/week), 3 (5–6 days/week), or 4 (Everyday drinkers).
[b] Physical activity was rated as 0 (Physical inactivity) and 1 (Regular physical activity).

Results

Subject characteristics are summarized in Table 1. The mean age of the subjects was 60.0 ± 11.5 years, and the mean BMD was 0.516 ± 0.075 g/cm^2.

Table 2 shows the correlations between age, BMI, albumin, CRP, BMD, FVC, %FVC, FEV_1, FEV_1 % predicted, and FEV_1/FVC. BMD positively correlated with BMI (r = 0.242 [p < 0.05]), FVC (r = 0.230 [p < 0.05]), %FVC (r = 0.168 [p < 0.05]), and FEV_1 (r = 0.230 [p < 0.05]) and negatively correlated with age (r = −0.229 [p < 0.05]) .

Table 3 shows the results obtained by multiple regression analysis that assessed factors influencing FVC, including age, BMI, BMD, pack-years, alcohol intake, and physical activity. FVC was positively associated with BMD (coefficient = 1399.91 [p < 0.05]) and negatively associated with age and BMI (coefficient = −30.53 [p < 0.001] and −47.79 [p < 0.05], respectively). The variance inflation factors in this regression model were all less than 1.22 and the adjusted R^2 value was 37%.

Table 4 shows the results obtained by multiple regression analysis that assessed factors influencing %FVC, including age, BMI, BMD, pack-years, alcohol intake, and physical activity. %FVC was positively associated with BMD (coefficient = 34.19 [p < 0.05]) and negatively associated with BMI (coefficient = −1.18 [p < 0.05]). The variance inflation factors in this regression model were all less than 1.22 and the adjusted R^2 value was 10%.

Table 5 shows the results obtained by multiple regression analysis that assessed factors influencing FEV_1, including age, BMI, BMD, pack-years, alcohol intake, and physical activity. FEV_1 was positively associated with BMD (coefficient = 1079.74 [p < 0.05]) and negatively associated with age, BMI, and pack-years (coefficient = −28.48 [p < 0.001], −29.79 [p < 0.05], and −4.33 [p < 0.05], respectively). The variance inflation factors in this regression model were all less than 1.22 and the adjusted R^2 value was 44%.

Discussion

In the present study, we found that respiratory function (FVC, %FVC, and FEV_1) positively correlated with BMD. This association was independent of possible confounding factors that might affect bone metabolism, such as age, BMI, pack-years, alcohol intake and physical activity. FEV_1 has been reported to be associated with BMD in British women [13] and men [14] from the

general community, but no previous studies have exclusively targeted Japanese men. To our knowledge, this is the first report to reveal an association between respiratory function and BMD in Japanese men.

The association between respiratory function and BMD among subjects with COPD has been demonstrated in a recent study [12]. There are several possible explanations for the association of low BMD with COPD. The first is the presence of systemic inflammation. COPD is not only a disease of the lungs but also a systemic inflammatory disorder [9]. Gan et al reported a systematic review and meta-analysis of 14 reports that confirmed a strong association between COPD and biological markers of systemic inflammation such as CRP, fibrinogen, white blood cell count and tumor necrosis factor-alpha (TNF-alpha) [17]. TNF-α is a potent inhibitor of bone collagen synthesis and stimulator of osteoclastic bone resorption, the net effect of which is to cause bone loss [18].

The second explanation is a low level of physical activity in COPD patients. Decreased physical activity has been shown to accelerate bone loss, resulting in decreased BMD; and advanced COPD is often associated with decreased physical activity [8].

The third reason is malnutrition. Gonlugur et al reported that serum albumin levels decreased with declining pulmonary function in COPD patients [19]. Albumin, the most abundant plasma protein, has been reported to increase glutathione levels in lung epithelial cells [20]. Glutathione plays a pivotal role in cellular antioxidant defenses and has been implicated in the regulation of nuclear factor kappa B (NF-kB) activation [21]. In addition, Wagner et al reported that COPD patients with cachexia had higher levels of TNF-α than those without [22]. However, in the current study, the association between respiratory function and BMD was apparent across the normal range of respiratory functions. The precise mechanism underlying the association between respiratory function and BMD is unclear.

Lakamwasam et al, who demonstrated positive correlations between BMD and FEV_1 in British women [13] and men [14] from the general community, suggested that this association is likely to reflect some common etiological factor or factors such as physical activity or nutritional status. CRP is a sensitive indicator of inflammation occurring within the body [23]. In addition, serum albumin concentration has been used as a biochemical marker of nutritional status [19, 24]; it is one of the easiest parameters to measure and that which best reflects the state of visceral protein [24]. In this study, we used CRP as a systemic marker and albumin as a marker of nutritional status. CRP levels were negatively correlated with respiratory function (FEV_1, FEV_1 % predicted, and FEV_1/FVC) and albumin was positively correlated with respiratory function (FEV_1 and FEV_1/FVC) although we no found the association between CRP or albumin and BMD. Further prospective studies are needed to clarify the reason why respiratory function is associated with BMD.

The current study had some limitations. First, our results are based on a cross-sectional analysis. A large-scale prospective study is required to elucidate whether the decrease in respiratory function lead to low BMD and can therefore be a useful indicator of increased risk of osteoporosis. Second, we assessed only men because we did not have information about women's menstrual status. Menstrual status is important because the peak BMD in Japanese women is reached at about 35–40 years of age and it falls rapidly during the first 10 years after menopause and then decreases gradually [25]. Further studies are required to determine whether there is an association between respiratory function and BMD in Japanese women.

In conclusion, our results suggest that respiratory function might be associated with BMD.

Acknowledgments

This work was supported in part by the scholarship for the Graduate School of Medical Sciences, Kumamoto University, Japan.

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（提出日　平成 24 年 12 月 12 日）