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Association between metabolic risks and bone mineral density in postmenopausal women

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Summary

Background: Menopause is associated with osteoporosis and an increased risk of metabolic disorders, including obesity, abdominal adiposity, hyperlipidemia, hypertension, and insulin resistance, which may increase the risk of cardiovascular disease (CVD). Recent studies have demonstrated a correlation between fat, glucose, and bone metabolism which could contribute to CVD and osteoporosis. This study examined the association between metabolic risk factors and bone mineral density (BMD) in postmenopausal women. *Materials and Methods:* The authors determined the anthropometric values [waist-hip ratio (WHR), visceral fat area (VFA), body fat mass (BFM), and skeletal muscle mass (SMM)], lipid profile, fasting plasma glucose levels, high-sensitivity C-reactive protein levels, homeostasis model assessment of insulin resistance (HOMA-IR) scores, serum leptin and adiponectin levels, serum osteocalcin level [total osteocalcin (tOC) and undercarboxylated osteocalcin (ucOC)], and BMDs of the lumbar spine and femoral neck in 137 postmenopausal women. *Results:* There was a positive correlation between BFM, HOMA-IR score, serum leptin level, and BMD of the lumbar spine, and a negative correlation between BFM, total cholesterol, serum adiponectin, and BMD of the lumbar spine after adjusting for age, years since menopause, current alcohol consumption, and current smoking status. In a multiple regression analysis, serum adiponectin level and SMM were the most important predictors of the BMD of the lumbar spine. *Conclusion:* There were several metabolic risk variables that had a harmful effect on the BMD of the lumbar spine, but not the femoral neck. However, higher serum adiponectin levels were negatively correlated with BMD of the lumbar spine as adiposity decreased.

Key words: Adipokine; Bone mineral density; Metabolic syndrome; Osteocalcin; Postmenopause.

Introduction

Estrogen deficiency during menopause is associated with decreased bone mineral density (BMD) and increased metabolic risk factors such as higher body fat mass (BFM), abdominal obesity, hyperlipidemia, elevated blood pressure, insulin resistance, and increased levels of proinflammatory cytokines [1, 2]. Metabolic syndrome (MetS) is defined as a cluster of metabolic risks that increases the risk of cardiovascular disease (CVD)[3]. MetS and osteoporosis in postmenopausal women are associated with increased morbidity and mortality; thus, many preventive efforts have been initiated.

Previous studies have shown interrelationships among bone, fat, and glucose metabolism and that a higher body mass index (BMI) and hyperinsulinemia have a protective effect on BMD by increasing mechanical loading and ovarian estrogen production [4, 5]. However, new concepts describing the fat-bone relationship have been introduced. For example, adipocyte hyperplasia induces increased proinflammatory cytokine secretion which is associated with an increased risk of insulin resistance and osteoporotic fracture [1, 6]. In addition, adipocyte-derived hormones, including adipokines such as leptin and adiponectin have direct skeletal and centrally mediated effects [7].

Experimental animal studies have shown that osteocalcin which regulates fat and glucose metabolism mediates crosstalk between fat and glucose metabolism and bone. Osteocalcin is a protein secreted mainly by osteoblasts that is γ-carboxylatedin a vitamin K-dependent manner. Undercarboxylated osteocalcin (ucOC) acts as a hormone in the body, causing β-cell proliferation, increased insulin secretion and insulin activity, and adiponectin expression in adipocytes [8, 9]. Given that these adipocyte- and osteoblast-produced hormones play regulatory roles in both bone and energy metabolism (e.g. glucose and fat), metabolic risk factors may affect bone mass; however, clinical studies have drawn conflicting conclusions regarding the association of metabolic risk factors with BMD [10, 11]. This study was performed to examine the association between metabolic risk factors and BMD of the lumbar spine and femoral neck in postmenopausal women.

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Materials and Methods

The authors recruited 188 postmenopausal women at Saint Vincent's Hospital (Suwon, South Korea) between September 2009 and August 2010. This prospective and cross-sectional study was approved by the Institutional Review Board of The Catholic University of Korea. Informed consent was obtained from each participant. The exclusion criteria were: current cancer, laboratory evidence of kidney, liver, or thyroid disease, diabetes, bone-altering conditions (bilateral oophorectomy, hyperparathyroidism, nephrolithiasis, renal disease, or therapy with biphosphonates, calcitonin, estrogen, steroids, tamoxifen, or chemotherapy in the past year), and use of anti-obesity agents or non-compliance with diet or behavioral therapy for weight control. Postmenopausal women had at least 12 consecutive months of amenorrhea with no other medical cause for amenorrhea, and a follicle-stimulating hormone level > 40 mIU/mL at the time of enrollment. After the applying exclusion criteria, 137 women were enrolled in the present study.

