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Negative Association between Metabolic Syndrome and Bone Mineral Density in Koreans, Especially in Men

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Abstract Cardiovascular disease and osteoporosis are thought to share common risk factors, and metabolic syndrome (MS) is composed of major risk factors for cardiovascular disease. This study was performed to investigate the relationships between specific MS components and bone mineral density (BMD). BMD was measured at the femoral neck of Korean men aged 40 years or more ($n = 1{,}780$) and postmenopausal women ($n = 1{,}108$) using dual-energy X-ray absorptiometry. We identified subjects with MS as defined by two criteria, International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI). Body fat and lean mass were measured via bioimpedance analysis. The prevalence of MS was 19.8% and 7.7% in men and 20.8% and 11.6% in postmenopausal women according to the AHA/NHLBI definition and the IDF definition, respectively. After multivariate adjustment, femoral neck BMD was significantly lower in subjects with MS regardless of diagnostic criteria. BMD decreased as the number of MS components increased ($P < 0.001$ for trends in both sexes). Among MS components, waist circumference was the most important factor in this negative association. When multiple linear regression models were applied to each 5-kg weight stratum to test for a linear trend, waist circumference and fat mass were negatively associated with BMD and lean mass was positively associated with BMD in men but not in women. MS was associated with a lower BMD in Korean men and postmenopausal women, suggesting that visceral fat may lead to bone loss, especially in men.

Keywords Bone mineral density · Metabolic syndrome · Visceral fat

The authors declare no conflict of interests.

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Introduction

Atherosclerotic cardiovascular disease and osteoporosis are major contributors to morbidity and mortality among the elderly. Several studies have demonstrated that men and women with osteoporosis or higher bone resorption have a higher risk of cardiovascular disease [1–4]. This is thought to result from the common risk factors and pathophysiologic mechanisms between these two diseases, such as smoking, sedentary lifestyle, sex hormone deficiency, low-grade inflammation, and increased oxidative stress [5–8]; but the exact nature of the relationship between osteoporosis and cardiovascular disease remains unclear.

Metabolic syndrome (MS) is defined as a cluster of risk factors for atherosclerosis, including abdominal obesity, glucose intolerance, hypertension, and dyslipidemia. Therefore, establishment of the exact relationship between MS and osteoporosis would help to understand the role of common risk factors in the link between atherosclerosis and osteoporosis. The association between each component of MS and osteoporosis has been extensively studied, but the results of these studies have been inconsistent. Obesity is the strongest predictor of BMD in both men and women; however, studies of the association between abdominal obesity and bone mineral density (BMD) have been contradictory. Despite the high risk of fracture among type 2 diabetic women, hyperinsulinemia accompanied by MS increases BMD. Studies of the relationships between BMD and high triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels, and hypertension have also been contradictory.

Studies on the combined effects of MS on BMD are extremely rare, and their results have been inconsistent. A study conducted in the United States found that femoral neck BMD was higher among subjects with MS after adjustment for age, sex, and other covariates [9]. Another prospective study showed that MS reduced the risk of nonvertebral fractures, although the authors did not measure BMD [10]. In contrast, men with MS had lower BMDs in the Rancho Bernardo Study after adjustment for body mass index (BMI) [11], and a recent study reported that women with MS also had lower BMDs [12]. Differences in the characteristics of the studied subjects (e.g., sex, age, and degree of obesity) may contribute to these conflicting results. Analytical methods also varied as some studies adjusted for BMI [9–11] and others adjusted for weight [12]. In addition, ethnic differences may influence the results. The capacity of insulin secretion and the distribution of body fat differ in Asians and Caucasians [13]. Asians are more prone than Caucasians to develop abdominal obesity and insulin resistance, despite similar rates of general obesity [14]. We performed a cross-sectional study to assess whether MS is associated with BMD in Korean adults. Furthermore, we attempted to determine which component of MS was the most important factor in the relationship between MS and osteoporosis.

Subjects and Methods

Subjects

The study population consisted of men older than 40 years and postmenopausal women whose BMD was measured at the Health Promotion Center of Asan Medical Center (Seoul, Korea) between January 2005 and December 2006. All subjects visited our hospital for a routine health examination spontaneously. The Health Promotion Center is located in an urban area and open for everybody. Subjects completed a questionnaire to determine their smoking habits (current, past, or never), alcohol intake (units per week), dairy product consumption (frequency per week), physical exercise (more or less than three times per week), medication history, and history of previous medical or surgical diseases. Education was assessed by highest grade of school completed, and income was assessed by household income. Korean census data (2005 census) were used to investigate the average household income.

