Association of Coronary Artery and Aortic Calcium With Lumbar Bone Density
The MESA Abdominal Aortic Calcium Study

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Atherosclerosis and osteoporosis share many risk factors, but their independent association is unclear. The authors investigated the independent associations between volumetric trabecular bone mineral density (vBMD) of the lumbar spine and coronary artery calcium (CAC) and abdominal aortic calcium (AAC). During 2002–2005, they used quantitative computed tomography to assess vBMD and the presence and extent of CAC and AAC among 946 women (mean age = 65.5 years) and 963 men (mean age = 64.1 years) in a substudy of the Multi-Ethnic Study of Atherosclerosis. Prevalences of CAC were 47% and 68% in women and men, respectively, and AAC prevalences were 70% and 73%. Sequential, sex-specific regression models included adjustment for age, ethnicity, body mass index, hypertension, dyslipidemia, diabetes mellitus, smoking, alcohol consumption, physical activity, interleukin-6, C-reactive protein, homocysteine, and sex hormones. After full adjustment, lower vBMD was associated with greater CAC score among women (P < 0.002) and greater AAC score among women (P = 0.004) and men (P < 0.001). After adjustment, vBMD quartile was inversely associated with CAC prevalence (P-trend = 0.05) in women and AAC prevalence (P-trend < 0.01) in men. Partially and fully adjusted models showed similar results. Though modest, these significant, independent associations suggest that atherosclerosis and bone loss may be related.

Atherosclerosis; calcium; arteries; atherosclerosis; bone and bones; bone density; calcium; coronary vessels; ethnic groups

Abbreviations: AAC, abdominal aortic calcium; CAC, coronary artery calcium; CT, computed tomography; MESA, Multi-Ethnic Study of Atherosclerosis; vBMD, volumetric trabecular bone mineral density.

Calcium in the coronary arteries and the abdominal aorta is closely related to the volume of atherosclerosis at arterial sites (1) and shares histologic patterns with bone tissues at skeletal sites (2). Both arterial calcium and bone density have demonstrated the incremental ability to predict future death from cardiovascular disease (3–5), while in large observational studies, investigators have reported significant inverse associations between bone density and atherosclerosis (5–9). Both are strongly correlated with age, sex, and ethnicity, but other determinants are less robust (10–12).

Laboratory investigations have demonstrated that oxidized low density lipoproteins inhibit normal osteoblast development from bone marrow stromal cells and also promote the calcification of vascular smooth muscle cells (13), suggesting that the link between bone density and atherosclerosis may be relevant in the context of calcified atherosclerosis (14). However, investigators discussing possible reasons for a bone-artery association typically implicate lipids (15), inflammation (2), or sex hormones (7, 16) to explain the common disease patterns. To our knowledge, no epidemiologic investigations to date have been able to evaluate simultaneously the roles of each of these factors in the association. With few exceptions (17), previous studies of the association have not included a multiethnic sample, and patterns of atherosclerosis and bone density are known to vary by ethnicity (10, 18).
We hypothesized that calcified atherosclerosis, specifically coronary artery calcium (CAC) and abdominal aortic calcium (AAC), would be inversely associated with volumetric trabecular bone mineral density (vBMD) of the lumbar spine in a population free of symptomatic cardiovascular disease. We further hypothesized that these associations would be attenuated upon adjustment for lipids, inflammatory markers, sex hormones, and other potential shared determinants (19).

MATERIALS AND METHODS

Study participants

The methods of the Multi-Ethnic Study of Atherosclerosis (MESA) have been described previously (20). In brief, the MESA cohort was recruited between July 2000 and August 2002 from 6 field centers around the United States. The study population consisted of 6,814 men and women aged 45–84 years who were free of clinically manifest cardiovascular disease and identified themselves as non-Hispanic white, Chinese-American, African-American, or Hispanic.