Data on age, years since menopause, health behaviors, including smoking and alcohol consumption, and personal history of diabetes and hypertension were provided by the participants through questionnaires. Alcohol consumers were defined as those with at least weekly consumption of alcohol. Subjects were classified as having a smoking habit if they smoked at the time of the study.

Body size and composition were measured by bioelectrical impedance analysis (BIA) using a body composition analyzer. The data collected included waist-hip ratio (WHR), visceral fat area (VFA), skeletal muscle mass (SMM), percentage body fat (PBF), and body fat mass (BFM). The degree of accuracy of body size and composition measurements had a 1.0% coefficient of variation. Blood pressure was measured twice with a mercury sphygmomanometer after a ten-minute seated rest and the average of the two measurements was used for statistical analysis. BMI was calculated as weight (in kg) divided by height (in meters) squared.

Blood was collected by venipuncture after an overnight fast, and the total cholesterol, triglycerides, HDL-cholesterol, fasting plasma glucose (FPG), and high-sensitivity C-reactive protein (hs-CRP)levels were measured using an automatic analyzer. LDL-cholesterol was calculated according to Friedewald's formula [total cholesterol (mg/dL) – HDL-cholesterol (mg/dL) – total triglyceride (mg/dL)/5]. The coefficients of variation of total cholesterol, triglycerides, HDL-cholesterol, fasting glucose, and hs-CRP were 2.0, 2.2, 2.6, 2.3, and 6.75% (intra-assay) and 1.6, 2.6, 0.9, 1.6, and 7.91% (inter-assay), respectively. Serum fasting insulin was measured by a chemiluminescent immunometric assay with Immulite 2000 insulin. The coefficients of variation for insulin were 3.7% (intra-assay) and 8.1% (inter-assay). Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) index [insulin (mIU/ml) × fasting blood glucose (mg/dL) / 405].

The serum and plasma were separated from samples of whole blood by centrifugation at 300 rpm for five minutes, and aliquots were stored at -80°C until analysis. Subsequently, the authors used the samples together and determined the serum leptin, adiponectin, total osteocalcin (tOC), and ucOC levels. Serum leptin and adiponectin levels were measured with a human leptin immunoassay and human adiponectin ELISA kit. The coefficients of variation for leptin and adiponectin were 3.2 and 3.8% (intra-assay), and 3.0 and 5.1% (inter-assay), respectively. Serum tOC and ucOC levels were measured using osteocalcin ELISA and human undercarboxylated osteocalcin ELISA kits, respectively. The coefficients of variation for tOC and ucOC were 4.2 and ≤ 8.0% (intra-assay), and 4.0 and ≤ 10% (inter-assay), respectively.

The BMD of the lumbar spine and femur neck were measured in all women by the same technician using the same dual-energy X-ray absorptiometer. The precision coefficient of variation was 1.0%. Dual-energy X-ray absorptiometry measurements of the hip and spine are currently used to establish or confirm a diagnosis of osteoporosis. A real BMD is expressed in grams of mineral/cm^2 scanned.

Statistical analysis was performed using SPSS (version 18.0). All data are described as means ± standard deviation (SD) or numbers (%). Variables, such as WHR, blood pressure, fasting insulin, HOMA-IR, hs-CRP, and serum leptin and adiponectin, were logarithmically transformed prior to statistical analyses to approximate a normal distribution. The correlations between the anthropometric profile, lipid profile, glucose and insulin levels, blood pressure, serum adipokine level, and serum osteocalcin level were examined using Pearson's correlation test. Multiple linear regression analysis was performed to examine the influence of the different variables on the BMD of lumbar spine and femoral neck. The variables entered in the model were as follows: age, years since menopause, current smoking status, current alcohol consumption, BMI, WHR, VFA, BFM, total cholesterol, total triglycerides, HDL-cholesterol, LDL-cholesterol, FPG, HOMA-IR, hs-CRP, hypertension, serum leptin and adiponectin, serum tOC and ucOC, and treatment for hyperlipidemia. In all analyses, p value ≤ 0.05 was taken to indicate statistical significance.

Results

The baseline characteristics of the study subjects are presented in Table 1. The mean age of the participants was 55.6 ± 5.8 years. The mean time since menopause was 7.1 ± 5.6 years, and the mean BMI was 23.8 ± 2.9 kg/m^2. The BMD of the lumbar spine and femoral neck was 0.896 ± 0.124 and 0.799 ± 0.161 g/cm^2, respectively.

