ORIGINAL ARTICLE
Endocrinology, Nutrition & Metabolism

JKMS

https://doi.org/10.3346/jkms.2017.32.1.70 • J Korean Med Sci 2017; 32: 70-76

Association between Lumbar Bone Mineral Density and Carotid Intima-Media Thickness in Korean Adults: a Cross-sectional Study of Healthy Twin Study

Jinyoung Shin,[1]* Joo-Hyun Park,[2]* Yun-Mi Song,[1] Kayoung Lee,[3] and Joohon Sung[4,5]

[1]Department of Family Medicine, Samsung Medical Center, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Family Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea; [3]Department of Family Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea; [4]Department of Epidemiology, School of Public Health, Seoul National University, Seoul, Korea; [5]Institute of Health and Environment, Seoul National University, Seoul, Korea

*Jinyoung Shin and Joo-Hyun Park contributed equally to this work.

Received: 1 July 2016
Accepted: 8 October 2016

Address for Correspondence:
Yun-Mi Song, MD
Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea
E-mail: yunmisong@skku.edu

Funding: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Science, ICT and Future Planning (2014R1A2A2A01002705). This study was supported by Samsung Biomedical Research Institute (SMO1161741).

Bone mineral density (BMD) has been suggested to be associated with atherosclerosis. In the present study, we evaluated the association between lumbar BMD and the segments of carotid intima-media thickness (CIMT), a surrogate marker of subclinical atherosclerosis, in Korean adults, with consideration of sex and menopause status. Among 1,679 Korean adults who enrolled in a Healthy Twin Study, 723 men, 690 premenopausal women, and 266 postmenopausal women measured the CIMT at the common carotid artery intima-media thickness (CCA-IMT), carotid bifurcation intima-media thickness (BIF-IMT), internal carotid artery intima-media thickness (ICA-IMT) using B-mode ultrasound and lumbar BMD using dual-energy X-ray absorptiometry. The composite CIMT was calculated as the mean value of three CIMTs. The association was evaluated using linear mixed models. In premenopausal women, lumbar BMD was positively associated with composite CIMT and with CCA-IMT ($P = 0.008$ and 0.002, respectively). However, no association was observed between BMD and CIMT in men or in postmenopausal women. Stratified analysis revealed the effect of body mass index (BMI) on the association between BMD and CIME. The positive association in premenopausal women persisted only in low BMI (< 25 kg/m^2) group, whereas a positive association appeared at high BMI (≥ 25 kg/m^2) group in men. A high lumbar BMD may indicate an elevated risk of subclinical atherosclerosis in premenopausal women and men with high BMI.

Keywords: Bone Mineral Density; Carotid Arteries; Osteoporosis; Atherosclerosis

INTRODUCTION

Low bone mineral density (BMD) and atherosclerosis are degenerative changes commonly accompanying aging. Low BMD increases the risk of osteoporotic fracture for the elderly, which results in functional decline and increased mortality (1,2). Atherosclerosis occurs in the subendothelial space (i.e., the intima) of medium-sized arteries and is triggered by mechanotransduction and inflammatory processes in endothelial cells (3).

A growing body of evidence indicates that BMD is associated with atherosclerosis. This association has been proposed to be explained by a number of biological mechanisms including similar processes of bone and vascular mineralization (4), osteoblastic differentiation by lipid oxidation (5), and shared risk factors including lifestyle factors (6), estrogen deficiency (7), and vitamin D receptor polymorphisms (8,9).

The association between BMD and carotid intima-media thickness (CIMT) as a surrogate marker of subclinical atherosclerosis has been evaluated in many studies (8,10-16). However, these studies have yielded inconsistent findings. Some studies found an inverse association (10,13), whereas others found a positive (12) or no association (11,14,16).

We thought that the association between BMD and CIMT may differ according to sex or menopausal status because the prevalence of atherosclerotic vascular disease and the distribution of BMD tend to differ according to these factors (17,18). In addition, the identification of segment-specific associations between intima-media thickness (IMT) and cardiovascular disease (19,20) suggests that the association between BMD and CIMT may vary according to carotid artery segment.

pISSN 1011-8934
eISSN 1598-6357

To resolve these discrepancies, we evaluated the association between BMD and segment-specific CIMT according to sex and menopausal status with adjustment for a wide range of cardiovascular risk factors.

MATERIALS AND METHODS

Subjects and study design

The study subjects consisted of 1,820 individuals (754 men, 734 premenopausal women, and 332 postmenopausal women) aged 18 to 83 years old. All subjects had undergone B-mode ultrasound for CIMT measurement, in addition to dual-energy X-ray absorptiometry for BMD measurement of the lumbar spine, between April 2009 and February 2012. All examinations took place at the same institution.