Postmenopausal status was defined as cessation of menses for at least 1 year, which was confirmed by a serum follicle-stimulating hormone concentration >30 IU/L. Women were excluded if any information about menopausal history was missing or if the subject had undergone a hysterectomy prior to natural menopause.

Subjects were excluded from the study if they had taken drugs (e.g., vitamin D, bisphosphonate, glucocorticoid, and hormone-replacement therapy) that could affect bone metabolism for more than 6 months or within the previous 12 months, if they had a disease that could affect bone metabolism (e.g., malignancy, thyroid disease, infection, and chronic inflammatory diseases), or if they had suffered a stroke or dementia that limited their physical activity. In addition, subjects were excluded if they had abnormal findings on complete blood counts; tests of liver, kidney and thyroid function; or serum concentrations of calcium, phosphorus, and alkaline phosphatase (ALP).

The study protocol was approved by the Ethics Committee of Asan Medical Center.

Metabolic Syndrome

MS was defined according to two criteria. Abdominal obesity was redefined on the basis of an Asian-specific cut-off point in both criteria.

According to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition, subjects were considered to have MS if they had three or more of the following abnormalities: abdominal obesity (i.e., waist circumference $\geq$ 90 cm for men and $\geq$ 80 cm for women), hypertriglyceridemia $\geq$ 150 mg/dL (1.7 mmol/L), low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men and <50 mg/dL [1.3 mmol/L] for women), high blood pressure ($\geq$ 130/85 mm Hg) or use of antihypertensive medication, and high fasting glucose ($\geq$ 100 mg/dL [5.6 mmol/L]) or use of antidiabetic medication (e.g., insulin or an oral agent) [15].

According to the International Diabetes Federation (IDF) definition, for subjects to be defined as having the MS they must meet three criteria: central obesity defined with ethnicity-specific values ($\geq$ 90 cm in men and $\geq$ 80 cm in women) plus any two of the following four

factors: hypertriglyceridemia (150 mg/dL [1.7 mmol/L] or specific treatment of this lipid abnormality), low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men and <50 mg/dL [1.3 mmol/L] for women or specific treatment), hypertension (≥ 130/85 mm Hg or previous treatment), and fasting hyperglycemia (≥ 100 mg/dL [5.6 mmol/L] or treated diabetes) [16].

Anthropometric Measurement

The height and weight of each subject were measured to the nearest 0.1 cm or 0.1 kg while subjects were wearing a light robe and no shoes. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured from the narrowest point between the lower border of the rib cage and the iliac crest. Blood pressure was measured in a sitting position at least two times after 10 min of relaxation.

Body composition was assessed via bioimpedance analysis, using eight tractile electrodes according to the manufacturer's instructions (Inbody 3.0; Biospace, Seoul, Korea). Fat mass (kg) and lean mass (kg) were measured. Previous studies indicated a high correlation (0.94) between dual-energy X-ray absorptiometry (DXA) and the multifrequency bioimpedance method [17, 18]. The within-day precision of Inbody 3.0 was ≤ 2.0%.

Biochemical Measurements

Morning blood samples were obtained after 12 h of fasting. The glucose oxidase–peroxidase colorimetry method (200 FR Autoanalyzer; Toshiba Medical System, Tokyo, Japan) was used to measure blood glucose levels. The intra- and interassay coefficients of variation (CVs) for this analysis were <2%.

An enzymatic colorimetric method was used to measure total cholesterol and triglyceride levels. The intra- and interassay CVs were 0.8–1.5% and 1.7–1.8%, respectively. HDL cholesterol and low-density lipoprotein (LDL) cholesterol levels were directly determined by α-cyclodextrin and the non-ionic surfactant method. The intra- and interassay CVs for these analyses were <5%.

Serum ALP concentration was measured at 37°C using the Bowers and McComb method with AMP buffer. Serum calcium was measured using the cresolphthalein complexone method, and serum phosphorus was measured using the phosphomolybdate ultraviolet method. The intra- and interassay CVs for these analyses were <3.5%.