When assessing correlative factors, the authors found that the BMDs of the lumbar spine and femoral neck were negatively correlated with age (r = -0.176 and p = 0.002, and r = -0.140 and p = 0.049, respectively) and years since menopause (r = -0.204 and p = 0.009, and r = -0.157 and p = 0.034, respectively), and positively correlated with BMI (r = 0.262 and p= 0.001 and r = 0.243 and p = 0.002, respectively, Table 2). In addition, the BMD of the lumbar spine was positively correlated with BFM (r = 0.169 and p = 0.024), SMM (r = 0.311 and p < 0.001), fasting insulin (r = 0.229 and p = 0.004), HOMA-IR score (r = 0.229 and p = 0.004), serum leptin level (r = 0.180 and p = 0.017), and was negatively correlated with HDL-cholesterol level (r = -0.194 and p = 0.011) and serum adiponectin level (r = -0.221 and p = 0.005). The BMD of the femoral neck was positively correlated with PBF (r = 0.188 and p = 0.014), BFM (r = 0.231 and p = 0.003), FPG level (r = 0.171 and p = 0.023), fasting insulin level (r = 0.211 and p = 0.007), HOMA-IR score (r = 0.214 and p = 0.006), and serum leptin level (r = 0.196 and p = 0.011; Table 2).

When adjusted for age, years since menopause, current

alcohol consumption, and current smoking status, BFM, serum TC level and serum adiponectin level were negatively correlated with the lumbar spine, while SMM was positively correlated with the BMD of lumbar spine (p = 0.010, p = 0.041, p = 0.042, and p = 0.005, respectively; Table 3). However, there were no metabolic risk factors associated with the femoral neck BMD (Table 3). A multiple regression analysis was performed to identify independent variables that may affect BMDs at the lumbar spine and femoral neck. Among the independent variables, SMM and serum adiponectin levels were the most important predictors of the BMD of the lumbar spine (B = 0.234, p = 0.005 and B = -0.216 and p= 0.010; Table 3). However, there were no predictors of BMD at the femoral neck (Table 3).

Table 1. — Clinical characteristics of study participants*.

Variables	All (N=137)
Age (years)	55.6 ± 5.8
Years since menopause (years)	7.1 ± 5.6
Height (cm)	156.2 ± 5.0
Weight (kg)	58.0 ± 7.2
FSH (mIU/mL)	52.1 ± 16.8
Estradiol (pg/mL)	17.5 ± 18.7
BMI (kg/m^2)	23.8 ± 2.9
WHR†	0.89 ± 0.05
PBF (%)	33.5 ± 5.9
VFA (cm^2)	99.6 ± 22.2
SMM (kg)	20.7 ± 2.6
BFM (kg)	19.7 ± 5.2
Total cholesterol (mg/dL)	205.0 ± 37.1
Total triglycerides (mg/dL)	121.1 ± 66.0
HDL-cholesterol (mg/dL)	49.8 ± 12.5
LDL-cholesterol (mg/dL)	130.5 ± 35.3
FPG (mg/dL)	95.2 ± 13.2
Fasting insulin†(μIU/mL)	3.7 ± 4.2
HOMA-IR†	0.91 ± 1.09
hs-CRP†(mg/dL)	0.11 ± 0.11
SBP (mmHg)	123.7 ± 16.3
DBP (mmHg)	77.3 ± 9.9
Serum tOC (ng/mL)	16.6 ± 6.4
Serum ucOC (ng/mL)	5.9 ± 3.1
Serum adiponectin* (ng/mL)	15.9 ± 7.7
Serum leptin* (ng/mL)	9.0 ± 4.8
Lumbar spine	
BMD (g/cm^2)	0.896 ± 0.124
T-score	-0.92 ± 1.06
Z-score	0.26 ± 0.93
Femoral neck	
BMD (g/cm^2)	0.799 ± 0.161
T-score	-0.36 ± 0.77
Z-score	0.26 ± 0.74
Current alcohol consumption (%)	
No	114 (83.2)
Yes	23 (16.8)
Current smoking status (%)	
No	135 (98.5)
Yes	2 (1.5)
Hypertension or treatment for hypertension (%)	
No	104 (75.9)
Yes	33 (24.1)
Lipid-lowering therapy (%)	
No	120 (87.6)
Yes	17 (12.4)

Data are presented as the mean ± SD or number (percentage and its 95% confidence interval [CI]). †Values were analyzed after logarithmic transformation. FSH=follicle stimulating hormone, BMI=body mass index, WHR=waist-to-hip ratio, PBF=percent body fat, VFA=visceral fat area, SMM=skeletal muscle mass, BFM=body fat mass, HDL=high-density lipoprotein, LDL=low-density lipoprotein, FPG=fasting plasma glucose,HOMA-IR=homeostasis model assessment of insulin resistance, hs-CRP=high sensitivity C-reactive protein, SBP=systolic blood pressure, DBP=diastolic blood pressure, tOC=total osteocalcin, ucOC=undercarboxylated osteocalcin.