The study subjects were the participants in the Healthy Twin Study, a nationwide population-based cohort study that has been conducted as part of the Korean Genome Epidemiology Study since 2005. The participants are composed of twins and their first-degree family members who were voluntarily recruited through a nationwide media advertisement and mailing campaign. Details about the study design and methodology of the Healthy Twin Study have been previously published (21,22).

Subjects with missing data (29 cases) and who had received osteoporosis treatment (51 cases) were excluded. In addition, subjects with a history of stroke (3 cases), myocardial infarction (21 cases), or cancer (37 cases) were also excluded. Finally, 1,679 subjects (723 men, 690 premenopausal women, and 266 postmenopausal women) were analyzed.

CIMT measurements

CIMT measurements were performed according to standardized protocols. Briefly, the CIMT was measured during the end-diastolic phase between the P and Q waves from the electrocardiogram trace using an automated IMT package using an automated IMT package of a high-resolution B-mode ultrasound machine (VIVID; General Electric, Horten, Norway) and an EKO 7 system (Samsung Medison Co., Ltd., Cypress, CA, USA) equipped with a seven-MHz linear transducer. CIMT scanning was performed on the far walls of the following three segments: 10–20 mm proximal to the tip of the flow divider into the common carotid artery (CCA), the carotid bifurcation (BIF) beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip, and the proximal 10 mm of the internal carotid artery (ICA). The composite CIMT was calculated as the mean value of the three carotid artery segment CIMTs from both sides. Since two different machines (Vivid, General Electric; and EKO 7, Samsung Medison, Co., Ltd.) were used for CIMT measurement, reproducibility of the IMT measurement was assessed in 14 randomly chosen subjects. The intra-class correlation coefficients between the repeatedly measured IMT were 0.93, 0.86, and 0.90 for CCA, BIF, and ICA, respectively.

Measurements of BMD and covariates

Area (cm^2), bone mineral concentration (g) of the lumbar spine, and lean mass (g) were measured using whole body dual-energy X-ray absorptiometry on a Delphi W system (Hologic, Boston, MA, USA). All measurements were recorded by a well-trained technician. For measurements of lumbar BMD, the lumbar spine region was defined superiorly by the transverse line between the twelfth thoracic vertebra (T12) and the first lumbar vertebra (L1). The lumbar spine region was defined inferiorly by the horizontal line at the iliac crest. Calibration of the dual-energy X-ray absorptiometer was conducted using a phantom according to standard quality control procedures recommended by the manufacturer. All coefficients of variation for the BMD measurements were ≤ 1.0% for the machine. Lumbar BMD was calculated by dividing the bone mineral concentration by the area of the lumbar spine region.

Blood pressure was measured manually using a standardized mercury sphygmomanometer. Weight (kg) and height (cm) were measured using standardized scales and stadiometers while wearing light clothing. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). All physical measurements were taken twice and analyses were performed on average values. After overnight fasting (> 12 hours), serum glucose and lipid levels were measured. All biochemical analyses were conducted in one central laboratory that is accredited by the Korea Association of Quality Assurance for Clinical Laboratory.

Demographic characteristics, smoking status, physical exercise habits, and medical histories of hypertension and diabetes were obtained using a self-administered standardized questionnaire. Incomplete or ambiguous responses were clarified in face-to-face interviews. Postmenopausal status was defined as having no menstrual periods for the preceding year and fulfilling at least one of the following conditions: natural menopause, use of estrogen replacement therapy, or 55 years of age or older. Study subjects were categorized into two groups (never smoker and ever smoker) according to smoking status. If the study subject reported performing physical exercise at least once a week, the subject was considered to be involved in regular physical exercise. Hypertension was defined as current treatment with antihypertensive medication or blood pressure exceeding 140 (systolic) or 90 (diastolic) mmHg. Diabetes mellitus was defined as current treatment with glucose-lowering medication, high serum glucose (≥ 6.99 mM/L), or a high level of hemoglobin A1C (≥ 6.5%).

Statistical analysis

We compared the characteristics of men, premenopausal women, and postmenopausal women using the *t*-test for continuous

variables and the chi-square test for categorical variables. Variations in CIMTs, cardiovascular risk factors, and lifestyle factors were analyzed according to composite IMT tertile using linear regression or by the Mantel-Haenszel χ^2 test.

To evaluate the extent of association between BMD and CIMT, the percent difference of CIMT per increase (in 1 g/cm^2) of BMD of the lumbar spine were assessed using linear mixed models. Since all study subjects were recruited for a twin/family study, correlations were considered within the context of family relationships by adjusting for each family unit and each twin unit as random effects in the linear mixed model. Age, height, hypertension status, diabetes status, thyroid-stimulating hormone level, low-density lipoprotein (LDL) cholesterol level, high-density lipoprotein (HDL) cholesterol level, triglyceride (TG) level, BMI, lipid-lowering medication status, smoking status, regular exercise habits, calcium supplementation status, and estrogen replacement therapy status (for postmenopausal women) were adjusted as fixed effects. Prior to this analysis, CIMT values were log transformed to approximate a normal distribution.