In this analysis, we used a random sample of MESA subjects who participated in the MESA Abdominal Aortic Calcium Study. Participants in the MESA Abdominal Aortic Calcium Study were recruited during follow-up visits between August 2002 and September 2005 from 5 MESA field centers: Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Of 2,202 MESA subjects recruited, 2,172 agreed to participate, and 1,990 satisfied the eligibility criteria, including postmenopausal status (for women), no recent prior diagnostic abdominal computed tomography (CT), and age and ethnicity subsampling from the MESA. In all, 1,968 participants (974 women and 994 men) completed CT scanning. Subsequently, 28 women and 31 men were excluded because of vertebral abnormalities complicating bone density measurement. Concurrent CAC scores were available for all but 28 women and 25 men. For these participants, CAC scores were replaced with scores from a study visit made 2 years prior. There were no missing AAC data, leaving 946 female and 963 male participants for investigation. Signed informed consent was obtained for all participants, and institutional review board approval was obtained from all participating institutions.

CT scanning

Participants underwent CT scanning of the chest at 1 of 2 clinical visits between August 2002 and September 2005. Scans were performed either with an electrocardiogram-triggered (at 80% of the R-R interval) electron-beam CT scanner (Imatron C-150; GE Medical Systems, Milwaukee, Wisconsin) or with prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector CT system (Somatom Sensation 64 (Siemens, Erlanger, Germany), Lightspeed QXi (GE Medical Systems), Siemens S4+ Volume Zoom (Siemens), and Siemens Sensation 16 (Siemens)) that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (New York, Forsyth County, and St. Paul field centers) (21). For accuracy, 2 chest scans were performed for each individual. CT of the abdomen was performed concomitantly with the CT scans of the chest for CAC. For electron-beam CT, scanners were set as follows: scan collimation of 3 mm, slice thickness of 6 mm, reconstruction using 25 6-mm slices with a 35-cm field of view, and normal kernel. For multidetector CT, images were reconstructed in a 35-cm field of view with a 5-mm slice thickness. All scans were brightness-adjusted with a standard phantom.

Calcium scoring

CT scans were read centrally by the MESA CT Reading Center, and calcium in the coronary arteries and in an 8-cm segment of the distal abdominal aorta ending at the aortic bifurcation was scored. Abdominal calcium score and the average Agatston CAC score were determined with high reliability, as has been previously described (21, 22). Rescan agreement for CAC score was found to be high with both electron-beam tomography and multidetector CT scanners (22). Interobserver agreement and intraobserver agreement were found to be very high (κ = 0.93 and κ = 0.90, respectively) (21–23).

Bone density measurement

Using CT scans of the abdomen, data were collected using the Image Analysis QCT 3D PLUS software program (Image Analysis, Columbia, Kentucky), and scans were read centrally at the MESA CT Reading Center by a reader blinded to the results of arterial calcium scoring. Measurements of vBMD in a virtual 10-mm-thick slice of trabecular bone from each vertebra (L2–L4) used software-directed, automated placement of the region of interest in the anterior one-half to one-third of the vertebral body, where it encompassed a large area exclusively of trabecular or cancellous bone, excluded cortical bone, and excluded the basivertebral plexus. A trained reader examined each region of interest and changed its placement to exclude vertebral abnormalities, including bone islands and diffuse density variations, or excluded a vertebra entirely if any of the following abnormalities were noted: fractures, metastatic lesions, osteophytes, or benign focal lesions within the vertebra. In the current analyses, we used bone density from the third lumbar vertebra.

In a random sample of 25 scans reread on 3 occasions, there was 100% agreement on inclusion or exclusion for all vertebrae assessed (L2–L4). Multivariate repeated-measures analysis of variance indicated no time effect in the data (Wilks’ test with 18 df: F-equivalent = 0.18, P = 0.839) (24). Pearson’s r for pairwise rereads was greater than 0.98.

Clinical measurements

Covariate data from the first MESA examination were used in the present analyses (20). Age, sex, ethnicity, height, weight, current use of prescription medications, physical activity patterns (metabolic equivalents × minutes/week),
smoking history, alcohol consumption (never/former/current), and previous medical diagnoses were recorded. Hormone therapy among women was defined as recent if hormone use in the previous 2 years was reported. Dietary calcium was calculated using a self-administered food frequency questionnaire and dietary supplement form. Body mass index was calculated as weight in kilograms divided by height in meters squared from data concurrent with bone density assessment. Blood pressure was measured 3 times with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon Company, LLC, Tampa, Florida) while the participant rested in a seated position. The average of the last 2 measurements was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication.