Discussion

Osteoporosis and metabolic risk factors, including obesity, abdominal adiposity, insulin resistance, hyperlipidemia, and hypertension are major causes of morbidity and mortality in postmenopausal women [1, 2]. Previous studies indicated that the metabolism of fat, glucose, and bone is regulated by distinct unrelated mechanisms. However, recent investigations have discovered hormones secreted from bone and fat that have led to interesting new concepts linking fat, glucose, and bone metabolism [12].

A higher fat mass has a protective effect on bone mass by increasing mechanical loading and hyperinsulinemia, which results in ß-cell hypersecretion [4]. Hyperinsulinemia increases free sex hormone level by decreasing sex hormone-binding globulin production in the liver and increasing both ovarian estrogen production and osteoblast activity [7]. However, recent studies have shown that increased adiposity is associated with a deleterious effect on bone, and several mechanisms linking fat and bone metabolism have been introduced. For example, adipocytes secrete proinflammatory cytokine including tumor necrosis factor-α, interleukin (IL)-1ß, IL-6, and hs-CRP, indicating an association between obesity and low-grade chronic inflammation. These inflammatory cytokines are not only important factors in the development and progression of obesity-related metabolic risk factor, they are also key mediators osteoclast differentiation and bone resorption by stimulating osteoclast activity via the receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK/osteoprotogerin (OPG) pathways [6, 13]. In a clinical study of older Puerto Rican adults, higher abdominal fat mass was associated with poor bone health in the lumbar spine and total femur, and was identified as a risk factor for osteoporosis [14]. Moreover, adipocytes and osteoblasts are derived from the same pool of mesenchymal stem cells (MSCs). Adipocyte-secreting proinflammatory cytokines enhance bone marrow adipogenesis and exert a lipotoxic effect on osteoblast[15]. In addition, leptin and adiponectin representative adipokines secreted by adipocytes, play a role in energy metabolism, and bone metabolism. Leptin, which regulates appetite and energy expenditure,is associated with central obesity, stimulating proinflammatory cytokines, and

Table 2. — Coefficients of correlation between lumbar spine and femoral neck BMD and body composition parameters, lipid profile, glucose metabolism-related parameters, hs-CRP, blood pressure, serum adipokine, and osteocalcin.

	Lumbar spine		Femoral neck	
	r	*p*	*r*	*p*
Age (years)	-0.176**	0.002	-0.130*	0.065
Years since menopause	-0.204**	0.009	-0.157*	0.034
BMI (kg/cm²)	0.262**	0.001	0.243**	0.002
WHR	0.093	0.141	0.113	0.094
VFA (cm²)	0.080	0.177	0.110	0.100
PBF (%)	0.049	0.285	0.188*	0.014*
BFM (kg)	0.169*	0.024	0.231**	0.003
SMM (kg)	0.311**	<0.001	0.120	0.082
TC (mg/dL)	-0.122	0.078	-0.102	0.117
TG (mg/dL)	0.012	0.445	0.065	0.224
HDL-C (mg/dL)	-0.194	0.011	-0.129	0.066
LDL-C (mg/dL)	-0.069	0.211	-0.095	0.134
FPG (mg/dL)	0.106	0.109	0.171*	0.023
Insulin (μIU/mL)	0.229**	0.004	0.211**	0.007
HOMA-IR	0.229**	0.004	0.214**	0.006
hs-CRP (mg/dL)	0.081	0.173	0.039	0.326
SBP (mmHg)	0.138	0.054	0.080	0.176
DBP (mmHg)	0.053	0.269	0.071	0.204
Adiponectin (ng/mL)	-0.221*	0.005	-0.091	0.146
Leptin (ng/mL)	0.180*	0.017	0.196*	0.011
tOC (ng/mL)	-0.043	0.308	0.114	0.092
ucOC (ng/mL)	0.014	0.436	-0.026	0.380

*Statistical analyses by Pearson's correlation test. * $p < 0.05$, ** $p < 0.01$.*

insulin resistance. In contrast, adiponectin has anti-inflammatory properties resulting in insulin-sensitizing and antiatherogenic effects, and serum adiponectin levels are lower among obese individuals[16]. Thus, leptin and adiponectin mediate the effects of fat mass on bone [17].

The effect of leptin on bone metabolism has both stimulatory and inhibitory effects. Leptin receptor is expressed on osteoblast, and it promotes osteogenesis and differentiation in bone marrow MSCs [18]. Leptin also inhibits adipogenesis, stimulates the differentiation of osteoblasts from blood stem cells in bone marrow, and suppresses the osteoclastic activity of human peripheral blood mononuclear cells [19, 20]. However, leptin decreases bone mass by inhibiting hypothalamic neuropeptide Y and the sympathetic nervous system by stimulating RANKL [21, 22]. Due to these conflicting central and peripheral mechanisms, many clinical studies have reported no correlation between leptin and BMD and that leptin is not an independent predictor of fracture risk [23].

