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ORIGINAL ARTICLE

The relationship between pulmonary function and bone mineral density in healthy nonsmoking women: the Korean National Health and Nutrition Examination Survey (KNHANES) 2010

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Abstract
Summary The aim of this study was to examine the association between pulmonary function and bone mineral density (BMD) in subjects who had never smoked. Pulmonary function was associated with BMD in premenopausal, but not postmenopausal, women.
Introduction It has been reported that low bone mass is common in patients with pulmonary disorders such as chronic obstructive pulmonary disease. However, in healthy nonsmoking women, the relationship between bone mass and pulmonary function has yet to be clarified. The object of this study was to determine whether pulmonary function is related to BMD in healthy nonsmoking women based on menopausal status.
Methods This study was a cross-sectional study based on data obtained from the Korean National Health and Nutrition Examination Survey (KNHANES), a nationwide representative survey conducted by the Korean Ministry of Health and Welfare in 2010. This study included 456 subjects who had never smoked and analyzed data concerning pulmonary function and BMD.
Results Functional vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were correlated with BMD at lumbar spine, femur neck (FN), and total hip in premenopausal women ($p = 0.030$, $p = 0.003$, $p = 0.019$, respectively, for FVC; $p = 0.015$, $p = 0.006$, $p = 0.059$, respectively, for FEV_1). However, FVC and FEV_1 were only correlated with BMD at FN in postmenopausal women ($p = 0.003$ for FVC; $p = 0.006$ for FEV_1). Body mass index (BMI), FVC, and FEV_1 were significantly related with BMD at FN, even after adjusting for age and other confounding factors ($\beta = 0.334$, $p < 0.001$; $\beta = 0.145$, $p = 0.017$; and $\beta = 0.129$, $p = 0.037$, respectively) in premenopausal women. However, only age and BMI were correlated with BMD at FN ($\beta = -0.268$, $p = 0.001$ and $\beta = 0.384$, $p > 0.001$) in postmenopausal women after adjusting for confounding factors.
Conclusions Pulmonary function, including FVC and FEV_1 are associated with BMD at FN in healthy nonsmoking premenopausal women but not in postmenopausal women.

Keywords Bone mineral density · Osteoporosis · Respiratory function · Smoking

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
Ca	Calcium
25(OH)D	25-Hydroxy vitamin D
FVC	Functional vital capacity
FEV_1	Forced expiratory volume in 1 s
FEV_6	Forced expiratory volume in 6 s
$FEF_{25–75}$	Forced expiratory flow rate of 25–75 %
PEFR	Peak expiratory flow rate

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Introduction

Osteoporosis is an important public health problem worldwide because it can lead to fractures that may result in high morbidity and mortality. The bone mineral density (BMD) is a simple and common method for predicting fractures using risk assessment tools. BMD has been associated with pulmonary function in patients suffering from respiratory diseases such as cystic fibrosis and chronic obstructive pulmonary disease (COPD) [1–4]. Several studies have investigated the relationship between moderate-to-severe airflow obstruction and osteoporosis [5, 6] and found that subjects with obstructive airway disease have lower BMD even though they had not previously been exposed to steroids [7, 8]. However, few studies have investigated the relationship between pulmonary function and BMD in healthy people, and the results are not consistent [9–11]. Moreover, these studies utilized heterogeneous populations with regard to their smoking habits and included nonsmokers, ex-smokers, and current smokers. Cigarette smoking is a well-known risk factor that leads to a decline in lung function in adults and is a primary cause of COPD in conjunction with pathological changes in inflammation, fibrosis, and the destruction of alveolar attachments [12]. Even after the cessation of smoking, the negative effects of smoke on lung function are thought to continue [13]. Additionally, smoking is hypothesized to be a risk factor for bone loss and fractures [14]. In short, smoking is likely to represent an inevitable confounding factor for studies because it affects lung function and bone metabolism. Therefore, this study was undertaken to investigate the relationship between respiratory function and BMD in healthy nonsmoking women using data from a nationwide representative survey.

Patients and methods

Design and participants

This was a cross-sectional study based on the data obtained from the Korea National Health and Nutrition Examination (KNHANES), a nationwide representative survey conducted by the Korean Ministry of Health and Welfare in 2010. The KNHANES has been periodically conducted since 1998 and is composed of data from the civilian noninstitutionalized population of the Republic of Korea using a stratified multistage sampling with a probability proportional to size. KNHANES V was conducted between January 2010 and December 2010 and collected data via household interviews and direct standardized physical examinations performed in specially equipped mobile examination centers [15]. The ethnic makeup of the Korean population is Asian.