We also examined the association between CIMT and lumbar BMD according to BMI. High BMI was defined as a BMI ≥ 25 kg/m^2; low BMI was defined as a BMI < 25 kg/m^2. We also evaluated whether BMI influences the association between BMD and CIMT by including an interaction term (BMI * lumbar BMD) into the analytic model. All statistical analyses were conducted using PASW Statistics 18 software (SPSS Inc., Chicago, IL, USA).

Ethics statement

Written informed consent was obtained from each participant. All study procedures were approved by the Institutional Review Board of Samsung Medical Center (2005-08-113).

RESULTS

The study variables for men, premenopausal women, and postmenopausal women were compared in Supplementary Table 1. The lumbar BMD, CCA-IMT, BIF-IMT, LDL-cholesterol level, HDL-cholesterol level, hypertension prevalence, diabetes prevalence, ever smoking prevalence, and calcium replacement prevalence all differed significantly between the three groups. However, the BMI, ICA-IMT, TG level, prevalence of thyroid disease, and

Table 1. Clinical characteristics and metabolic parameters according to tertiles of composite intima-media thickness

Characteristics	Men (n = 723)				Premenopausal women (n = 690)				Postmenopausal women (n = 266)			
	Lowest (0.28–0.48)	Intermediate (0.49–0.64)	Highest (0.65–3.36)	*P* trend*	Lowest (0.25–0.41)	Intermediate (0.42–0.53)	Highest (0.54–2.10)	*P* trend*	Lowest (0.35–0.56)	Intermediate (0.57–0.74)	Highest (0.75–1.78)	*P* trend*
No. of subjects	243	254	226		248	210	232		89	89	88	
Age, yr	35.5 (10.3)	45.2 (11.8)	57.6 (11.2)	< 0.001	33.3 (7.7)	39.7 (6.8)	43 (6.9)	< 0.001	56.4 (5.9)	60.6 (6.9)	64.8 (7.6)	< 0.001
IMT at specific sites, mm												
Common carotid artery	0.38 (0.06)	0.52 (0.07)	0.82 (0.33)	< 0.001	0.35 (0.04)	0.45 (0.05)	0.60 (0.11)	< 0.001	0.47 (0.06)	0.61 (0.09)	0.86 (0.26)	< 0.001
Carotid bifurcation	0.47 (0.11)	0.71 (0.14)	1.30 (0.71)	< 0.001	0.42 (0.09)	0.59 (0.10)	0.84 (0.22)	< 0.001	0.57 (0.13)	0.84 (0.19)	1.41 (0.41)	< 0.001
Internal carotid artery	0.36 (0.07)	0.46 (0.09)	0.72 (0.43)	< 0.001	0.32 (0.06)	0.40 (0.08)	0.53 (0.13)	< 0.001	0.39 (0.08)	0.50 (0.13)	0.67 (0.26)	< 0.001
Lumbar spine BMD, g/cm^2	1.06 (0.14)	1.07 (0.16)	1.08 (0.23)	0.453	1.08 (0.13)	1.11 (0.21)	1.12 (0.16)	0.026	1.00 (0.31)	1.00 (0.39)	0.93 (0.21)	0.282
Height, cm	172.4 (6.40)	169.5 (6.00)	167.8 (6.10)	< 0.001	159.9 (5.80)	158.2 (5.20)	157.8 (5.50)	< 0.001	155.0 (4.90)	155.9 (5.30)	153.8 (5.40)	0.044
BMI, kg/m^2	24.3 (3.20)	24.7 (2.80)	24.8 (2.80)	0.126	21.6 (2.90)	22.8 (3.50)	23.1 (3.20)	< 0.001	23.9 (2.80)	24.6 (3.60)	24.9 (3.20)	0.098
TSH, μIU/L	1.95 (1.23)	1.87 (1.56)	1.74 (1.08)	0.228	2.00 (1.18)	2.09 (1.31)	2.07 (1.32)	0.689	1.94 (1.11)	3.90 (14.10)	2.15 (1.99)	0.224
Total cholesterol, mM/L	4.70 (0.90)	5.00 (0.99)	4.98 (0.95)	< 0.001	4.53 (0.77)	4.68 (0.95)	4.88 (0.84)	< 0.001	5.26 (0.99)	5.36 (1.05)	5.16 (0.95)	0.414
LDL cholesterol, mM/L	2.77 (0.85)	3.00 (0.87)	3.00 (0.88)	0.003	2.51 (0.64)	2.67 (0.85)	2.87 (0.72)	< 0.001	3.20 (0.89)	3.34 (0.96)	3.16 (0.81)	0.381
HDL cholesterol, mM/L	1.22 (0.29)	1.21 (0.27)	1.16 (0.30)	0.037	1.44 (0.33)	1.38 (0.33)	1.38 (0.29)	0.074	1.32 (0.33)	1.29 (0.35)	1.20 (0.28)	0.031
Triglyceride, mM/L	1.57 (1.74)	1.58 (0.90)	1.64 (0.89)	0.807	0.93 (0.52)	0.96 (0.67)	1.01 (0.66)	0.307	1.41 (0.81)	1.54 (0.82)	1.65 (0.94)	0.188
Lipid lowering medication, %	0.4	2.8	2.7	0.066	0.0	1.4	0.9	0.254	4.5	2.2	5.7	0.702
Hypertension, %	8.6	19.7	32.7	< 0.001	1.2	4.3	12.5	< 0.001	14.6	21.3	37.5	< 0.001
Diabetes, %	5.3	12.2	25.7	< 0.001	2.4	2.9	5.6	0.062	24.7	20.2	25.0	0.69
Ever smoking, %	50.2	65.0	57.1	0.004	7.7	10.0	8.2	0.880	1.1	5.6	3.4	0.402
Regular exercise, %	36.2	37.8	44.2	0.129	24.2	32.4	30.2	0.123	42.7	39.3	34.1	0.528
Thyroid disease, %	0.4	0.4	0.0	0.395	1.6	1.9	3.0	0.302	1.1	1.1	3.4	0.266
Calcium replacement, %	2.5	3.1	4.4	0.239	5.6	6.2	12.5	0.004	19.1	20.2	25.0	0.341