Laboratory measurements

Levels of C-reactive protein, interleukin-6, and homocysteine were measured using standardized methods (20).

Serum sex hormone concentrations were measured from stored samples at the University of Massachusetts Medical Center in Worcester, Massachusetts. Total testosterone and dehydroepiandrosterone were measured directly using radioimmunoassay kits, and sex hormone-binding globulin was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, California). Estradiol was measured by use of an ultrasensitive radioimmunoassay kit from Diagnostic Systems Laboratories, Inc. (Webster, Texas).

Levels of total cholesterol, high density lipoprotein cholesterol, triglycerides, and glucose were measured from blood samples obtained after a 12-hour fast. For the analyses described here, we used measurements ascertained at the initial visit to minimize missing values. Low density lipoprotein cholesterol was calculated with the Friedewald equation (25). Diabetes was defined as either a fasting plasma glucose concentration greater than 126 mg/dL, or reported previous diagnosis of diabetes, or the use of glycemic medication.

Statistical analyses

All analyses were stratified by sex, given the significantly different distributions of calcified atherosclerosis (26) and bone density (27) in men and women. Chi-square tests of association and generalized linear models were used to compare distributions of categorical and continuous variables, respectively, across ethnic groups and bone density quartiles. Trend tests used integer scores across quartiles.

To determine the association between bone density and calcified atherosclerosis, we used 2-part analyses. We tested the overall association between bone density and arterial calcium for each bed using multiple linear regressions to estimate the mean of the natural logarithm of Agatston score plus 1 for each bone density quartile. In addition, the association between bone density and the presence or absence of calcified atherosclerosis was directly estimated as the prevalence ratio (relative prevalence) using a generalized linear regression model with a log link, Gaussian error, and robust estimates of variance. This model was selected because the odds ratio requires the rare disease assumption to estimate accurately the prevalence ratio or risk ratio (28).

We aimed to test the contributions of different groups of variables to the associations between bone density and atherosclerosis. The following terms were defined as mutually exclusive theoretical concepts, as follows: a confounder is a covariate that is associated with both bone density and atherosclerosis but is a risk factor for only the outcome (here, calcified atherosclerosis); mediators are covariates that mediate or lie within the causal pathway between atherosclerosis and bone density; and common risk factors are covariates that cause both atherosclerosis and low bone density. The empirical effect of adjusting for a confounder, mediator, or common risk factor in these serial models is attenuation or augmentation of an association. No change in the association with adjustment indicates that the added covariates make no contribution to the association (19).

Associations were adjusted for groups of covariates in serial models. In model 1, we adjusted for age in quartiles and ethnicity. In model 2, we adjusted additionally for total cholesterol, high density lipoprotein cholesterol, use of lipid medication, hypertension, diabetes mellitus, smoking (never/former/current), body mass index, physical activity, the natural logarithm of dietary calcium, alcohol consumption (never/former/current), and (women only) hormone therapy. In the final model (model 3), we additionally adjusted the prevalence ratio for novel risk markers—ln(interleukin-6), ln(C-reactive protein), homocysteine, and sex-specific quartiles of total testosterone, estradiol, and sex hormone-binding globulin (but not for recent hormone therapy). For women, quartiles of sex hormones were investigated when defined separately for those using and not using supplemental estrogens in an unordered 8-level variable and when groups were collapsed to form quartiles making a 4-level variable. Models were inspected for attenuation and/or augmentation of an association across quartiles.

Regression diagnostics included tests of interaction by age, ethnicity, and (in women) hormone therapy. We investigated possible multicollinearity by screening for tolerance values less than 0.15 for variables in fully adjusted models; no multicollinearity was found.

RESULTS

The characteristics of women and men in this study are shown in Table 1. The average age of the women was 65 years, and the average age of the men was 64 years. Nonwhite participants comprised 62% of women and 59% of men. In women, the prevalences of CAC and AAC were 47% and 70%, respectively. In men, CAC and AAC prevalences were 68% and 73%. Among women, 37% had taken estrogen within 2 years of bone density assessment.