Women with BMD data and interpretable pulmonary function test data (n=1,496) were included in this study. Participants with diseases such as cancer, arthritis, cardiovascular disease, or fractures or who were using medications for osteoporosis or pulmonary disease that could affect BMD or pulmonary function tests were excluded (n=942). A history of smoking can affect pulmonary function; thus, subjects who had ever smoked during their lifetime were excluded (n=48). The menopausal status was defined based on a questionnaire survey and was self-designated using the question of whether 1 year had passed since the time of last menstruation; women with premature surgical menopause were excluded. A total of 506 subjects (281 premenopausal women and 225 postmenopausal women) were included in this study, and all underwent a routine physical examination that recorded age, body weight, height, smoking history, drinking history, exercise levels, and calcium (Ca) intake. Dietary Ca intake was estimated using the 24 h dietary recall method. Exercise was recorded as "yes" when the subject exercised regularly at moderate levels, for more than 30 min at a time and more than five times a week. Blood samples for measuring serum 25-hydroxy vitamin D [25(OH)D] were obtained from all participants for biochemical analyses, immediately refrigerated, transported to the Central Testing Institute in Seoul, Korea, and analyzed within 24 h.

Bone mineral density

Subjects were in light clothing without shoes or jewelry that may have interfered with the BMD test. BMD levels were measured at the lumbar spine (L1–4) and proximal femur (total hip region) using dual-energy X-ray absorptiometry (DXA, Discovery-W model, Hologic, Bedford, MA, USA) in mobile examination centers. BMD is expressed in grams per square centimeter, and if the subject had prosthetic devices or implants, it was considered as missing data. For the purpose of DXA quality control, daily automatic calibration was performed according to the manufacturer's instructions to maintain a precision standard of 1.5 % for total hip measurements [16].

Measurement of lung function

Lung function was measured using a dry rolling seal spirometer (model 2130; SensorMedics, Yorba Linda, CA, USA) according to the American Thoracic Society/European Respiratory Society criteria for standardization [17]. Spirometric data obtained on-site by clinical technicians were transferred to an internet review center for processing where the information was carefully examined and compared against criteria metrics for acceptability, reproducibility, and quality control. A principal investigator validated and stored the data in a Korea Centers for Disease Control and Prevention repository management system. Only interpretable data were included in this study.

Statistical analysis

All statistical analyses were performed with SPSS for Windows statistical package version 17.0 (SPSS Inc., Chicago, IL, USA). The baseline characteristics of the study groups were compared using independent Student's *t* tests for continuous variables, and Pearson correlation coefficients were calculated in order to evaluate the correlations among femur neck (FN) BMD and age, body mass index (BMI), the pulmonary function test, serum 25(OH)D, and 24 h Ca intake. A partial correlation coefficient was used to measure the dependence of FN BMD on pulmonary function, and a multiple linear regression analysis was used to identify independent predictors of FN BMD in nonsmoking premenopausal and postmenopausal women. Results were considered to be significant when the *p* value was less than 0.5

Results

Baseline characteristics of participants

The baseline clinical and biochemical characteristics of subjects are presented (Table 1). The mean age of premenopausal and postmenopausal women was 44.9±3.7 and 55.5±6.5 years, respectively. BMI and the estimate of 24 h Ca intake were not significantly different between the two groups, but 25(OH)D levels were slightly higher in postmenopausal women. The BMDs at the lumbar spine, FN, and total hip were lower in postmenopausal women, and most of the lung function parameters were higher in premenopausal women.

The BMD at all three sites showed significant positive correlations with functional vital capacity (FVC, L; $p<0.05$ for the lumbar spine and total hip, $p<0.01$ for FN), forced expiratory volume in 1 s (FEV_1, L; $p<0.01$ for the lumbar spine and FN, $p<0.05$ for total hip), forced expiratory volume in 6 s (FEV_6, L; $p<0.01$ the for lumbar spine and FN, $p<0.05$ for total hip), and forced expiratory flow rate of 25–75 % ($FEF_{25–27}$ (L/s); $p<0.01$ for the lumbar spine and FN, $p<0.05$ for total hip) in premenopausal women. However, in postmenopausal women, only the FN was positively correlated with these parameters ($p<0.05$ for FVC(L), FEV_1(L), FEV_6(L), and $FEF_{25–75}$ (L/s)). Age was not related with BMD at any site in premenopausal women, but these factors were positively related in postmenopausal women. BMI was positively related with BMD in both premenopausal and postmenopausal women, and 25(OH)D was negatively correlated with BMD in postmenopausal women (Table 2).

