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Bone mineral density and atherosclerosis: The Multi-Ethnic Study of Atherosclerosis, Abdominal Aortic Calcium Study

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Abstract

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Context—Molecular and cell biology studies have demonstrated an association between bone and arterial wall disease, but the significance of a population-level association is less clear and potentially confounded by inability to account for shared risk factors.

Objective—To test population-level associations between atherosclerosis types and bone integrity.

Main Outcome Measures—Volumetric trabecular lumbar bone mineral density (vBMD), ankle-brachial index (ABI), intima-media thickness of the common carotid (CCA-IMT) and internal carotid (ICA-IMT) arteries, and carotid plaque echogenicity.

Design, Setting and Participants—A random subset of participants from the Multi-Ethnic Study of Atherosclerosis (MESA) assessed between 2002 and 2005.

Results—904 post-menopausal female (62.4 years; 62% non-white; 12% ABI<1; 17% CCA-IMT>1mm; 33% ICA-IMT>1mm) and 929 male (61.4 years; 58% non-white; 6% ABI<1; 25% CCA-IMT>1mm; 40% ICA-IMT>1mm) were included. In serial, sex-specific regression models adjusting for age, ethnicity, body mass index, dyslipidemia, hypertension, smoking, alcohol consumption, diabetes, homocysteine, interleukin-6, sex hormones, and renal function, lower vBMD was associated with lower ABI in men (p for trend <0.01) and greater ICA-IMT in men (p for trend <0.02). CCA-IMT was not associated with vBMD in men or women. Carotid plaque echogenicity was independently associated with lower vBMD in both men (trend p=0.01) and women (trend p<0.04). In all models, adjustment did not materially affect results.

Conclusions—Lower vBMD is independently associated with structural and functional measures of atherosclerosis in men and with more advanced and calcified carotid atherosclerotic plaques in both sexes.

INTRODUCTION

Evidence from cell-culture, animal models, and large epidemiologic studies have demonstrated significant associations between low bone mineral density and atherosclerosis, two of the most common diseases of aging.[1-5] Since the association was first noted,[6] many bone-artery studies have emphasized calcified atherosclerosis rather than other measures, reflecting the practicality of investigating outcomes that can be assessed with similar technologies and the observation that calcified atherosclerotic lesions are histologically similar to skeletal bone.[5] A few observational studies have demonstrated inverse associations between bone mineral density and measures of atherosclerosis not specific to calcification.[7-10] These studies have been variously limited by exclusively white and/or female populations, limited measurements of atherosclerosis or inability to adjust for many proposed confounders, mediators, or shared risk factors of atherosclerosis and osteoporosis.[7-10] Thus, the magnitude and nature of a potential association between atherosclerosis types and osteoporosis remain uncertain.

With data from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, an ethnically-diverse population free of clinical cardiovascular disease, we tested the hypotheses that volumetric bone mineral density (vBMD) is inversely associated with functional and structural measures of peripheral atherosclerosis not specific to calcification and that vBMD

was associated with atherosclerotic plaque type, a measurement that is related to arterial calcification. These analyses evaluate associations in the context of cardiovascular and osteoporosis risk factors, including inflammatory markers and sex hormones not previously studied outside of the MESA.

MATERIALS AND METHODS

Study participants

The methods of the Multi-Ethnic Study of Atherosclerosis (MESA) have been described previously.[11] Briefly, volunteers for the MESA observational cohort were recruited between July 2000 and August 2002 from six field centers around the United States. The study population consists of 6814 men and women who were aged between 45 and 84 years of age, were free of clinical cardiovascular disease (CVD), and identified themselves as Non-Hispanic White (NHW), Chinese American, African American or Hispanic.