BMD Measurements

Areal BMD (g/cm^2) was measured at the nondominant femoral neck using DXA (Expert XL with software version 1.90; Lunar, Madison, WI), calibrated daily using a standard phantom provided by the manufacturer. The in vivo precision of the machine was 1.12% for the femoral neck.

Analyses

All data are presented as means ± standard deviations (SDs) or as numbers and percentages. The baseline characteristics of controls and subjects with MS were compared using Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables.

Correlation analyses of BMD with known BMD covariates were performed with Pearson's correlation analyses. Analysis of covariance (ANCOVA) was used to compare the BMD levels of subjects with and without MS at the femoral neck after adjusting for significant BMD covariates including age, height, weight, current smoking status, and physical exercise. BMDs were compared according to the number of MS components present.

Multiple regression models were used to examine the relationship between BMD and each component of MS. Age, weight, height, current smoking status, and frequency of physical activity were included with the Enter method and the components of MS were included with the Stepwise method as continuous variables. The collinearity diagnostics method was used to avoid the problem of collinearity.

To assess the effects of abdominal obesity on BMD independently from the effects of body weight, BMD was plotted against the quartile of waist circumference, fat mass, and lean mass in 5-kg strata of weight. For maximal statistical power, only strata with >100 persons were included. Multiple linear regression models adjusted for age, height, current smoking, and physical exercise were used in each stratum to test for a linear trend in the relationship BMD with waist circumference, fat mass, and lean mass.

All statistical tests were two-tailed, and statistical significance was defined as $P < 0.05$. The SPSS software package version 10.0 (SPSS, Inc., Chicago, IL) was used for all analyses.

Results

Among the 4,601 participants whose BMD was measured in the health examination, 2,888 (1,108 postmenopausal women and 1,780 men >40 years old) were deemed eligible for and included in the study. The baseline characteristics of subjects are presented in Table 1.

Men over 40 years were younger and had greater BMI, lean mass, waist circumference, and serum concentrations of fasting glucose and triglycerides. On average, men had more years of education and higher income than women.

Table 1 Baseline characteristics of subjects

	Men (≥40 years)	Postmenopausal women
Age (years)	55.7 ± 8.1	57.1 ± 6.7
Weight (kg)	70.1 ± 8.7	57.7 ± 7.4
Height (cm)	169.0 ± 5.8	155.8 ± 5.2
BMI (kg/m^2)	24.5 ± 2.5	23.8 ± 2.9
Fat mass (kg)	14.0 ± 4.1	16.5 ± 4.8
Lean mass (kg)	56.1 ± 6.1	41.2 ± 4.0
Waist circumference (cm)	90.9 ± 14.2	85.5 ± 18.0
SBP (mm Hg)	123.0 ± 14.5	122.1 ± 16.5
DBP (mm Hg)	76.8 ± 8.6	76.0 ± 9.5
Glucose (mmol/L)	5.8 ± 1.3	5.4 ± 1.0
Cholesterol (mmol/L)	4.9 ± 0.8	5.2 ± 0.9
Triglyceride (mmol/L)	1.6 ± 0.9	1.4 ± 0.8
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.6 ± 0.4
LDL cholesterol (mmol/L)	3.2 ± 0.7	3.4 ± 0.8
Corrected calcium (mmol/L)	0.2 ± 0.0	0.2 ± 0.0
Phosphorus (mmol/L)	1.2 ± 0.1	1.4 ± 0.1
ALP (ukat/L)	1.1 ± 0.2	1.3 ± 0.3
%		
Current smoker	32.0	2.8
Exercise >3/week	53.6	47.1
Less than high school	15.6	41.5
Less than average income	18.9	51.1

Values are presented as mean ± SD. *SBP* systolic blood pressure, *DBP* diastolic blood pressure

The prevalence of MS was 19.8% in men and 20.8% in postmenopausal women according to the AHA/NHLBI definition and 7.7% in men and 11.6% in postmenopausal women according to the IDF definition. Compared with subjects without MS, those with MS were older and had greater weight, BMI, fat mass, lean mass, waist circumference, blood pressure, and serum concentrations of fasting glucose and triglycerides, while they had lower serum HDL cholesterol concentrations. Serum concentrations of corrected calcium were similar except in men with MS according to the IDF definition, and phosphorus was lower in subjects with MS. Serum ALP activity was higher only in postmenopausal women with MS. There were no significant differences in smoking status and exercise habits between the two groups (Table 2).