Adiponectin also influences osteoblastogenesis and osteoclastogenesis by different pathways. Adiponectin promotes osteoblastic proliferation and increases matrix mineralization via the p38 mitogen-activated protein kinase pathway [24]. In contrast, another study reported that increased adiponectin levels activate RANKL and inhibit

Table 3. — *Multiple regression analysis for metabolic risk factors and the BMD of lumbar spine and femoral neck.*

	Lumbar spine				Femoral neck			
	A1		A2		A1		A2	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*p*	B (95% CI)	*P*
WHR	-0.261 (-1.386 ~ 0.140)	0.109	-0.409 (-2.276 ~ 0.324)	0.140	-0.154 (-1.501 ~ 0.543)	0.355	-0.148 (-1.488 ~ 0.565)	0.375
VFA (cm²)	-0.139 (-0.002 ~ 0.001)	0.345	0.238 (-0.001 ~ 0.004)	0.266	-0.035 (-0.002 ~ 0.002)	0.814	0.211 (-0.002 ~ 0.005)	0.410
BFM (kg)	-0.333 (-0.012 ~ -0.002)	0.010	-0.190 (-0.013 ~ 0.004)	0.318	0.047 (-0.006 ~ 0.009)	0.727	-0.019 (-0.004 ~ 0.007)	0.957
SMM (kg)	0.240 (0.003 ~ 0.019)	0.005	0.234 (0.003 ~ 0.008)	0.005	0.041 (-0.008 ~ 0.013)	0.648	0.017 (-0.011 ~ 0.013)	0.865
TC (mg/dL)	-0.170 (-0.001 ~ 0.000)	0.041	0.343 (-0.005 ~ 0.008)	0.726	-0.139 (-0.001 ~ 0.000)	0.102	1.277 (-0.003 ~ 0.015)	0.206
TG (mg/dL)	-0.092 (-0.001 ~ 0.000)	0.310	-0.165 (-0.001 ~ 0.000)	0.068	-0.024 (-0.001 ~ 0.000)	0.794	-0.114 (-0.001 ~ 0.000)	0.234
HDL-C (mg/dL)	-0.133 (-0.003 ~ 0.000)	0.117	-0.114 (-0.003 ~ 0.001)	0.191	-0.069 (-0.003 ~ 0.001)	0.428	-0.080 (-0.003 ~ 0.001)	0.352
LDL-C (mg/dL)	-0.100 (-0.001 ~ 0.000)	0.223	-0.102 (-0.001 ~ 0.000)	0.210	-0.120 (-0.001 ~ 0.000)	0.151	-0.118 (-0.001 ~ 0.000)	0.155
FPG (mg/dL)	0.063 (-0.001 ~ 0.002)	0.448	0.089 (-0.001 ~ 0.002)	0.274	0.138 (0.000 ~ 0.004)	0.101	0.137 (0.000 ~ 0.004)	0.101
HOMA-IR	0.054 (-0.015 ~ 0.028)	0.567	0.012 (-0.021 ~ 0.024)	0.908	0.098 (-0.013 ~ 0.042)	0.307	0.059 (-0.021 ~-0.038)	0.564
hs-CRP (mg/dL)	0.080 (-0.087 ~ 0.254)	0.335	0.061 (-0.103 ~ 0.230)	0.454	0.034 (-0.184 ~ 0.276)	0.693	0.027 (-0.203 ~ 0.275)	0.767
Adiponectin (ng/mL)	-0.169(-0.006 ~ -0.001)	0.042	-0.216 (-0.008 ~-0.002)	0.010	-0.036(-0.012 ~ 0.008)	0.670	0.049 (-0.010 ~-0.007)	0.516
Leptin (ng/mL)	0.054 (-0.009 ~ 0.005)	0.574	0.149 (-0.023 ~-0.003)	0.136	0.101(-0.027 ~ 0.083)	0.303	0.128 (-0.003 ~ 0.008)	0.186
tOC (ng/mL)	-0.035 (-0.004 ~ 0.003)	0.668	-0.073 (-0.004 ~ 0.002)	0.357	0.126(-0.001 ~ 0.007)	0.136	0.122 (-0.001 ~ 0.007)	0.144
ucOC (ng/mL)	0.048 (-0.005 ~ 0.008)	0.558	0.066 (-0.004 ~ 0.009)	0.424	0.004(-0.009 ~ 0.008)	0.966	-0.011 (-0.001 ~ 0.009)	0.900
Hypertension	0.170 (-0.018 ~ 0.108)	0.161	0.240 (-0.013 ~-0.152)	0.099	0.044(-0.044 ~ 0.074)	0.619	-0.011 (-0.010 ~ 0.009)	0.900
Lipid lowering therapy	0.057 (-0.006 ~ 0.119)	0.077	0.025 (-0.041 ~ 0.090)	0.754	0.014 (-0.029 ~ 0.057)	0.645	0.014 (-0.032 ~ 0.060)	0.543