Data were presented as mean (standard deviation) or %.
IMT = intima-media thickness, BMD = bone mineral density, BMI = body mass index, TSH = thyroid stimulating hormone, LDL = low density lipoprotein, HDL = high density lipoprotein.
*Linear trend was assessed by Mantel-Haenszel χ^2 test or linear regression test.

https://doi.org/10.3346/jkms.2017.32.1.70

exercise status did not differ between men and postmenopausal women. The prevalence of thyroid disease did not significantly differ between premenopausal women and postmenopausal women. Similarly, the level of thyroid-stimulating hormone and the prevalence of lipid-lowering medication were not significantly different between men and premenopausal women.

The study variable relationships for men, premenopausal women, and postmenopausal women with respect to composite CIMT tertile distribution are shown in Table 1. In all three groups, subjects with a higher composite CIMT tended to be older. With increasing composite CIMT, the lumbar BMD gradually increased in premenopausal women (P for trend = 0.026), whereas no specific trend was observed in postmenopausal women or in men. As the composite CIMT increased, height decreased in all three groups, whereas BMI increased only in premenopausal women. Moreover, as the composite CIMT increased, total cholesterol and LDL-cholesterol levels increased in both men and premenopausal women, while the HDL-cholesterol level decreased in both men and postmenopausal women. The prevalence of hypertension gradually increased as composite CIMT increased in all three groups. The prevalence of diabetes increased as composite CIMT increased; however, this trend was observed only in men. In premenopausal women, calcium supplementation was more prevalent among women with higher composite CIMT.

The relationship between lumbar BMD and CIMT is shown in Table 2. After adjusting for age, positive associations were observed between BMD and composite IMT and CCA-IMT in men and between BMD and composite CIMT, CCA-IMT, and ICA-IMT in premenopausal women. After adjusting for covariates, this significant association persisted for composite CIMT and CCA-IMT. Borderline significant associations were also observed between lumbar BMD and BIF-IMT and between lumbar BMD and ICA-IMT in premenopausal women. However, the association in men between CIMT and lumbar BMD did not persist after this adjustment. In postmenopausal women, no association was observed between CIMT and BMD. We repeated the multivariable adjusted analysis after stratifying male subjects into two groups by the age cut-off level ($\geq$ 50 years, $<$ 50 years) and found no difference in the association between BMD

Table 2. Association* between CIMT and BMD at lumbar spine

Variables	Men (n = 723)		Premenopausal women (n = 690)		Postmenopausal women (n = 266)	
	Percent difference (95% CI)	*P* value	Percent difference (95% CI)	*P* value	Percent difference (95% CI)	*P* value
Age adjusted						
Composite	12.0 (0.3–25.0)	0.0396	15.4 (5.3–26.6)	0.005	–3.1 (–10.9–5.3)	0.704
Common carotid	13.3 (1.4–26.6)	< 0.001	18.0 (7.9–29.1)	0.002	–0.8 (–8.8–7.8)	0.991
Carotid bifurcation	12.6 (–29.7–31.2)	0.194	11.1 (–2.1–26.1)	0.084	–3.4 (–14.5–9.1)	0.720
Internal carotid	8.3 (–44.1–24.3)	0.190	14.8 (2.1–29.0)	< 0.001	–6.5 (–16.5–4.7)	0.396
Multivariable adjusted†						
Composite	9.7 (–3.9–25.2)	0.170	14.0 (6.1–25.7)	0.008	–2.2 (–10.3–6.5)	0.614
Common carotid	8.3 (–5.6–24.1)	0.255	16.1 (5.7–27.6)	0.002	–1.4 (–9.5–7.4)	0.751
Carotid bifurcation	10.7 (–7.7–32.8)	0.273	13.0 (–1.3–29.3)	0.071	–2.3 (–13.9–10.9)	0.724
Internal carotid	6.6 (–9.5 - 25.6)	0.443	11.9 (–1.2–26.7)	0.068	–5.5 (–15.9–6.1)	0.200