When correlation analyses between femoral neck BMD and the known BMD covariates were performed, weight and physical exercise showed a positive correlation and age and height showed a negative correlation with BMD in both sexes. Smoking showed a negative correlation with BMD only in men (Table 3). When we performed multiple regression analysis, femoral neck BMD was associated with age, weight, height, physical exercise, and smoking independently (data not shown).

Table 4 shows the adjusted femoral neck BMD values in men and postmenopausal women with and without MS. When we used the IDF criteria, age-adjusted BMD values were decreased in men. According to the AHA/NHLBI criteria, the BMD values were similar in groups with and without MS in an age-adjusted model. However, after adjustment for body weight, the BMD values were significantly lower in subjects with MS regardless of diagnostic criteria. The differences remained after all confounding variables were taken into account. Figure 1 shows the BMD values according to the number of MS components. All adjusted femoral neck BMDs significantly decreased with increasing MS components in both sexes (all $P < 0.001$ for trend).

Multiple regression analyses were performed to examine the association of each component of MS with femoral neck BMD after adjusting for confounding variables. To avoid the problem of collinearity, we performed collinearity diagnostics in the SPSS program. The tolerance of all variables was >0.1 and the variance inflation factor (VIF) was <10. As shown in Table 5, waist circumference showed an independent negative association with BMD values in both sexes. Serum triglyceride concentration was negatively associated with BMD in postmenopausal women. There were no significant associations between other components (i.e., systolic blood pressure and serum concentrations of fasting glucose and HDL cholesterol).

We further investigated the relationship between body composition and BMD in subjects matched by body weight. We divided the subjects into 5-kg strata according to body weight. Six strata for men (55.0–84.9 kg) and five strata for postmenopausal women (45.0–69.9 kg) were identified, with each stratum having more than 100 subjects. For each stratum, we stratified each component—fat mass, lean mass, and waist circumference—into quartiles. Among the components, waist circumference exhibited significantly negative associations in all strata of men (Fig. 2a) and in one stratum of women (Fig. 2b). In addition, fat mass showed a negative association in three strata of men (Fig. 2c), and lean mass showed a positive association in four strata of men (Fig. 2e). In women, we did not observe a significant relationship between fat mass and lean mass with BMD (Fig. 2d, f).

Discussion

The present study demonstrated that men over 40 years and postmenopausal women with MS have significantly lower BMD after adjusting for confounding variables. Furthermore, our findings reveal that BMD decreased with