This report describes an age-stratified random sample of MESA participants who participated in the MESA Abdominal Aortic Calcium Study (MESA-AACS). MESA-AACS participants were recruited during follow-up visits which included computed tomography scanning between August 2002 and September 2005 from five MESA field centers: Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Of 2202 MESA participants recruited, 2172 agreed to participate, and 1968 (974 women and 994 men) satisfied eligibility criteria, including including post-menopausal status (women), no recent prior diagnostic abdominal computer tomography, and age- and ethnicity-sub-sampling from the MESA, and completed scanning. Subsequently, 28 women and 31 men were excluded because of vertebral pathology complicating bone mineral density measurement. An additional 41 women and 21 men were excluded due to missing measures of carotid atherosclerosis or ankle-brachial index (ABI). An additional 1 woman and 13 men were excluded based on “stiff arteries” as characterized by an ABI greater than 1.4.[12] Written informed consent was provided by all participants, and institutional review board approval was obtained from each participating institution.

Bone mineral density

Participants were randomly selected to undergo computed tomography (CT) scanning during follow-up visits. CT scanning of the lumbar spine was performed on each participant using electron-beam computed tomography scanner (Chicago, New York City and Los Angeles; Imatron C-150, General Electric Medical Systems)[13] or with a multi-detector computed tomography system that utilized helical scanning with reconstruction in 5 mm thick cuts and 350 mm field of view (New York, Forsyth County, and St. Paul field centers; Siemens Inc, GE Medical Systems). A previous study had demonstrated the comparability, accuracy and reproducibility of these scanners.[14] Participants were scanned along with phantoms of known physical calcium concentration to convert CT numbers directly to equivalent volumetric bone mineral density (vBMD) in mg/cc.[15] CT data were collected using the Image Analysis QCT 3D PLUS software program (Image Analysis, Columbia, Kentucky) to determine vBMD in a virtual 10mm-thick slice of trabecular bone from the third lumbar

vertebra. Scans were read centrally at the MESA Reading Center by a trained reader blinded to the results of ABI and carotid measures. In a random sample of 25 scans re-read on three occasions by the blinded scan reader, there was 100 percent agreement as to vertebrae data inclusion and no evidence of systematic differences between reads.

Ankle-brachial Index

Measurements for calculation of the ankle-brachial index were made between July 2000 and August 2002. Using a hand-held Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, Colorado), systolic blood pressure measurements were obtained from bilateral brachial, dorsalis pedis, and posterior tibial arteries.[16] Brachial artery pressures were averaged to obtain the ABI denominator. When the two brachial artery pressures differed by 10 mmHg or more, the highest brachial artery pressure was used as the denominator.[17] For each lower extremity, the ABI numerator was the highest pressure (dorsalis pedis or posterior tibial) from that leg.

Carotid artery imaging

Carotid artery intima-media thickness was assessed between July 2000 and August 2002. Images of both far and near walls of the bilateral common carotid and internal carotid arteries were obtained by trained personnel using high-resolution B-mode ultrasonography. [18] A Logiq 700 ultrasound machine (GE Medical Systems, Waukesha, Wisconsin) was used at all centers.

Carotid artery intima-media thickness

Central reading of intima-media thickness (IMT) was done at the Tufts-New England Medical Center (Boston, Massachusetts).[18] Common carotid artery IMT (CCA-IMT) and internal carotid artery IMT (ICA-IMT) were calculated from pre-determined sets of long and short axis views. CCA-IMT was determined from maximal values obtained from the near and far walls of the left and right common carotid arteries. ICA-IMT was determined from maximal measures from internal carotid arteries obtained from near and far walls of the right and left anterior-oblique, lateral, and posterior-oblique views. On a random sample of 77 participants, Pearson correlations for between-reader values were 0.767 for CCA-IMT and 0.917 for ICA-IMT values. Among 71 randomly selected participants, Pearson correlations for within-reader values were 0.965 for CCA-IMT and 0.990 for ICA-IMT.

Carotid plaque echogenicity

Carotid plaque echogenicity was assessed by sonographic echogenicity relative to the surrounding arterial wall in the largest plaque imaged. Readers graded plaques into four categories based on grayness, noting if a plaque was darker than the surrounding tissue (echolucent, implying a lipid-rich lesion), had the same level of brightness as the surrounding tissue (isolucent), appeared brighter than the surrounding tissue and some of the tissue beneath the plaque was shadowed (echogenic, implying a lesion with dense fibrous tissue), or if the plaque appeared much brighter than the surrounding tissue and all of the tissue beneath the plaque was shadowed (implying a calcified, more advanced lesion).[19] Between-reader (n=77) kappa scores for plaque classification were 0.675 and 0.724 for right

and left carotid plaque echogenicity, respectively. Within-reader (n=71) kappa scores for carotid plaque echogenicity were 0.970 and 0.914 for right and left carotid arteries, respectively.