CIMT = carotid intima-media thickness, BMD = bone mineral density, CI = confidence interval, BMI = body mass index.
*β coefficients (95% CI) for log-transformed carotid intima media thickness per 1 g/cm^2 increase in BMD were assessed by linear mixed model. Then, percent difference of carotid intima media thickness was calculated by multiplying 100 to the value of (exponentiated β coefficient –1). In all analytic models, household and twin pair was adjusted as the random effects; †In the multivariable-adjusted model, age, height, BMI, hypertension, diabetes, thyroid stimulating hormone, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, lipid lowering medication, smoking habit, physical exercise, calcium supplement and estrogen replacement therapy (for postmenopausal women) were additionally adjusted as fixed effects.

Table 3. Percent difference (95% CI)* of CIMT according to BMI†

Sites of IMT measure	Men			Premenopausal women			Postmenopausal women		
	Low BMI (n = 361)	High BMI (n = 362)	*P* interaction	Low BMI (n = 536)	High BMI (n = 154)	*P* interaction	Low BMI (n = 141)	High BMI (n = 125)	*P* interaction
Composite	–9.6 (–25.6–9.9)	24.5 (5.2–47.5)‡	0.014	14.5 (2.7–27.7)‡	16.1 (–4.9–41.6)	0.976	–4.2 (–18.2–12.2)	6.3 (–9.2–24.5)	0.437
Common carotid	–5.7 (–23.8–16.6)	24.1 (4.1–48.0)‡	0.062	13.5 (2.3–25.9)‡	30.0 (–4.6–61.4)	0.233	–1.4 (–5.0–14.2)	4.4 (–10.7–21.9)	0.794
Carotid bifurcation	–14.7 (–34.6–11.3)	24.0 (–2.3–57.4)	0.007	12.5 (–3.0–30.5)	8.1 (–18.1–42.6)	0.812	–8.5 (–28.6–17.4)	13.5 (–9.4–42.2)	0.246
Internal carotid	–13.5 (–31.7–9.4)	12.0 (–9.0–37.7)	0.047	13.8 (–0.5–30.2)	15.5 (–12.0–51.4)	0.948	–1.5 (–22.7–25.4)	–0.8 (–16.9–18.5)	0.986

CI = confidence interval, CIMT = carotid intima-media thickness, BMI = body mass index.
*β coefficients (95% CI) for log-transformed carotid intima media thickness per 1 g/cm^2 increase in lumbar BMD according to two BMI groups were assessed by linear mixed model. Then, percent thickness difference of carotid intima media thickness was calculated by multiplying 100 to the value of (exponentiated β coefficient –1). In the model, household and twin pair was adjusted as the random effects. Age, height, hypertension, diabetes, thyroid stimulating hormone, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, lipid lowering medication, smoking habit, physical exercise, calcium replacement therapy and estrogen replacement therapy (for postmenopausal women) were additionally adjusted as fixed effects; †BMI was divided as two-group ($<$ 25 or $\geq$ 25 kg/m^2); ‡$P < 0.05$.

and CIMT depending on the age level in men (data not shown).

The findings from stratified analysis regarding the association between lumbar BMD and CIMT according to the BMI level are shown in Table 3. In premenopausal women, a positive association was observed, while statistically significant positive association with BMD was confirmed only with composite CIMT and CCA-IMT in low BMI women. In premenopausal women, no significant association was observed between BMI and lumbar BMD. Lumbar BMD tended to be positively associated with CIMT in men with high BMI, while an inverse but statistically insignificant relationship was observed in men with low BMI. The interaction between BMI and lumbar BMD on the association with CIMT was statistically significant in men. In postmenopausal women, no association between BMD and CIMT was observed at any site, regardless of BMI level.

DISCUSSION

In this Korean study, we observed a positive association between lumbar BMD and CIMT, although this association was restricted to premenopausal women and obese men, and mainly to composite CIMT and CCA-IMT. The positive associations between lumbar BMD, composite CIMT, and CCA-IMT in premenopausal women are consistent with the findings of a previous study in Mexican American young women (mean age = 26.7 years) in which the BMDs at the hip, radius, and spine were found to be positively associated with CCA-IMT (8). Cecelja et al. (12) also observed positive associations between hip and lumbar BMD and CIMT in British women (mean age 57.7 years, standard deviation 8.9 years). However, these associations were not evaluated according to menopausal status in the British study.