Table 2 Baseline characteristics of subjects by MS status

	AHA/NHLBI criteria						IDF criteria					
	Men (≥40 years)			Postmenopausal women			Men (≥40 years)			Postmenopausal women		
	Absence (n = 1,428)	Presence (n = 352)	P	Absence (n = 877)	Presence (n = 231)	P	Absence (n = 1,643)	Presence (n = 137)	P	Absence (n = 917)	Presence (n = 191)	P
Age (years)	55.4 ± 8.1	56.8 ± 7.9	<0.01	56.2 ± 6.6	60.3 ± 6.4	<0.001	55.6 ± 8.1	56.3 ± 8.0	0.304	56.6 ± 6.7	60. 7 ± 6.0	<0.001
Weight (kg)	69.3 ± 8.5	73.3 ± 8.5	<0.001	56.7 ± 6.7	61.4 ± 8.6	<0.001	69.7 ± 8.6	74.1 ± 8.9	<0.001	56.9 ± 6.7	63.8 ± 9.4	<0.001
Height (cm)	169.0 ± 5.8	168.8 ± 5.7	0.502	156.0 ± 5.1	154.8 ± 5.5	<0.01	169.0 ± 5.8	168.8 ± 5.8	0.708	155.9 ± 5.2	154.8 ± 5.4	0.021
BMI (kg/m^2)	24.2 ± 2.5	25.7 ± 2.4	<0.001	23.3 ± 2.6	25.6 ± 3.2	<0.001	24.4 ± 2.5	26.0 ± 2.5	<0.001	23.4 ± 2.6	26.6 ± 3.5	<0.001
Fat mass (kg)	13.5 ± 3.9	16.2 ± 4.0	<0.001	15.7 ± 4.3	19.2 ± 5.6	<0.001	13.8 ± 3.9	17.3 ± 4.7	<0.001	15.8 ± 4.2	21.2 ± 6.0	<0.001
Lean mass (kg)	55.8 ± 6.1	57.1 ± 6.1	<0.01	40.9 ± 3.8	42.1 ± 4.5	<0.001	56.0 ± 6.1	56.9 ± 6.0	0.113	41.0 ± 3.9	42.5 ± 4.6	<0.001
Waist circumference (cm)	88.5 ± 12.1	100.7 ± 17.4	<0.001	82.5 ± 16.0	97.0 ± 20.5	<0.001	88.5 ± 11.5	119.9 ± 11.3	<0.001	82.3 ± 15.2	110.4 ± 18.0	<0.001
SBP (mm Hg)	121.0 ± 13.7	131.3 ± 14.7	<0.001	119.4 ± 15.7	132.1 ± 15.8	<0.001	122.2 ± 14.0	133.3 ± 16.1	<0.001	120.5 ± 15.9	134.2 ± 15.8	<0.001
DBP (mm Hg)	75.8 ± 8.4	80.9 ± 8.4	<0.001	74.6 ± 9.1	81.2 ± 9.1	<0.001	76.5 ± 8.6	80.3 ± 8.4	<0.001	75.2 ± 9.2	81.9 ± 9.2	<0.001
Glucose (mmol/L)	5.6 ± 1.2	6.5 ± 1.7	<0.001	5.2 ± 0.7	6.1 ± 1.4	<0.001	5.7 ± 1.3	6.4 ± 1.6	<0.001	5.3 ± 0.8	6.0 ± 1.4	<0.001
Cholesterol (mmol/L)	4.9 ± 0.8	5.0 ± 0.9	0.008	5.2 ± 0.8	5.3 ± 0.9	0.035	4.9 ± 0.8	5.1 ± 1.0	0.059	5.2 ± 0.8	5.3 ± 0.9	0.154
Triglyceride (mmol/L)	1.4 ± 0.7	2.4 ± 1.1	<0.001	1.2 ± 0.5	2.1 ± 1.0	<0.001	1.6 ± 0.9	2.1 ± 1.2	<0.001	1.3 ± 0.7	2.0 ± 0.9	<0.001
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.2 ± 0.3	<0.001	1.6 ± 0.4	1.2 ± 0.2	<0.001	1.4 ± 0.3	1.2 ± 0.3	<0.001	1.6 ± 0.4	1.3 ± 0.3	<0.001
LDL cholesterol (mmol/L)	3.2 ± 0.7	3.3 ± 0.8	0.040	3.4 ± 0.8	3.6 ± 0.8	<0.001	3.2 ± 0.7	3.3 ± 0.8	0.108	3.4 ± 0.8	3.6 ± 0.8	0.010
Corrected calcium (mmol/L)	0.2 ± 0.0	0.2 ± 0.0	0.590	0.2 ± 0.0	0.2 ± 0.0	0.236	0.2 ± 0.0	0.2 ± 0.0	0.032	0.2 ± 0.0	0.2 ± 0.0	0.517
Phosphorus (mmol/L)	1.2 ± 0.1	1.2 ± 0.1	0.036	1.4 ± 0.1	1.3 ± 0.1	0.054	1.2 ± 0.1	1.2 ± 0.1	0.043	1.4 ± 0.1	1.3 ± 0.1	0.024
Alkaline phosphatase (ukat/L)	1.1 ± 0.2	1.2 ± 0.3	0.133	1.2 ± 0.3	1.3 ± 0.3	<0.001	1.1 ± 0.2	1.2 ± 0.3	0.144	1.2 ± 0.3	1.3 ± 0.3	0.005
%												
Current smoker	32.0	31.8	ns	2.9	2.2	ns	54.0	48.8	ns	2.9	1.9	ns
Exercise >3/week	53.3	54.8	ns	48.2	43.2	ns	32.3	27.7	ns	48.2	38.9	ns

Values are presented as mean ± SD. *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 3 Correlation analysis between femoral neck BMD and clinical profiles