Table 2 demonstrates the distribution of participants by sex-specific quartile of vBMD. For both sexes, participants in higher quartiles of vBMD were significantly younger (P < 0.05), although there was substantial overlap in age across vBMD quartiles. The natural logarithms of CAC and
AAC scores were greater with decreasing vBMD quartile (in both sexes, \( P < 0.01 \)). CAC and AAC prevalences were greater among persons in lower vBMD quartiles before adjustment (in both sexes, \( P < 0.001 \) for both outcomes), and associations were attenuated after adjustment for age and ethnicity, with marginally significant associations in women for CAC (\( P = 0.052 \)) and in men for AAC (\( P < 0.001 \)).

Table 3 displays the adjusted quartile differences in mean values of the natural logarithm of CAC score plus 1 and AAC score plus 1 among all participants. The adjusted differences were calculated for persons in the lower 3 quartiles as compared with the highest quartile. In women, lower vBMD was significantly associated with greater CAC score in all models (in all models, \( P < 0.01 \) for trend). Lower vBMD was also significantly associated with greater AAC score among women, regardless of adjustments (in all models, \( P < 0.01 \) for trend). In men, lower vBMD quartile was associated with greater CAC score, and this association was

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Table 1. Characteristics of Women and Men in the MESA Abdominal Aortic Calcium Study, 2000–2005

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n = 946)</th>
<th>Men (n = 963)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.2 (9.2)</td>
<td>64.1 (9.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>360</td>
<td>38</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>119</td>
<td>13</td>
</tr>
<tr>
<td>African-American</td>
<td>218</td>
<td>23</td>
</tr>
<tr>
<td>Hispanic</td>
<td>249</td>
<td>26</td>
</tr>
<tr>
<td>Bone densitya, mg/cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery calciumb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>442</td>
<td>47</td>
</tr>
<tr>
<td>ln(Score + 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal aortic calciumb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>662</td>
<td>70</td>
</tr>
<tr>
<td>ln(Score + 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity, MET-minutes/week/100</td>
<td>120 (59)</td>
<td>120 (73)</td>
</tr>
<tr>
<td>Body mass indexc</td>
<td>28.4 (5.8)</td>
<td>27.8 (4.4)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>201  (33)</td>
<td>191 (34)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>57 (16)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>Use of cholesterol medication</td>
<td>165</td>
<td>17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>110</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>447</td>
<td>47</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Former smoker</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>ln(Dietary calcium), mg/day</td>
<td>6.4 (0.6)</td>
<td>6.5 (0.6)</td>
</tr>
<tr>
<td>ln(Interleukin-6), pg/mL</td>
<td>0.85 (0.36)</td>
<td>0.81 (0.37)</td>
</tr>
<tr>
<td>ln(C-reactive protein), mg/L</td>
<td>1.35 (0.78)</td>
<td>1.03 (0.64)</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>8.7 (4.6)</td>
<td>10.0 (3.4)</td>
</tr>
<tr>
<td>Recent hormone therapyd</td>
<td>346</td>
<td>37</td>
</tr>
<tr>
<td>Estradiol, nmol/L</td>
<td>0.14 (0.18)</td>
<td>0.12 (0.04)</td>
</tr>
<tr>
<td>Sex hormone-binding globulin, nmol/L</td>
<td>77.3 (56.8)</td>
<td>43.2 (17.9)</td>
</tr>
<tr>
<td>Total testosterone, nmol/L</td>
<td>1.06 (0.98)</td>
<td>15.0 (5.6)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; SD, standard deviation.

a Volumetric trabecular bone mineral density of the lumbar spine.
b Mean calcium scores include only participants with positive scores.
c Weight (kg)/height (m)².
d Estrogen use in the previous 2 years.

significant after full adjustment (for trend across quartiles, \( P = 0.03 \)). In men, lower vBMD quartile was significantly associated with greater AAC score regardless of adjustment (\( P < 0.001 \)).