Multiple linear regression analyses of pulmonary function and FN BMD are shown (Table 3). In model 1, FN BMD showed a positive relationship with FVC and FEV_1 in premenopausal women. In model 2, FVC and FEV_1 remained the most significant independent variables among age, BMI, and pulmonary function. In model 3, after adding hormone therapy and physical activity as independent parameters, FVC and FEV_1 were identified as significant factors that predicted FN BMD. Serum 25(OH)D and 24 h Ca intake were additionally adjusted in model 4. In premenopausal women, FVC and FEV_1 showed significant positive correlations with FN BMD, even after adjusting for confounding factors. However, the same kind of relationship was not observed between pulmonary function and FN BMD in

Table 1 Baseline characteristics according to menopausal status

	Premenopausal	Postmenopausal	*p*-value
N	275	181	
Age (years)	44.9±3.7	55.5±6.5	< 0.001
Weight (kg)	59.2±8.0	57.0±7.2	0.003
Height (cm)	158.5±4.8	154.4±5.4	< 0.001
WC (cm)	77.5±8.2	80.1±7.9	0.001
BMI (kg/cm$^{2)}$	23.6±2.9	23.9±2.8	0.209
24-hr Ca intake (mg)	492±290	486±323	0.838
25(OH)D (ng/mL)	15.4±5.0	18.0±6.4	< 0.001
Bone Parameters			
Total hip			
Area (cm^2)	32.5±2.8	32.6±2.8	0.894
BMC (g)	29.6±4.4	26.8±4.3	< 0.001
BMD (g/cm^2)	0.907±0.103	0. 821±0.107	< 0.001
T-score	0.49±0.90	−0.26±0.93	< 0.001
Femur Neck			
Area (cm^2)	4.9±0.4	4.9±0.3	0.890
BMC (g)	3.8±0.6	3.3±0.5	< 0.001
BMD (cm^2)	0.764±0.099	0.678±0.105	< 0.001
T-score	−0.37±0.93	−1.17±0.98	< 0.001
Lumbar spine			
Area (cm^2)	60.2±5.4	56.3±7.2	< 0.001
BMC (g)	60.7±10.2	47.3±10.7	< 0.001
BMD (g/cm^2)	1.006±0.122	0.836±0.137	< 0.001
T-score	0.03±1.06	−1.48±1.20	< 0.001
Respiratory parameters			
FVC (L)	3.33±0.39	2.98±0.44	< 0.001
FVC (%)	97.7±9.0	96.5±12.1	0.263
FEV_1 (L)	2.74±0.31	2.39±0.36	<0.001
FEV_1 (%)	96.4±9.3	96.8±12.8	0.715
FEV_1/FVC (%)	0.82±0.04	0.80±0.05	<0.001
FEV_6 (L)	3.29±0.38	2.93±0.43	<0.001
FEF 25-75 % (L/s)	6.06±0.68	5.37±0.78	<0.001
PEFR (L/s)	6.74±0.97	6.11±1.02	<0.001

WC waist circumference, *BMI* body mass index, *24-hr Ca intake* estimated Ca intake using the 24-hr dietary recall method, *25(OH)D* 25-hydroxy vitamin D, *BMD* bone mineral density, *BMC* bone mineral content, *FVC* functional vital capacity, *FEV_1* forced expiratory volume in 1 second, *FEV_6* forced expiratory volume in 6 seconds, *FEF 25 - 75 %* forced expiratory flow rate 25 - 75 %, *PEFR* peak expiratory flow rate

Table 2 Simple correlations between the bone mineral density and clinical characteristics, including pulmonary function test