Estrogen may play a role in the positive association between BMD and atherosclerosis observed in premenopausal women, given the biological relationships that have been described between BMD and CIMT. Specifically, both BMD and CIMT have been shown to be regulated by estrogen receptor-alpha gene polymorphisms (23,24); mitogen-activated protein (MAP) kinase, a serine/threonine kinase that mediates tumor necrosis factor-α signaling, and various interleukins that are associated positively with CIMT have been shown to be regulated by estrogen (25,26); single nucleotide polymorphism variants of the estrogen receptor have been reported to be associated with CIMT in Taiwanese women, but not in men (24); and the vitamin D receptor polymorphism was reported to affect BMD by combining the estrogen receptor polymorphism (27). These biological mechanisms may underlie the association between BMD and CIMT and strongly suggest that future studies on BMD and atherosclerosis in women should consider menopausal status.

Estrogen levels are known to decrease after menopause, which results in reduced estrogen-mediated protection against atherosclerosis and osteoporosis in postmenopausal women (7). Postmenopausal women also experience changes in their body composition such as increased fat distribution and decreased lean mass (28) that are associated with both BMD and atherosclerosis (29,30). Moreover, increasing calcium supplementation during the menopausal period may accelerate vascular atherogenesis (31). Therefore, an inverse association between BMD and atherosclerosis seems plausible in postmenopausal women. Some studies found an inverse association between BMD and CIMT (8,13,32). However, other studies in Morocco, the USA, Finland, China, Japan, and Korea (including the present study) did not find any association between lumbar BMD and CIMT, or any other surrogate marker of atherosclerosis, in postmenopausal women (10,11,14,16,20).

These discrepancies have a number of potential explanations. Variation regarding the site of BMD measurement is one possible reason. In support of this explanation, one study found that femur BMD was inversely associated with CIMT, whereas lumbar BMD was not (10). However, since even the findings regarding the association of lumbar spine BMD with CIMT vary between studies (10,11,32), variation regarding the site of BMD measurement cannot fully explain the discrepancies between these studies. Second, different age distributions between studies may have resulted in these discrepancies. The age distribution of postmenopausal women in our study (mean age = 59.5 years) was somewhat younger than that in another study that found an inverse association (mean age = 69.2 years) (8). However, another study of older women (mean age = 73.6 years) did not find any association, which is consistent with our findings. To clarify this issue, the association needs to be studied according to age or time after menopause. Third, study-to-study variation of covariates such as osteoporosis treatment and hormonal replacement therapy may also explain the different findings. However, we did not observe any significant influence by covariates after adjustment in the present study. Forth, differences in ethnicity/race might be another reason (13,20). Finally, the association between BMD and CIMT might not be shown distinctly due to the effect modification by other factors such as BMI level on the association. In our study, stratified analysis by BMD level in postmenopausal women has revealed that BMD may be associated with CIMT inversely in lower BMI group but positively in higher BMI group. Although the estimates lacked statistical significance, this finding seems compatible with the findings observed in men. In our study the sample size of postmenopausal women may not be enough to do a subgroup analysis to examine the effect modifying role of BMI. We think further study with larger sample size of postmenopausal women would be needed to clarify this issue.

Few studies have been conducted in men regarding the relationship between BMD and CIMT compared with women. Although two studies in Chinese population did not identify significant association (16,33), the direction was consistent with

 https://doi.org/10.3346/jkms.2017.32.1.70

our study. However, another study in multiethnic population reported an inverse association (20). In our study, age-adjusted analysis revealed a positive relationship between lumbar BMD and CIMT, but this relationship did not persist after adjusting for covariates. All other studies also considered known confounding variables such as smoking status, BMI, lipid level, hypertension status, and diabetes status. Thus, these discrepancies do not seem to be due to different covariate adjustments.

Obesity is known to be positively associated with BMD, since a high BMI can increase the mechanical load on the bones (29, 34). Moreover, a high BMI increases the risk of atherosclerosis through mechanisms related to chronic inflammation and insulin resistance (35). The known relationships between obesity and both BMD and atherosclerosis prompted us to carefully investigate the effects of BMI via stratified analysis. Although our results need to be confirmed in future studies, interestingly, we found that BMD was positively associated with CIMT in men with high BMI but not in men with low BMI. This finding seems to suggest an effect modification by BMI in men. We assume that obesity related factors such as increased mechanical load, chronic inflammation and insulin resistance may explain the effect modifying role of BMI on the association between CIMT and BMD. However, we were unable to examine the biological mechanism. Further study is needed to investigate and to explain the association between BMD and CIMT in men.

The present study has a number of strengths. First, a large number of subjects were included, which allowed us to consider both sex and menopausal status. Second, a wide range of covariates including thyroid-stimulating hormone status, estrogen replacement therapy status, and calcium supplementation status could be considered. Therefore, we believe that the influence of most confounding factors on our results was minimized.