Table 4 displays prevalence ratios for any CAC and AAC derived from sex-specific sequential models. Among women, quartile decrement of vBMD was significantly associated with CAC > 0. Comparing the highest quartile of bone density with the lowest quartile, this association differed little when results were adjusted for age and ethnicity (prevalence ratio \( = 1.17, 95\% \) confidence interval: 0.95, 1.43; for trend across quartiles, \( P = 0.052 \)) or when results were fully adjusted (prevalence ratio \( = 1.15, 95\% \) confidence interval: 0.96, 1.39; for trend across quartiles, \( P = 0.048 \)). In contrast, vBMD quartile was not significantly associated with AAC presence in any models among women.

In men, vBMD was not significantly associated with CAC presence but was significantly associated with AAC presence. After adjustment for age and ethnicity, men in the lowest quartile of vBMD had a 19\% greater prevalence (95\% confidence interval: 1.07, 1.32; for trend across quartiles, \( P = 0.001 \)) of AAC than men in the highest quartile of vBMD. The magnitude and significance of this association did not change after full adjustment.

For the results presented in Tables 3 and 4, we conducted multiple sensitivity analyses, including substitution of L4 vBMD values for L3 vBMD values, exclusion of participants without concurrent vBMD and CAC assessment, alternative adjustment and exclusions for sex hormone measurements, and redefinition of calcium presence as an Agatston score of 10 or greater; multiple variable forms for age, including linear, continuous age, were investigated, as well as time since the menopause began (women only). Across models, patterns of associations were similar, and the results from final models did not differ materially from those shown. In addition, for any outcome, each analysis specified by models 1 and 2 was repeated with the smaller samples available for model 3. Results did not differ materially from those presented. Tests of interaction by ethnicity were not statistically significant for either sex or outcome. In a final rigorous adjustment for age, a series of models in which vBMD quartile was assigned specifically by sex and quartile of age yielded findings similar to those shown, with the exception of a loss of statistical significance of the association between linear CAC and vBMD among men in model 3 and statistical significance of the association between AAC prevalence and vBMD in women.

**DISCUSSION**

In this study, we demonstrated inverse, independent associations between vBMD and calcified atherosclerosis. Lower vBMD was significantly associated with greater...
Table 4. Prevalence Ratio for the Association of Coronary Artery Calcium and Abdominal Aortic Calcium With Sex-Specific Quartile of Volumetric Trabecular Bone Mineral Density of the Lumbar Spine, MESA Abdominal Aortic Calcium Study, 2000–2005

<table>
<thead>
<tr>
<th>Measure and Bone Density Quartile</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ln(CAC + 1)</td>
<td>n = 946</td>
<td>n = 859</td>
<td>n = 769</td>
<td>n = 963</td>
<td>n = 887</td>
<td>n = 848</td>
<td>n = 963</td>
<td>n = 887</td>
<td>n = 848</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.61 (0.22)&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>0.81 (0.24)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.77 (0.25)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.34 (0.24)</td>
<td>0.47 (0.25)</td>
<td>0.52 (0.25)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.34 (0.24)</td>
<td>0.47 (0.25)</td>
<td>0.52 (0.25)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.30 (0.21)</td>
<td>0.32 (0.21)</td>
<td>0.27 (0.24)</td>
<td>0.06 (0.23)</td>
<td>0.14 (0.23)</td>
<td>0.26 (0.24)</td>
<td>0.06 (0.23)</td>
<td>0.14 (0.23)</td>
<td>0.26 (0.24)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.05 (0.20)</td>
<td>-0.04 (0.20)</td>
<td>-0.01 (0.23)</td>
<td>-0.08 (0.22)</td>
<td>0.10 (0.23)</td>
<td>0.10 (0.23)</td>
<td>-0.08 (0.22)</td>
<td>0.10 (0.23)</td>
<td>0.10 (0.23)</td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.002</td>
<td>0.137</td>
<td>0.067</td>
<td>0.034</td>
<td>0.137</td>
<td>0.067</td>
<td>0.034</td>
<td></td>
</tr>
</tbody>
</table>