A1 – Adjusted for age, years since menopause, BMI, current smoking status, and current alcohol consumption
A2 –Adjusted for age, years since menopause, BMI, current smoking status, and current alcohol consumption, WHR, VFA, BFM, SMM, TC, TG, HDL-C, LDL-C, FPG, HOMA-IR, hs-CRP, adiponectin, leptin, tOC, ucOC, hypertension, and lipid lowering therapy.

OPG resulting in osteoclastogenesis [25].

However, in a meta-analysis, Liu *et al.* reported an inverse relationship between serum adiponectin levels and BMD, although higher serum adiponectin levels were associated with lower adiposity [23]. They also stated that the conflicting result obtained in biological and clinical studies could be accounted for by the difference in serum adiponectin levels due to age, menopausal status, hormone levels, smoking, and diabetic status, and by the gap between serum and bone marrow levels of adiponectin which has a paracrine effect [23]. Similar to the results reported by Liu *et al.*, the present study showed that BFM and adiponectin, but not leptin, have a negative effect on BMD at the lumbar spine and serum adiponectin is independent factor affecting the BMD of the lumbar spine.

Osteocalcin is a bone matrix protein expressed by osteoblasts and a known marker of bone formation. Osteocalcin has three glutamic acid residues, which are converted to γ-carboxyglutamic acid by γ-carboxylase, which uses vitamin K as a cofactor. Vitamin K is thus essential for the γ-carboxylation of osteocalcin, and it confers increased affinity for calcium and hydroxyapatite in the bone extracellular matrix. ucOC lacks structural integrity and the ability to bind hydroxyapatite. ucOC migrates via the blood stream and has non-skeletal effects that induce the proliferation of pancreatic β-cells and increase insulin and adiponectin secretion, resulting in insulin sensitivity and fat metabolism [26]. Vitamin K influences the carboxylation of osteocalcin and indirectly increases osteoblastic activity and bone formation; it also prevents bone loss [27]. It is thought that a low vitamin K level and high ucOC level are associated with increased insulin sensitivity, and a negative effect on bone density; however, human studies supporting this hypothesis are lacking. Indeed, the present study showed no correlation between ucOC and lumbar and femoral neck BMDs.

Menopause is associated with a decreased SMM due to reduced physical activity, reduced protein intake, increased oxidative stress, and increased myokine secretion which have an anti-estrogen-like effect and a negative effect on BMD [28, 29]. Increased muscle mass is associated with metabolically healthy obesity and increased biomechanical loading on bones, resulting in BMD maintenance and a reduced fracture risk [30]. The present study showed that a higher SMM not only had a positive effect on lumbar spine BMD, but also was an independent factor affecting lumbar spine BMD. Increased SMM is considered to be an important protective factor in maintaining bone mass.

In vitro and in vivo studies indicated that cholesterol and its metabolites can influence the functional activity of osteoblasts. Oxidized lipids and hyperlipidemia inhibit osteoblastic differentiation in bone, and reduced bone mineralization was observed in mice and rabbits fed an atherogenic high-fat diet [31, 32]. In a recent clinical study, Makovey *et al.* showed an inverse relationship between lumbar spine and serum TC and LDL-cholesterol levels in postmenopausal women [33]. The present study indicated the negative correlation between serum TC and the BMD of the lumbar spine (but not femoral neck), consistent with the findings of Makovey *et al.* [33].

In the present study,VFA, HOMA-IR score, and blood pressure were not correlated with the BMDs of the lumbar spine and femoral neck although negative effects on bone density have been demonstrated in several clinical studies [34, 35].

The present study also indicates an association between previously identified metabolic risk factors including a high BFM, TC level and low SMM, and low BMD of the lumbar spine (but not the femoral neck). These metabolic risk factors are associated with oxidative stress and estrogen deficiency in menopause, which causes oxidative stress [36-38]. Estrogen has osteoprotective effects on trabecular bone formation rather than cortical bone via estrogen receptor-alpha [39]. The lumbar spine is primarily composed of trabecular bone, while the femoral neck is predominantly cortical bone. Thus, postmenopausal osteoporosis of the lumbar spine is more heavily influenced by postmenopausal metabolic risk factors than that of the femoral neck.