However, the present study has some limitations. First, we measured lumbar BMD using whole body dual-energy X-ray absorptiometry, which does not provide BMD at each segment of the lumbar spine. Thus, measurement error could have affected our results. Second, we could not take into consideration of the probable influence by aortic calcification or osteophytes of spine on the measurement of lumbar BMD because we could not obtain those information. Third, we were unable to evaluate the extent of association of CIMT with femoral BMD, which was a measurement that is commonly used in the clinical setting along with lumbar BMD, because whole body dual-energy X-ray absorptiometry does not provide femoral BMD information. Fourth, the sample size of postmenopausal women might be relatively limited to disclose the association between CIMT and BMD with enough power.

We found that lumbar BMD has a positive association with CIMT in premenopausal women and men with high BMI. This finding suggests that the association between lumbar BMD and subclinical atherosclerosis may differ according to sex and menopausal status.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Participating in the conception and design: Sung J. Analysis and interpretation of data: Shin J, Park JH, Song YM, Lee K, Sung J. Drafting the article or critically revising: Shin J, Park JH, Song YM, Lee K, Sung J. Approving the final version submitted: all authors.

ORCID

Jinyoung Shin http://orcid.org/0000-0001-9558-1853
Joo-Hyun Park http://orcid.org/0000-0002-4358-4208
Yun-Mi Song http://orcid.org/0000-0001-9232-5563
Kayoung Lee http://orcid.org/0000-0002-2816-554X
Joohon Sung http://orcid.org/0000-0001-9948-0160

REFERENCES

1. Sarkisian CA, Liu H, Gutierrez PR, Seeley DG, Cummings SR, Mangione CM. Modifiable risk factors predict functional decline among older women: a prospectively validated clinical prediction tool. The study of osteoporotic fractures research group. *J Am Geriatr Soc* 2000; 48: 170-8.
2. Bliuc D, Nguyen ND, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Accelerated bone loss and increased post-fracture mortality in elderly women and men. *Osteoporos Int* 2015; 26: 1331-9.
3. Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. *J Cell Biol* 2015; 209: 13-22.
4. Hofbauer LC, Brueck CC, Shanahan CM, Schoppet M, Dobnig H. Vascular calcification and osteoporosis--from clinical observation towards molecular understanding. *Osteoporos Int* 2007; 18: 251-9.
5. Demer LL. Vascular calcification and osteoporosis: inflammatory responses to oxidized lipids. *Int J Epidemiol* 2002; 31: 737-41.
6. Stevenson JC, Lees B, Devenport M, Cust MP, Ganger KF. Determinants of bone density in normal women: risk factors for future osteoporosis? *BMJ* 1989; 298: 924-8.
7. Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. *Circulation* 1994; 89: 1501-10.
8. Kammerer CM, Dualan AA, Samollow PB, Périssé AR, Bauer RL, MacCluer JW, O'Leary DH, Mitchell BD. Bone mineral density, carotid artery intimal medial thickness, and the vitamin D receptor BsmI polymorphism in Mexican American women. *Calcif Tissue Int* 2004; 75: 292-8.
9. Anagnostis P, Karagiannis A, Kakafika AI, Tziomalos K, Athyros VG, Mikhailidis DP. Atherosclerosis and osteoporosis: age-dependent degenerative processes or related entities? *Osteoporos Int* 2009; 20: 197-207.
10. Hmamouchi I, Allali F, Khazzani H, Bennani L, El Mansouri L, Ichchou L, Cherkaoui M, Abouqal R, Hajjaj-Hassouni N. Low bone mineral density