| ln(AAC + 1) | n = 946 | n = 859 | n = 769 | n = 963 | n = 887 | n = 848 | n = 963 | n = 887 | n = 848 |
| 1 | 0.59 (0.30)<sup>a</sup> | 0.75 (0.29)<sup>a</sup> | 0.74 (0.30)<sup>a</sup> | 0.97 (0.27)<sup>a</sup> | 0.98 (0.26)<sup>e</sup> | 1.00 (0.27)<sup>a</sup> | 0.97 (0.27)<sup>a</sup> | 0.98 (0.26)<sup>e</sup> | 1.00 (0.27)<sup>a</sup> |
| 2 | 0.23 (0.27) | 0.23 (0.26) | 0.15 (0.28) | 0.52 (0.26)<sup>e</sup> | 0.57 (0.25)<sup>e</sup> | 0.64 (0.26)<sup>e</sup> | 0.52 (0.26)<sup>e</sup> | 0.57 (0.25)<sup>e</sup> | 0.64 (0.26)<sup>e</sup> |
| 3 | -0.33 (0.26) | -0.39 (0.24) | -0.41 (0.27) | 0.35 (0.25) | 0.43 (0.24) | 0.40 (0.24) | 0.35 (0.25) | 0.43 (0.24) | 0.40 (0.24) |
| 4<sup>f</sup> | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| P for trend | 0.020 | 0.003 | 0.004 | <0.001 | <0.001 | <0.001 | 0.020 | 0.003 | 0.004 |

Abbreviations: AAC, abdominal aortic calcium; CAC, coronary artery calcium; CI, confidence interval; MESA, Multi-Ethnic Study of Atherosclerosis.
<sup>a</sup> Adjusted for age and ethnicity.
<sup>b</sup> Additionally adjusted for total cholesterol, high density lipoprotein cholesterol, use of lipid medication, hypertension, diabetes mellitus, smoking, body mass index, physical activity, dietary calcium, alcohol consumption, and (women only) hormone therapy.
<sup>c</sup> Additionally adjusted for interleukin-6, C-reactive protein, homocysteine, total testosterone, estradiol, and sex hormone-binding globulin.
<sup>d</sup> Numbers in parentheses, standard error.
<sup>e</sup> Significant difference from reference category.
<sup>f</sup> Reference category.
coronary and aortic calcium in both women and men. In addition, vBMD was significantly associated with CAC prevalence in women and with AAC prevalence in men. In sequential models, these modest associations between bone density and atherosclerosis showed little evidence of attenuation or augmentation upon adjustment for lipids, inflammatory markers, and sex hormones, as well as other covariates, including shared risk factors for atherosclerosis and bone density such as physical activity and smoking. Only adjustment for age attenuated the associations (19).

The modest, significant, inverse associations between bone density and atherosclerosis in the present study are consistent with previous investigations in large samples of white women and extend previous findings to the coronary arteries, to men, and to nonwhite populations (29–31). To our knowledge, the present study was the first population-based study of a possible bone-artery association to assess bone density volumetrically, which uniquely permits the specific measurement of trabecular bone, the exclusion of vertebrae with bony islands or osteophytes, and volumetric accounting of differences in vertebra size by age, sex, and ethnicity (32, 33). This study was also the first to examine the effects of adjustment for lipids, multiple inflammatory markers, and sex hormones (34, 35). In addition, the present study was the first of its kind (17) to include both white and nonwhite participants, and patterns across ethnic groups did not differ significantly.

Evidence indicating possible roles for lipids, inflammation, and sex hormones in the association between osteoporosis and atherosclerosis comes indirectly from epidemiologic studies, animal models, and cell culture studies (36). In some epidemiologic investigations (37), but not all (38), investigators have reported that lipid level or saturated fat intake is associated with bone density (39). Atherosclerosis, as well as osteoporosis-like disease, can be induced in atherosclerosis-prone mice by assigning the animals to a high-fat diet (40). Cell-culture studies have demonstrated that oxidized low density lipoprotein can inhibit the differentiation of osteoblasts in bone, as in osteoporosis, and promote the calcification of smooth muscle vascular cells, as in atherosclerosis (13). In prospective observational studies, interleukin-6 has been independently associated with cardiovascular disease events (41) and bone loss (42), and homocysteine has been demonstrated to be a risk factor for cardiovascular disease (43) and osteoporotic fractures (44, 45). Finally, the uncertain role of sex hormones in cardiovascular disease is contrasted by their clearer roles in bone loss (27, 46).