Clinical profiles	Men (≥40 years)		Postmenopausal women	
	Pearson correlation	*P*	Pearson correlation	*P*
Age (years)	−0.16	<0.001	−0.35	<0.001
Weight (kg)	0.31	<0.001	0.23	<0.001
Height (cm)	0.15	<0.001	0.25	<0.001
Smoking	−0.05	0.050	0.03	0.420
Alcohol	0.00	0.883	0.03	0.637
Exercise	0.06	0.011	0.10	0.002
Dairy product	−0.02	0.620	0.03	0.334

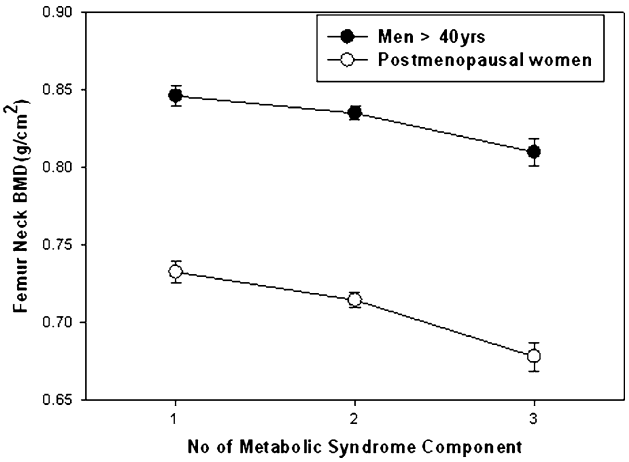

Fig. 1 Femoral neck BMD for subjects with different numbers of components of MS. Femoral neck BMD adjusted for age, weight, height, current smoking, and physical exercise. 1, no component; 2, two or fewer components; 3, three to five components

increasing numbers of MS components. Both body weight and BMI are strong protective factors for bone loss. BMI, an index of generalized obesity, can be regarded as one component of MS, whereas body weight is a principal factor that reflects mechanical loading. Therefore, our data were adjusted for body weight rather than BMI. In addition, waist circumference was the most important factor underlying this negative association. The association was particularly noted in men in all subgroups divided by 5-kg weight strata, further demonstrating its independence from body weight.

Our data showed that femoral neck BMD decreased in men over 40 years and postmenopausal women with MS after adjusting for body weight or all confounders. In the age-adjusted model, there was a difference between the diagnostic criteria. According to IDF criteria, all subjects with MS had abdominal obesity. Men over 40 years with MS according to IDF criteria had lower femoral neck BMD in the age-adjusted model. These findings are consistent with other studies of Asian populations. Although the mechanism underlying this relationship is not clear, the finding that waist circumference is a major contributor to this association suggests that visceral fat may be harmful to bone. The negative association between fat mass and BMD further supports this hypothesis, especially in men, consistent with other studies [19, 20]. It has been widely accepted that visceral fat is not only specialized with regard to the storage and mobilization of lipids but also a remarkable endocrine organ that releases adipokines and cytokines, including proinflammatory molecules such as

Table 4 Mean BMD by MS status

	Men (≥40 years)			Postmenopausal women		
	Without MS	MS	*P*	Without MS	MS	*P*
AHA/NHLBI criteria						
Crude	0.834 ± 0.004	0.826 ± 0.007	0.394	0.726 ± 0.004	0.689 ± 0.008	<0.001
Age-adjusted	0.833 ± 0.004	0.829 ± 0.007	0.682	0.721 ± 0.004	0.708 ± 0.008	0.152
Age- and weight-adjusted	0.837 ± 0.004	0.812 ± 0.007	0.002	0.726 ± 0.004	0.691 ± 0.008	<0.001
All adjusted[a]	0.839 ± 0.004	0.813 ± 0.008	0.002	0.721 ± 0.004	0.684 ± 0.008	<0.001
IDF criteria						
Crude	0.835 ± 0.003	0.792 ± 0.012	<0.001	0.723 ± 0.004	0.685 ± 0.011	0.001
Age-adjusted	0.835 ± 0.003	0.794 ± 0.012	0.001	0.720 ± 0.004	0.708 ± 0.010	0.281
Age- and weight-adjusted	0.837 ± 0.003	0.773 ± 0.011	<0.001	0.724 ± 0.004	0.679 ± 0.010	<0.001
All adjusted[a]	0.839 ± 0.003	0.766 ± 0.012	<0.001	0.719 ± 0.004	0.675 ± 0.011	<0.001