is related to atherosclerosis in postmenopausal Moroccan women. *BMC Public Health* 2009; 9: 388.
11. Frost ML, Grella R, Millasseau SC, Jiang BY, Hampson G, Fogelman I, Chowienczyk PJ. Relationship of calcification of atherosclerotic plaque and arterial stiffness to bone mineral density and osteoprotegerin in postmenopausal women referred for osteoporosis screening. *Calcif Tissue Int* 2008; 83: 112-20.
12. Cecelja M, Jiang B, Bevan L, Frost ML, Spector TD, Chowienczyk PJ. Arterial stiffening relates to arterial calcification but not to noncalcified atheroma in women. A twin study. *J Am Coll Cardiol* 2011; 57: 1480-6.
13. Shaffer JR, Kammerer CM, Rainwater DL, O'Leary DH, Bruder JM, Bauer RL, Mitchell BD. Decreased bone mineral density is correlated with increased subclinical atherosclerosis in older, but not younger, Mexican American women and men: the San Antonio Family osteoporosis study. *Calcif Tissue Int* 2007; 81: 430-41.
14. Yamada S, Inaba M, Goto H, Nagata M, Ueda M, Nakatuka K, Tahara H, Yokoyama H, Emoto M, Shoji T, et al. Significance of intima-media thickness in femoral artery in the determination of calcaneus osteo-sono index but not of lumbar spine bone mass in healthy Japanese people. *Osteoporos Int* 2005; 16: 64-70.
15. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; 115: 459-67.
16. Liang DK, Bai XJ, Wu B, Han LL, Wang XN, Yang J, Chen XM. Associations between bone mineral density and subclinical atherosclerosis: a cross-sectional study of a Chinese population. *J Clin Endocrinol Metab* 2014; 99: 469-77.
17. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. *Menopause* 2013; 20: 8-14.
18. Iki M, Dohi Y, Nishino H, Kajita E, Kusaka Y, Tsuchida C, Yamamoto K, Ishii Y. Relative contributions of age and menopause to the vertebral bone density of healthy Japanese women. *Bone* 1996; 18: 617-20.
19. Underhill HR, Yuan C, Terry JG, Chen H, Espeland MA, Hatsukami TS, Saam T, Chu B, Yu W, Oikawa M, et al. Differences in carotid arterial morphology and composition between individuals with and without obstructive coronary artery disease: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2008; 10: 31.
20. Hyder JA, Allison MA, Barrett-Connor E, Detrano R, Wong ND, Sirlin C, Gapstur SM, Ouyang P, Carr JJ, Criqui MH. Bone mineral density and atherosclerosis: the multi-ethnic study of atherosclerosis, abdominal aortic calcium study. *Atherosclerosis* 2010; 209: 283-9.
21. Sung J, Cho SI, Lee K, Ha M, Choi EY, Choi JS, Kim H, Kim J, Hong KS, Kim Y, et al. Healthy twin: a twin-family study of Korea--protocols and current status. *Twin Res Hum Genet* 2006; 9: 844-8.
22. Gombojav B, Song YM, Lee K, Yang S, Kho M, Hwang YC, Ko G, Sung J. The healthy twin study, Korea updates: resources for omics and genome epidemiology studies. *Twin Res Hum Genet* 2013; 16: 241-5.
23. Nam HS, Shin MH, Kweon SS, Park KS, Sohn SJ, Rhee JA, Choi JS, Son MH. Association of estrogen receptor-alpha gene polymorphisms with bone mineral density in postmenopausal Korean women. *J Bone Miner Metab* 2005; 23: 84-9.
24. Wu MM, Hsieh YC, Lien LM, Chen WH, Bai CH, Chiu HC, Chen HH, Chung WT, Lee YC, Hsu CY, et al. Association of estrogen receptor {alpha} genotypes/ haplotypes with carotid intima-media thickness in Taiwanese women. *Angiology* 2010; 61: 275-82.
25. Miller VM, Petterson TM, Jeavons EN, Lnu AS, Rider DN, Heit JA, Cunningham JM, Huggins GS, Hodis HN, Budoff MJ, et al. Genetic polymorphisms associated with carotid artery intima-media thickness and coronary artery calcification in women of the Kronos early estrogen prevention study. *Physiol Genomics* 2013; 45: 79-88.
26. Mahmoodzadeh S, Dworatzek E, Fritschka S, Pham TH, Regitz-Zagrosek V. 17beta-Estradiol inhibits matrix metalloproteinase-2 transcription via MAP kinase in fibroblasts. *Cardiovasc Res* 2010; 85: 719-28.
27. Kim JG, Lim KS, Kim EK, Choi YM, Lee JY. Association of vitamin D receptor and estrogen receptor gene polymorphisms with bone mass in postmenopausal Korean women. *Menopause* 2001; 8: 222-8.
28. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. *Am J Clin Nutr* 1992; 55: 950-4.
29. Park JH, Song YM, Sung J, Lee K, Kim YS, Kim T, Cho SI. The association between fat and lean mass and bone mineral density: the healthy twin study. *Bone* 2012; 50: 1006-11.
30. Song Y, Lee K, Sung J, Lee D, Lee MK, Lee JY. Genetic and environmental relationships between Framingham risk score and adiposity measures in Koreans: the healthy twin study. *Nutr Metab Cardiovasc Dis* 2012; 22: 503-9.
31. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. *Osteoporos Int* 2011; 22: 1649-58.
32. Fodor D, Bondor C, Albu A, Muntean L, Simon SP, Poanta L, Craciun A. Relation between intima-media thickness and bone mineral density in postmenopausal women: a cross-sectional study. *Sao Paulo Med J* 2011; 129: 139-45.
33. Wang YQ, Yang PT, Yuan H, Cao X, Zhu XL, Xu G, Mo ZH, Chen ZH. Low bone mineral density is associated with increased arterial stiffness in participants of a health records based study. *J Thorac Dis* 2015; 7: 790-8.
34. Skerry TM, Suva LJ. Investigation of the regulation of bone mass by mechanical loading: from quantitative cytochemistry to gene array. *Cell Biochem Funct* 2003; 21: 223-9.
35. Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. *Metabolism* 2006; 55: 113-8.

 https://doi.org/10.3346/jkms.2017.32.1.70