Clinical Measurements

Participants completed a clinical examination and detailed questionnaire. Age, sex, ethnicity, height, weight, current medications from pill bottles, physical activity patterns (mets times the number of minutes of each met in one week, or met * min/week), smoking history and alcohol consumption (never/former/current), and previous medical diagnoses were recorded. Recent hormone therapy among women was defined (yes/no) as estrogen use within the past two years. Body mass index was calculated as mass in kilograms divided by height in meters squared. Blood pressure was measured 3 times with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon) with participants at rest in the seated position. The average of the last 2 measurements was used to define hypertension as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg or current use of antihypertensive medication.

Laboratory measurements

C-reactive protein (CRP), interleukin-6 (IL-6) and homocysteine were measured in a standardized manner upon recruitment and enrollment between July 2000 and August 2002.[11] Serum sex hormone concentrations were measured from stored samples. Total testosterone was measured directly using radioimmunoassay kits, and SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). Estradiol was measured by use of an ultra-sensitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX).

Total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and glucose levels were measured from plasma samples obtained after a 12-hour fast. Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[20] Diabetes was categorized if fasting plasma glucose was greater than 126 mg/dL or if the participant reported prior diagnosis of diabetes or use of hypoglycemic medications. Renal function was determined from serum creatinine obtained after a 12-hour overnight fast, using the amidinohydrolase method[21] and were normalized to a reference standard at the Cleveland Clinic Foundation laboratory. Using the sex- and race/ethnicity-specific method of Modification of Diet in Renal Diease,[22] renal dysfunction was classified as estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.72 m^2.

Statistical analyses

Given documented differences between men and women in the distributions[23] of bone mineral density and the relatively few publications on the association between bone and atherosclerosis in men, all analyses were stratified by sex. Age and vBMD were categorized by sex-specific quartiles. Differences in characteristics were tested with analysis of variance (linear variables) and chi-square tests (categorical variables.)

Mean ABI, CCA-IMT and ICA-IMT by vBMD quartile were tested by analysis of covariance first after adjustment for age and race/ethnicity and then after full adjustment. Adjusted means for log-transformed ICA-IMT values are geometric means.[24] For each outcome, formal tests of interactions of vBMD by age, race/ethnicity, and recent hormone therapy (women only) were performed. None were significant at the $p<0.05$ level, so age, race/ethnicity and hormone therapy groups were collapsed. For all outcomes, race/ethnic-specific results are reported after adjustment for race/ethnic differences in other covariates. Associations between vBMD and carotid artery plaque echogenicity were also tested by analysis of covariance with vBMD was the outcome.

We aimed to test the contributions of different sets of variables to the associations between vBMD and atherosclerosis. The following terms were conceived in mutually exclusive theoretical concepts as follows: confounders are covariates that are associated with both vBMD and atherosclerosis but are causally associated with only one of those outcomes; mediators are covariates that are in a causal pathway between atherosclerosis and vBMD; common risk factors are covariates that independently cause both atherosclerosis and low vBMD. The empirical effect of adjusting for a confounder, mediator or common risk factor in the serial models is either attenuation or augmentation of the association between atherosclerosis and vBMD. No change in the association with adjustment indicates that the added covariate made no contribution to the association.[25]

Associations were adjusted for individual as well as sets of covariates in serial models. Model 1 adjusted for age in quartiles and race/ethnicity, given the known associations of these covariates with both atherosclerosis and vBMD. Model 2 adjusted additionally for total cholesterol, HDL-cholesterol, lipid medication, hypertension, diabetes, smoking (never/former/current), body mass index, physical activity, the natural log (ln) of dietary calcium, alcohol consumption (never/former/current), and recent hormone therapy (women only). The final model, Model 3, additionally adjusted the means for ln(interleukin-6), ln(C-reactive protein), homocysteine, and sex-specific and hormone-therapy-specific quartiles of total testosterone, estradiol, and sex hormone binding globulin, and renal function. Models were inspected for attenuation and/or augmentation of an association, defined as a change corresponding to a 25% change in effect size. Multi-collinearity was not detected during screening for tolerance values of less than 0.15 for all variables in fully adjusted models. All analyses were executed using SAS version 8.1 (SAS Institute, Cary, NC, U.S.A.).