	Correlation coefficient (r) with BMD					
	Premenopausal			Postmenopausal		
	Lumbar	Femur neck	Total hip	Lumbar	Femur neck	Total hip
Age (years)	−0.063	−0.052	−0.046	−0.379**	−0.334**	−0.340**
Weight (kg)	0.323**	0.382**	0.416**	0.359**	0.472**	0.507**
Height (cm)	0.165**	0.180**	0.142*	0.277**	0.232**	0.213**
BMI (kg/cm^2)	0.273**	0.334**	0.390**	0.225**	0.373**	0.411**
Ca intake (mg/24 hr)	−0.057	−0.082	−0.081	0.093	0.005	0.000
25(OH)D (ng/mL)	−0.005	0.027	0.031	−0.184*	−0.218**	−0.211**
FVC (l)	0.131*	0.180**	0.142*	0.142	0.147*	0.123
FVC (%)	0.000	0.042	0.016	−0.140	−0.111	−0.143
FEV_1 (L)	0.147*	0.165**	0.114	0.115	0.116	0.110
FEV_1 (%)	0.056	0.067	0.035	−0.221**	−0.169*	−0.166*
FEV_1/FVC (%)	0.026	−0.047	−0.077	−0.060	−0.069	−0.033
FEV_6 (L)	0.133*	0.178**	0.134*	0.139	0.143	0.122
FEF 25-75 % (L/s)	0.143*	0.179**	0.133*	0.133	0.136	0.120
PEFR (L/s)	0.169**	0.087	0.048	0.091	0.061	0.079

BMD bone mineral density, *BMI* body mass index, *Ca* calcium, *25(OH)D* 25-hydroxy vitamin D, *FVC* functional vital capacity, FEV_1=forced expiratory volume in one second, FEV_6 forced expiratory volume in six second, *FEF 25-75 %* forced expiratory flow rate 25-75 %, *PEFR* peak expiratory flow rate

* $p<0.05$

** $p<0.01$

postmenopausal women (Table 3). In postmenopausal women, age and BMI showed negative and positive associations with FN BMD, respectively ($p=-0.268$ and $p=0.001$ for age, $p=0.384$ and $p<0.001$ for BMI).

Discussion

This study demonstrated that FN BMD is closely associated with pulmonary functions such as FVC and FEV_1 in

Table 3 Pulmonary function indices are predictive factors for FN BMD in premenopausal, but not postmenopausal women

Model	Premenopausal (n=275)			Postmenopausal (n=181)		
	Standard β	*P* value	Adjusted R^2	Standard β	*p*-value	Adjusted R^2
FVC						
1	0.180	0.003	0.029	0.147	0.048	0.016
2	0.136	0.018	0.129	0.103	0.141	0.246
3	0.139	0.017	0.127	0.105	0.140	0.242
4	0.145	0.017	0.124	0.104	0.167	0.250
FEV_1						
1	0.165	0.006	0.024	0.116	0.119	0.008
2	0.119	0.044	0.125	0.036	0.607	0.238
3	0.120	0.043	0.122	0.037	0.606	0.234
4	0.129	0.037	0.119	0.026	0.736	0.241

The most significant factors correlated with FN BMD as selected by multiple linear regression analysis with the ENTER method. Input variables were listed as follows:

Model 1: crude

Model 2: model 1 plus age and BMI

Model 3: model 2 plus moderate physical activity

Model 4: model 3 plus 25(OH)D and estimate of Ca intake in 24 hrs

FN femur neck, *BMI* body mass index, *25(OH)D* 25-hydroxy vitamin D, *BMD* bone mineral density, *BMI* body mass index, *25(OH)D* 25-hydroxy vitamin D, *FVC* functional vital capacity, *FEV1* forced expiratory volume in one second

nonsmoking healthy women. However, after adjusting for possible confounding factors including age, BMI, physical activity, and hormone replacement, FN BMD was significantly correlated with pulmonary function in premenopausal, but not postmenopausal, women. In postmenopausal women, only age and BMI were the significant factors associated with FN BMD.

Several studies have investigated the relationship between respiratory function and BMD in healthy people, but the results are inconsistent. In contrast to the current study, Lekamwasam et al. [9] found a positive relationship between FEV_1 and BMD at the hip and lumbar spine even though the number of subjects was large, and the subject characteristics were heterogeneous. In that study, subjects were 45–76 years old, their menopausal statuses were not evaluated, and subjects with pulmonary disease such as COPD and those having used cancer or steroid medications that could affect pulmonary function and bone metabolism were included. Choi et al. [10] also found a positive correlation between pulmonary function and BMD, but there was a small population of subjects and they were from a single center. Both of these studies also included subjects with a history of smoking, which could affect pulmonary function and BMD, even after cessation. Moreover, these authors did not consider age, BMI, or behavioral habits; all of these factors are implicated in bone metabolism.