Values are presented as mean ± SD

[a] Adjusted for age, weight, height, current smoking, and physical exercise

Table 5 Multiple linear regression between femoral neck BMD and each MS component

	Men (≥40 years)		Postmenopausal women	
	Standardized ß	*P*	Standardized ß	*P*
Age (years)	−0.085	<0.001	−0.349	<0.001
Height (cm)	−0.122	<0.001	0.000	0.990
Weight (kg)	0.480	<0.001	0.324	<0.001
Current smoking	−0.043	0.060	−0.022	0.450
Physical exercise	0.048	0.040	0.097	0.001
Waist circumference	−0.250	<0.001	−0.138	<0.001
SBP	0.020	0.410	0.019	0.550
Glucose	0.043	0.060	−0.037	0.220
Triglyceride	−0.033	0.170	−0.097	0.001
HDL cholesterol	0.032	0.180	0.058	0.100

SBP systolic blood pressure

IL-6 and TNF-α [21, 22]. Many studies have shown that inflammatory cytokines play an important role in osteoclastic bone resorption and in the pathogenesis of osteoporosis [23–26]. The production of IL-1, IL-6, and/or TNF-α is positively correlated with bone loss in healthy premenopausal [27] and/or postmenopausal [7, 28, 29] women. Thus, it is feasible that low-grade inflammation derived by visceral adiposity in MS patients may be associated with bone loss, aside from the protective effects of general obesity.

General obesity and body weight are the strongest protectors against bone loss [10]. Our data suggest that lean mass size may explain this effect, especially in men. Increased lean mass exerts mechanistic stimuli on bone, resulting in the stimulation of bone formation. In reverse, increased lean mass may occur as a result of exercise. However, we did not observe any trends between fat mass/lean mass and BMD in postmenopausal women. This inconsistency may reflect sexual differences in the distribution of abdominal adipose tissue. Previous studies have reported that, for a given waist circumference, men have significantly higher amounts of visceral fat than do women [30–32]. In fact, our male subjects had higher waist circumferences. In addition, men in our study had higher lean mass than postmenopausal women. Therefore, the effects of visceral adiposity and lean mass on BMD may be emphasized in men.

We obtained some contradictory results regarding the association of MS and its components with bone. The negative association between MS and BMD noted in this study differs from the results of studies in Caucasians [9, 10], perhaps because the effects of abdominal obesity or visceral adiposity are reinforced in Koreans. Visceral adiposity has been linked to reduced bone mass [33], and Asians have more visceral adiposity than do Caucasians, despite a similar rate of general obesity [13, 14]. Therefore, general obesity and body weight, the strongest protective factors of bone loss [10], may exert a greater influence on Caucasians with MS, whereas Asians with MS may be more influenced by visceral adiposity. In relation to other components of MS—blood pressure, serum concentrations of glucose, triglyceride, and HDL cholesterol—there have been many conflicting results [11, 33–36]. In our study, triglyceride levels were negatively associated with femoral neck BMD only in postmenopausal women, and we did not observe a significant relationship between other components and femoral neck BMD. Our results suggest that MS components except waist circumference may not be an important factor for BMD.

Several potential limitations should be considered in the interpretation of our data. First, our study population was restricted to persons who underwent a private health examination in a university hospital. These subjects may not be representative of the general population, possibly contributing to selection bias. To minimize the possibility of bias, we applied strict exclusion criteria based on medical history and routine lab findings. Second, we used waist circumference as a surrogate for visceral obesity instead of directly measuring visceral fat. For a given waist circumference, body fat distribution differs significantly according to gender, menopausal status, and age. Subcutaneous fat is more common than abdominal visceral fat [37], particularly in premenopausal women; thus, waist circumferences may overestimate visceral obesity. However, a curvilinear relationship between waist circumference and visceral fat has been reported in older men and women [31]. Therefore, it is preferable to use waist circumference to evaluate visceral obesity in postmenopausal women and men older than 40 years. Third, we analyzed only femoral neck BMD. We do not have results for trochanter, total hip, and nonfemoral bone. It is possible that the effects of MS on BMD vary by anatomic site. Finally, because this was cross-sectional study, we could assess only the temporal relationship between MS and femoral neck BMD. Further prospective studies should be performed to determine a causal relationship between these variables.