RESULTS

The sex-specific characteristics of 904 female and 929 male participants are shown in Table 1. The average age of women was 65 years, and the average age of men was 64 years. Non-Hispanic white participants were 38% of women and 42% of men. For both men and women, IMT mean values and variability were greater for the ICA-IMT than for the CCA-IMT.

Bone mineral density was significantly, inversely associated with age in both women ($p<0.001$) and men ($p<0.001$). In all, there were few strong correlates of vBMD other than age and race/ethnicity in either men or women (data not shown).

Table 2 displays mean ankle-brachial index (ABI) and internal carotid artery IMT (ICA-IMT) values by sex-specific quartiles of vBMD and after multiple, sequential adjustments for covariates. In women, there were no significant associations between vBMD and ABI or ICA-IMT, in any model. In men, however, lower vBMD was significantly associated with greater ICA-IMT in all models (Model 3, p for trend p=0.022). And in men, lower vBMD was associated with lower ABI in all models with no evidence of attenuation or augmentation of associations across models (Model 3, p for trend=0.008). CCA-IMT was not associated with vBMD in women or men (results not shown).

Table 3 presents the sex-specific distributions of carotid plaque types by echolucency and mean vBMD for each plaque type after multiple adjustments. The most common findings on carotid ultrasound were no carotid lesion (61%) and iso-echoic carotid lesions (23%) in women and no carotid lesions (56%) and iso-echoic carotid lesions (26%) in men. In both men (p=0.015) and women (p=0.015), greater plaque echogenicity, indicative of greater fibrous tissue content and calcium, was significantly associated with lower vBMD in all models, independent of adjustments. Significant associations persisted in both sexes when those with hyperechoic and calcified carotid lesions or no lesions were excluded (results not shown).

In sensitivity analyses, results did not differ materially when the analyses were repeated using vBMD from the fourth lumbar vertebra (L4) instead of L3, when alternative adjustments for sex hormones, including use of bio-available testosterone in place of total testosterone, and, in women, when analyses were stratified by use of hormone therapy or when multiple strategies for age adjustment were attempted.

DISCUSSION

In the present study, low trabecular lumbar volumetric bone mineral density (vBMD) was independently associated with greater levels of subclinical atherosclerosis assessed by internal carotid intima-media thickness (ICA-IMT) and ankle-brachial index (ABI) in men but not women. In both sexes, more advanced carotid plaque morphology, evidenced by greater plaque echogenicity and calcification, was significantly associated with lower vBMD. In all cases, significant associations attenuated slightly after adjustment for age, but minimally for other covariates including standard cardiovascular disease risk factors, inflammatory measures, sex hormones and renal function.

The present study differs from previous investigations with its multi-ethnic, population-based sample, extensive covariate data including multiple inflammatory markers, homocysteine, and sex hormones, as well as the use of volumetric rather than areal bone mineral density measurements. Areal bone mineral density values summarize data from cortical and trabecular bone in a single measure and vary by bone size and type as well as density. The volumetric estimates here are independent of secular trends in height or age-, race/ethnic- or sex-differences in bone size and shape and are specific to the trabecular bone compartment.[26-32] Patterns of cortical and trabecular bone loss differ. Trabecular bone loss begins before cortical or net bone loss, as early as the second and third decades of life, [32] at the time when early atherosclerotic lesions (fatty streaks) are thought to develop.

Differences between this report and previous reports may be driven in part by the precision of trabecular measures here compared to areal bone measures in other reports.