On the other hand, the current findings are consistent with the Hertfordshire Cohort study [11]. The subjects were males and females over 60 years of age and did not show any relationship between pulmonary function and BMD. These authors speculated that the different results were due a comparatively healthy cohort and that differences between countries regarding factors such as smoking, hypoxia, physical activity, water hardness, and fluoride concentration may have played a role. Similarly, the current study did not find a relationship between pulmonary function and BMD in postmenopausal women but did observe a positive relationship between these factors in premenopausal women. The unique difference in this study is that there was an attempt to minimize the effects of confounding factors such as cigarette smoking, pulmonary disease, and medications, including steroids. Smoking is a prominent factor that could affect pulmonary function, including FEV_1. In a large study from the Netherlands that followed up with subjects over 24 years [13], pulmonary function changed according to smoking status, which was categorized as formal smokers, recidivist smokers, brief smokers, or new starters. All smoking subjects exhibited a more rapid decrease of FEV_1, as compared to lifetime nonsmokers. It was suggested that the rapid decrease of FEV_1 is related to hormonal fluctuations based on inflammation, disturbances in airway responsiveness, and hypersensitivity.

Smoking is a known risk factor for bone loss and fractures. In one cross-sectional study, BMD was lower by approximately 4–5 % at the FN, lumbar spine, and total body in smokers [18]. One follow-up study over 2 years found that smokers had lower spinal BMD [19], while another showed that the annual rate of bone loss at the radius was greater in smokers and proportionally related to pack years of smoking exposure, even after controlling for BMI and postmenopausal years [20]. Additionally, a prospective study found that current smokers had an increased risk for hip fracture compared with never-smokers [21]. The primary underlying mechanisms are not yet fully understood, although they are thought to involve impaired Ca absorption [22], reduced vitamin D levels [23], reduced estrogenic activity [24], and increased concentration of free radicals, which may interfere with bone resorption [25]. In vitro studies have found that nicotine decreases proliferation and collagen synthesis in osteoblast-like cells [26, 27]. In summary, smoking can interfere not only with bone metabolism, including BMD and fractures, but also with pulmonary function. Thus, this study excluded subjects with a history of smoking because smoking is an important confounding factor that needs to be controlled in order to accurately evaluate the relationship between pulmonary function and BMD.

In lifetime nonsmoking women, BMI is the most predictive factor for BMD at the FN for both premenopausal and postmenopausal women. In the multiple linear regression analysis, FVC and FEV_1 were also factors that could predict FN BMD in premenopausal women, but only age was a predictive factor in postmenopausal women, even after adjustment for confounding factors such as age, BMI, hormonal replacement, physical activity, 24 h Ca intake, and serum 25(OH)D levels. This discrepancy is not sufficiently comprehensive to provide a clear understanding because hormonal differences could also result in differences; this deserves further investigation. Physical activity needs to be adjusted as a confounding factor. Physical activity is not only related to levels of lung function [28] but is also reported to have positive effects on lung function [29]. In addition, physical activity has been suggested to be a favorable factor affecting BMD [30]. Recently, increasing daily activity has been reported to help prevent decrease of BMD [31]. It was not hypothesized here that serum 25(OH)D levels would show a negative correlation with FN BMD based on the assumption that people who are concerned about bone health or who are at a high risk for osteoporosis tend to take more vitamin D, which is beneficial for bone health.

This study has some limitations. First, this is a retrospective study and includes an inherent selection bias because it was based on KNHANES data with interpretable lung function data and BMD information. Second, physical activity was not classified as strength training or aerobic exercise. Third, serum 25(OH)D levels were not adjusted for vitamin D supplementation. Finally, 24 h Ca intake was recorded based on remembered food estimates. Nevertheless, this is the first clinical study demonstrating a positive relationship between FN BMD and lung function in healthy nonsmoking premenopausal

women. FN BMD did not show a relationship with pulmonary function, but there was a negative relationship with age in postmenopausal women. It is proposed here that if subjects exhibit decreased pulmonary function, BMD levels should be evaluated, even though premenopausal women are not thought to be at risk for low bone mass.

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Conflicts of interest The authors declare no conflicts of interest

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