In summary, our findings reveal that healthy Korean men older than 40 years and postmenopausal women with MS had lower BMD after adjusting for body weight. Waist circumference is the most important factor in this association, suggesting that inflammatory cytokines secreted from visceral fat might be an important factor in bone loss.

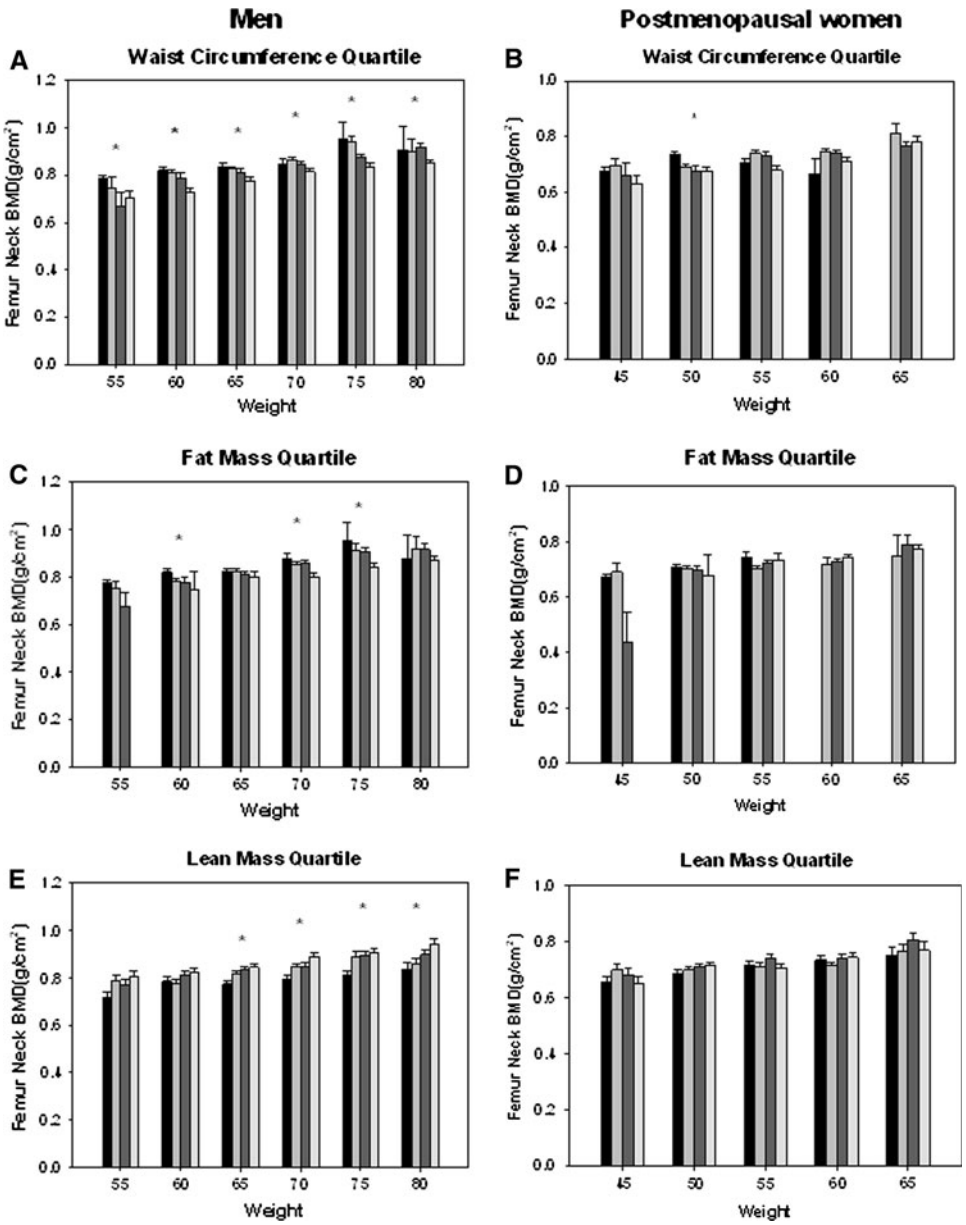

Fig. 2 Mean femoral neck BMD by quartile of waist circumference (**a**, **b**), fat mass (**c**, **d**), and lean mass (**e**, **f**) in 5-kg strata of body weight in men and postmenopausal women. Femoral neck BMD adjusted for age, height, current smoking, and physical exercise

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