Three previous studies of similar size have used areal measurements of bone mineral density to demonstrate significant associations between ABI and hip bone mineral density, but none detected associations with lumbar bone mineral density[8, 10, 33] and none found associations in men alone.[10, 33] The significant association between vBMD and the ABI in men in this study may have resulted from the use of volumetric rather than areal bone densitometry and/or evaluation of the lumbar spine which may have differential susceptibility to confounding by low physical activity,[8, 34, 35] a known risk factor for bone loss and both a cause and consequence of low ABI. [36]

Few studies of similar size have tested associations between bone mineral density and carotid atherosclerosis. An investigation by Jorgenson and colleagues of over 5,000 white men and women found no association between areal BMD of the forearm and total carotid IMT.[7] A study of 165 postmenopausal Hispanic women found an association between areal bone mineral density (hip, spine, radius) and CCA-IMT that was stronger for the distal radius than for the less trabecular midshaft radius, suggesting that the bone-artery association is stronger for trabecular bone than for cortical bone.

The significance, if any, of sex differences in bone-artery associations found in the present study are unclear. These differences may not be specifically due to sex differences in bone-artery biology per se, since the sexes shared the association between plaque type and vBMD. In this cohort free of clinical CVD at enrollment, the sex differences for ICA-IMT and ABI associations may be driven by sex differences in disease burdens rather than sex differences in associations. Indeed, other investigations have found that bone density is associated with cardiovascular events in women.[37-39] In the present study, significant associations between vBMD and atherosclerosis were demonstrated where atherosclerosis is greatest - among men (rather than women) and in the internal carotid artery (rather than the common carotid artery). For instance, the ICA typically has ultrasound evidence of atherosclerotic disease earlier, more frequently, and in greater amounts that the CCA.[40] In addition, compared to CCA-IMT, ICA-IMT baseline and change correlate more strongly with male sex.[41, 42] Regardless, factors other than the magnitude of CVD may explain potential sex differences in the associations between bone mineral density and atherosclerosis by anatomic site, and sex.

Numerous factors affect disease development in both the bones and arteries. In addition to sex hormones, inflammation, and renal disease, other factors may explain the associations demonstrated in this investigation. Among these are the cannabinoid system, which includes cannabinoid receptors in atherosclerotic lesions, [43, 44] the osteoprotegerin/RANK/RANKL system, which receives input from estrogen and, itself, affects both atherosclerotic[45] and osteoporotic change[46], bone morphogenic proteins, oxidative stress including oxidized LDL and oxysterols,[47, 48] and the contribution of flow-limiting atherosclerotic disease to bone.[49-52] Oxidized LDL, commonly found in atherosclerotic lesions, is known to promote the calcification of vascular smooth muscle cells as well as inhibit the differentiation of bone-building osteoblastic cells which are typically located

adjacent to the subendothelial matrix of bone vessels. In all, cell and molecular data may indicate that associations between bone and atherosclerosis are more obvious for calcified atherosclerosis than atherosclerosis measured by other markers.

The present study examined a similar population sample as a previous report from the MESA where vBMD was independently, and significantly associated with coronary and aortic calcium in women and with aortic calcium in men [53]. In the present study, associations between vBMD and IMT and ABI, measures of atherosclerosis that do not specifically include calcium, were not as consistent across sex or measure of atherosclerosis. However associations with more advanced, or more fibrous and calcified carotid plaques were significant in both men and women, findings consistent with a previous investigation from the MESA which demonstrated significant associations between lumbar bone density and calcified atherosclerosis in the coronary arteries and abdominal aorta.[54] The present findings extend conclusions from the Tromso Study[7] where bone mineral density was not associated with carotid IMT or lipid-rich echolucent plaques but was significantly associated with fibrous and calcified echogenic plaques by demonstrating similar patterns independent of potential confounders, mediators and shared risk factors. Although the clinical significance of calcified versus non-calcified carotid artery plaque is not certain, the bone-artery association may be stronger for measures of calcified atherosclerosis than other measures of atherosclerosis in general.