This study has several limitations. First, due to its cross-sectional design, the authors failed to determine the causal mechanism of metabolic risks that affect BMD. Second, the small sample size limited the authors' interpretation of the association between metabolic risk factors and BMD. Thus, the authors organized to recruit a greater number of subjects for a more extensive analysis. Third, although many adjusting factors were applied and statistically controlled, the possibility of hidden adjusting factors cannot be ruled out.

The main strength of the present study is that the authors investigated the effects of various metabolic risk factors, adipokines, and bone-produced hormones on the BMDs of the lumbar spine and femoral neck in postmenopausal women. Various metabolic risk factors had a negative effect on the BMD of the lumbar spine, while serum adiponectin had a conflict effect on the BMD of the lumbar spine as adiposity decreased.

In conclusion, the present results suggest that persistent pre- and peri-menopausal obesity has a negative effect on metabolic changes, as well as postmenopausal BMD. Select postmenopausal women who have some metabolic risk factors should be followed up regarding their individual risks for osteoporosis and osteoporotic fracture. To prevent bone loss during menopause, these women should participate in an adequate muscle-strengthening and fat-burning exercise program pre- and peri-menopause. Conflicting and inconclusive definitive mechanisms regulating the effects of adipokines and bone-secreted hormones should be clarified in future human studies.

References

[1] Carr M.C.: "The emergence of the metabolic syndrome with menopause". *J. Clin. Endocrinol. Metab.,* 2003, *88*, 2404.

[2] Kanis J.A., McCloskey E.V., Johansson H., Cooper C., Rizzoli R., Reginster J.Y., *et al.*: "European guidance for the diagnosis and management of osteoporosis in postmenopausal women". *Osteoporos. Int.,* 2013, *24*, 23.

[3] Eckel R.H., Grundy S.M., Zimmet P.Z.: "The metabolic syndrome". *Lancet,* 2005, *365*, 1415.

[4] Klein-Nulend J., Bacabac R.G., A.D. Bakker: "Mechanical loading and how it affects bone cells: the role of the osteocyte cytoskeleton in maintaining our skeleton". *Eur. Cell. Mater.,* 2012, *24*, 278.

[5] Cornish J., Callon K.E., Reid I.R.: "Insulin increases histomorphometric indices of bone formation In vivo". *Calcif. Tissue Int.,* 1996, *59*, 492.

[6] Mundy G.R.: "Osteoporosis and inflammation". *Nutr. Rev.,* 2007, *65*, S147.

[7] Reid I.R.: "Relationships between fat and bone". *Osteoporos. Int.,* 2008, *19*, 595.

[8] Lee N.K., Sowa H., Hinoi E., Ferron M., Ahn J.D., Confavreux C., *et al.*: "Endocrine regulation of energy metabolism by the skeleton". *Cell,* 2007, *130*, 456.

[9] Ferron M., Wei J., Yoshizawa T., Del Fattore A., DePinho R.A., Teti A., *et al.*: "Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism". *Cell,* 2010, *142*, 296.

[10] Fodor D., Vesa S., Albu A., Simon S., Craciun A., Muntean L.: "The relationship between the metabolic syndrome and its components and bone status in postmenopausal women". *Acta Physiol. Hung.,* 2014, *101*, 216.

[11] Yoldemir T., Erenus M.: "The impact of metabolic syndrome on bone mineral density in postmenopausal women". *Gynecol Endocrinol.,* 2012, *28*, 391.

[12] Lello S., Capozzi A., Scambia G.: "Osteoporosis and cardiovascular disease: an update". *Gynecol. Endocrinol.,* 2015, *31*, 590.

[13] Shoelson S.E., Herrero L., Naaz A.: "Obesity, inflammation, and insulin resistance". *Gastroenterology,* 2007, *132*, 2169.

[14] Bhupathiraju S.N., Dawson-Hughes B., Hannan M.T., Lichtenstein A.H., Tucker K.L.: "Centrally located body fat is associated with lower bone mineral density in older Puerto Rican adults". *Am. J. Clin. Nutr.,* 2011, *94*, 1063.

[15] Rosen C.J., Bouxsein M.L.: "Mechanisms of disease: is osteoporosis the obesity of bone?" *Nat. Clin. Pract. Rheumatol.,* 2006, *2*, 35.

[16] Piya M.K., McTernan P.G., Kumar S.: "Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin". *J. Endocrinol.,* 2013, *216*, T1.

[17] Liu P.Y., J.Z. Ilich, K. Brummel-Smith, and S. Ghosh: "New insight into fat, muscle and bone relationship in women: determining the threshold at which body fat assumes negative relationship with bone mineral density". *Int J Prev Med.* 2014, *5*, 1452.

[18] Iwamoto I., Douchi T., Kosha S., Murakami M., Fujino T., Nagata Y.: "Relationships between serum leptin level and regional bone mineral density, bone metabolic markers in healthy women". *Acta Obstet. Gynecol. Scand.,* 2000, *79*, 1060.