In this study, multiple adjustments for all measured factors did not attenuate the associations between bone density and atherosclerosis, nor did multiple attempts to adjust for age fully attenuate the associations. Reports from this and other large, population-based observational studies, including the Framingham (6), Rancho Bernardo (7), Tromsø (8), and Rotterdam (9) studies, suggest that evidence for the association is less likely to be spurious. Three separate explanations for our results seem possible. First, lipids, inflammation, and sex hormones may account for the association, but the cross-sectional study design did not allow for a comprehensive assessment of their effects. Alternatively, factors not measured here, such as genotypes, may explain what is a noncausal association. Finally, atherosclerosis and bone density loss may be related processes.

A cross-sectional study is limited in its ability to evaluate the effects of long-acting factors such as lipids, inflammation, and sex hormones. However, large cross-sectional studies often detect associations with lipids, inflammatory markers, or sex hormones that are subsequently validated in prospective studies. Regarding other factors, many factors not measured in the MESA are known to affect disease development in both the bones and the arteries. In recent studies, the cannabinoid system has been implicated in atherosclerosis and osteoporosis (47, 48). Cannabinoid receptors are found in atherosclerotic lesions but also exert effects on bone, partly through the osteoprotegerin/RANKL system, which affects both atherosclerotic (49) and osteoporotic (50) change.

Alternatively, trabecular bone loss may result, in part, from atherosclerotic disease in bone arteries and may represent bone vascular disease (51). Recent magnetic resonance imaging studies have demonstrated that diminished bone perfusion is independently correlated with greater carotid atherosclerosis, lower bone density, and greater bone marrow fat content—the latter 2 being highly characteristic of osteoporosis (52, 53). Lower bone density is common in type 1 diabetics among whom microvascular disease is present (54); and in a trial among rats, assignment to hormone therapy or nitroglycerin, a potent vasodilator, resulted in equal improvements in bone density after surgical menopause (55). The recent application of volumetric roentgenographic methods has demonstrated that trabecular bone loss may begin as early as the second and third decades of life in men, coinciding with the early development of atherosclerotic disease, typically in the aorta (26, 33). The rapid loss of trabecular bone in early menopause among women crudely mirrors the “catch-up” phase of increased cardiovascular risk that occurs among women during that time (33). Trabecular bone density may prove useful for refined cardiovascular disease risk stratification.

There are few strong correlates of arterial calcium other than age, sex, and ethnicity (10–12). In the present study, associations between the ranges of CAC in women and AAC in both sexes, though modest, were highly significant and changed little after multiple adjustments. The relative prevalence estimates in this study were small; however, this was largely a result of the high prevalence of calcified disease in the lowest vBMD quartiles. Associations between bone density and arterial calcium were comparable to associations of calcium with standard cardiovascular risk factors such as hypertension and high density lipoprotein cholesterol (not shown).

Limitations of our study include its cross-sectional design, the use of bone density measurements from a single site, the onetime measurements of sex hormone levels and inflammatory factors, and a lack of data describing vitamin D status, parathyroid hormone levels, use of selective estrogen receptor modulators, and antiresorptive agents such as bisphosphonates. In light of these limitations, conclusions about causality from these data are speculative. Local effects of lipids, inflammation, or sex hormones in the bone
Arteries—effects not quantifiable by assessment of systemic venous blood here—may yet explain the association. This is the first investigation of its kind with a multiethnic sample, but conclusions about any ethnic differences are further limited by the small sizes of the ethnic subgroups.

In summary, we investigated a large, multiethnic, population-based sample with accurate measures of atherosclerosis from multiple sites, volumetric bone density, and extensive data on risk factors for atherosclerosis and low bone density. We found that vBMD was significantly associated with CAC presence and amount in women, AAC amount in women, and AAC prevalence in men. These associations did not change upon adjustment for multiple hypothesized correlates of an association, suggesting that bone loss and atherosclerosis may be linked processes. Clinically, the utility of bone density for refined cardiovascular disease risk stratification and/or assessment of biologic age merits further investigation. Joint epidemiologic and laboratory investigations may further elucidate the determinants and implications of a bone-artery association.

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