Limitations of our study include the cross-sectional design, which limits conclusions about causality, bone mineral density measured from a single bone site, and lack of data describing the use of selective estrogen receptor modulators, and anti-resorptive agents. The interpretation of cross-sectional associations for the ABI, the carotid IMT and vBMD are further complicated because these outcomes may have different determinants for initial values than for change.[55, 56] In all, conclusions about causality are tentative at best. The strengths of this study include a multi-ethnic sample of both men and women, multiple measurements of subclinical atherosclerosis at two sites, volumetric bone mineral density measurements, and extensive data on potential risk factors for atherosclerosis and osteoporosis.

In conclusion, this investigation demonstrated significant associations between lumbar vBMD and atherosclerosis, as assessed by the ankle-brachial index and internal carotid intima-media thickness, in men but not women. In both men and women significant, independent associations between vBMD and more echogenic carotid plaques were demonstrated and may indicate that vBMD is more strongly associated with more advanced or more calcified atherosclerosis.

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Table 1

Characteristics of participants from the MESA, Abdominal Aortic Calcium Study, 2000-2005

Characteristic	WOMEN	MEN
N	904	929
Age y	65 (9)	64 (10)
Race/Ethnicity (%)		
White	344 (38)	389 (42)
Chinese	116 (13)	133 (14)
Black	206 (23)	167 (18)
Hispanic	238 (26)	240 (26)
ABI	1.09 (0.10)	1.15 (0.11)
Mean CCA-IMT† mm	0.85 (0.18)	0.89 (0.20)
Mean ICA-IMT ‡ mm	1.02 (0.58)	1.11 (0.60)
Bone mineral density, mg/cc	112 (40)	121 (39)
Body mass index, kg/m^2	28.3 (5.8)	27.8 (4.3)
Total cholesterol, mg/dL	201 (33)	190 (34)
HDL-cholesterol, mg/dL	57 (16)	45 (12)
Cholesterol medication (%)	151 (17)	130 (14)
Diabetes (%)	93 (10)	127 (13)
Hypertension (%)	422 (47)	408 (44)
Cigarette smoking (%)		
Never	543 (60)	386 (42)
Former	254 (28)	416 (45)
Current	106 (12)	40 (14)
Alcohol consumption (%)		
Never	278 (31)	102 (11)
Former	175 (19)	230 (25)
Current	445 (50)	596 (64)
LN(Interleukin-6) pg/mL	0.84 (0.36)	0.81 (0.37)
LN(C-reactive protein) mg/L	1.35 (0.77)	1.02 (0.65)
Homocysteine, μmol/L	8.7 (4.7)	10.0 (3.4)
Physical activity, met-min/week/100	121 (59)	119 (73)
Hormone therapy§ (%)	332 (37)	- - -
Estradiol, nmol/L	0.07 (0.07)	0.12 (0.04)
SHBG, nmol/L	56.7 (33.7)	43.2 (18.0)
Testosterone, nmol/L	1.10 (0.89)	15.0 (5.5)

Mean (SD) and percentage (N) are shown for continuous and discrete variables

* ABI is ankle-brachial index

† CCA-IMT is common carotid artery intima-media thickness

‡ ICA-IMT is internal carotid artery intimal-media thickness, not transformed

[§]Estrogen use in the previous two years; Values for estradiol, SHBG (sex hormone binding globulin) and testosterone in women include only 559 women not taking estrogens

Table 2

Mean ankle-brachial index (ABI), common carotid artery intima-media thickness (CCA-IMT), and internal carotid artery IMT (ICA-IMT) by sex-specific quartile of trabecular lumbar bone mineral density (vBMD), MESA, Abdominal Aortic Calcium Study, 2000-2005