[19] Holloway W.R., Collier F.M., Aitken C.J., Myers D.E., Hodge J.M., Malakellis M., *et al.*: "Leptin inhibits osteoclast generation". *J. Bone Miner. Res.,* 2002, *17*, 200.

[20] Xu J., Wu T., Zhong Z., Zhao C., Tang Y., Chen J.: "Effect and mechanism of leptin on osteoblastic differentiation of hBMSCs". *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi,* 2009, *23*, 140.

[21] Allison S.J., Baldock P.A., Herzog H.: "The control of bone remodeling by neuropeptide Y receptors". *Peptides,* 2007, *28*, 320.

[22] Elefteriou F., Ahn J.D., Takeda S., Starbuck M., Yang X., Liu X., *et al.*: "Leptin regulation of bone resorption by the sympathetic nervous system and CART". *Nature,* 2005, *434*, 514.

[23] Liu Y., Song C.Y., Wu S.S., Liang Q.H., Yuan L.Q., Liao E.Y.: "Novel adipokines and bone metabolism". *Int. J. Endocrinol.,* 2013, *2013*, 895045.

[24] Luo X.H., Guo L.J., Yuan L.Q., Xie H., Zhou H.D., Wu X.P., *et al.*: "Adiponectin stimulates human osteoblasts proliferation and differentiation via the MAPK signaling pathway". *Exp. Cell. Res.,* 2005, *309*, 99.

[25] Kanazawa I.: "Adiponectin in metabolic bone disease". *Curr. Med. Chem.,* 2012, *19*, 5481.

[26] Neve A.,Corrado A., Cantatore F.P.: "Osteocalcin: skeletal and extra-skeletal effects". *J. Cell. Physiol.,* 2013, *228*, 1149.

[27] Gundberg C.M., Lian J.B., Booth S.L.: "Vitamin K-dependent carboxylation of osteocalcin: friend or foe?". *Adv. Nutr.,* 2012, *3*, 149.

[28] Messier V., Rabasa-Lhoret R., Barbat-Artigas S., Elisha B., Karelis A.D., Aubertin-Leheudre M.: "Menopause and sarcopenia: A potential role for sex hormones". *Maturitas,* 2011, *68*, 331.

[29] Hamrick M.W.: "A role for myokines in muscle-bone interactions". *Exerc. Sport Sci. Rev.,* 2011, *39*, 43.

[30] Bergmann P., Body J.J., Boonen S., Boutsen Y., Devogelaer J.P., Goemaere S., *et al.*: "Loading and skeletal development and maintenance". *J. Osteoporos.,* 2010, *2011*, 786752.

[31] Parhami F., Garfinkel A., Demer L.L.: "Role of lipids in osteoporosis". *Arterioscler. Thromb. Vasc. Biol.,* 2000, *20*, 2346.

[32] Parhami F., Tintut Y., Beamer W.G., Gharavi N., Goodman W., Demer L.L.: "Atherogenic high-fat diet reduces bone mineralization in mice". *J. Bone Miner. Res.,* 2001, *16*, 182.

[33] Makovey J., Chen J.S., Hayward C., Williams F.M., Sambrook P.N.: "Association between serum cholesterol and bone mineral density". *Bone,* 2009, *44*, 208.

[34] Yazici S., Yazici M., Korkmaz U., Engin Erkan M., Erdem Baki A., Erden I., *et al.*: "Relationship between blood pressure levels and bone mineral density in postmenopausal Turkish women". *Arch. Med. Sci.,* 2011, *7*, 264.

[35] Arikan S., Tuzcu A., Bahceci M., Ozmen S., Gokalp D.: "Insulin resistance in type 2 diabetes mellitus may be related to bone mineral density". *J. Clin. Densitom.,* 2012, *15*, 186.

[36] Roberts C.K., Sindhu K.K.: "Oxidative stress and metabolic syndrome". *Life Sci.,* 2009, *84*, 705.

[37] Meng S.J., Yu L.J.: "Oxidative stress, molecular inflammation and sarcopenia". *Int. J. Mol. Sci.,* 2010, *11*, 1509.

[38] Sanchez-Rodriguez M.A., Zacarias-Flores M., Arronte-Rosales A., Correa-Munoz E., Mendoza-Nunez V.M.: "Menopause as risk factor for oxidative stress". *Menopause,* 2012, *19*, 361.

[39] Kondoh S., Inoue K., Igarashi K., Sugizaki H., Shirode-Fukuda Y., Inoue E., *et al.*: "Estrogen receptor alpha in osteocytes regulates trabecular bone formation in female mice". *Bone,* 2014, *60*, 68.

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