	WOMEN			MEN		
	Model 1 *	**Model 2** †	**Model 3** ‡	**Model 1** *	**Model 2** †	**Model 3** ‡
	n=904	n=868	n=807	n=929	n=898	n=884
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Mean ABI						
vBMD Q1	1.09±0.007	1.08±0.008	1.08±0.009	1.12±0.008	1.11±0.008	1.11±0.008
vBMD Q2	1.10±0.007	1.09±0.007	1.09±0.008	1.14±0.007	1.13±0.008	1.13±0.008
vBMD Q3	1.08±0.007	1.08±0.007	1.08±0.008	1.15±0.007	1.15±0.008	1.15±0.008
vBMD Q4	1.10±0.007	1.09±0.008	1.09±0.009	1.14±0.007	1.13±0.008	1.14±0.008
p for ANCOVA	0.119	0.202	0.215	0.017	0.007	0.004
p for trend	0.828	0.928	0.976	0.041	0.017	0.009
Mean ICA-IMT (mm) §						
vBMD Q1	0.90±0.03	0.97±0.04	0.98±0.04	1.01±0.03	1.04±0.03	1.05±0.03
vBMD Q2	0.86±0.03	0.89±0.03	0.91±0.03	0.95±0.03	0.96±0.03	0.97±0.03
vBMD Q3	0.87±0.03	0.89±0.03	0.91±0.03	0.96±0.03	0.99±0.03	0.98±0.03
vBMD Q4	0.86±0.03	0.89±0.03	0.89±0.03	0.91±0.03	0.93±0.03	0.93±0.03
p for ANCOVA	0.703	0.167	0.163	0.106	0.061	0.053
p for trend	0.462	0.106	0.071	0.033	0.023	0.015

§Mean values are geometric means for ICA-IMT

*Adjusted for age and race/ethnicity.

†Adjusted for age, race/ethnicity, body mass index, total cholesterol, HDL, use of cholesterol medication, hypertension, diabetes, cigarette smoking, alcohol consumption, physical activity, homocysteine, C-reactive protein, interleukin-6 and hormone therapy (women only)

‡Adjusted for age, race/ethnicity, body mass index, total cholesterol, HDL, use of cholesterol medication, hypertension, diabetes, cigarette smoking, alcohol consumption, physical activity, homocysteine, C-reactive protein, interleukin-6 and unordered quartiles of total testosterone, sex hormone binding globulin and estradiol. In women, these quartiles are specific for women taking and not taking supplemental estrogens.

Table 3

Mean lumbar bone mineral density (vBMD) by sex and carotid artery plaque characteristic, MESA, Abdominal Aortic Calcium Study, 2000-2005

	WOMEN				MEN			
		Model 1 *	Model 2 †	Model 3 ‡		Model 1 *	Model 2 †	Model 3 ‡
		n=904	n=868	n=807		n=929	n=898	n=884
	% (N)	vBMD	vBMD	vBMD	% (N)	vBMD	vBMD	vBMD
		Mean±SE	Mean±SE	Mean±SE		Mean±SE	Mean±SE	Mean±SE
Carotid plaque								
No plaque	61 (548)	113±1	113±2	113±2	56 (516)	126±1	125±2	126±2
Echolucent	7 (66)	108±4	108±4	108±4	9(87)	125±4	123±4	122±4
Isolucent	23 (207)	109±2	109±3	109±3	26 (244)	121±2	120±3	120±2
Echogenic	5 (41)	106±5	105±5	106±5	3 (30)	121±6	119±6	119±6
Calcified	5 (42)	103±5	104±5	106±5	6 (52)	117±5	116±5	118±5
p for ANCOVA		0.316	0.231	0.295		0.230	0.175	0.129
p for trend		0.043	0.014	0.035		0.025	0.013	0.010

* Adjusted for age and race/ethnicity.

† Adjusted for age, race/ethnicity, body mass index, total cholesterol, HDL, use of cholesterol medication, hypertension, diabetes, cigarette smoking, alcohol consumption, physical activity, homocysteine, C-reactive protein, interleukin-6 and hormone therapy (women only)

‡ Adjusted for age, race/ethnicity, body mass index, total cholesterol, HDL, use of cholesterol medication, hypertension, diabetes, cigarette smoking, alcohol consumption, physical activity, homocysteine, C-reactive protein, interleukin-6 and unordered quartiles of total testosterone, sex hormone binding globulin and estradiol. In women, these quartiles are specific for women taking and not taking supplemental estrogens.