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No Association Between Bone Mineral Density and Breast Arterial Calcification Among Postmenopausal Women

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Context: The association between bone mineral density (BMD) and breast arterial calcification (BAC) remains poorly understood and controversial.

Objective: The objective of this article is to examine the association between BMD and BAC in a large cohort of postmenopausal women undergoing routine mammography.

Design: A cross-sectional analysis of baseline data from a multiethnic cohort was performed.

Setting: The setting for this analysis is an integrated health care delivery system in Northern California in the United States.

Patients: A total of 1273 women age 60 to 79 years (mean age, 67 years) were recruited within 12 months of screening mammography.

Main outcome measure: A BAC score (mg) was obtained from digital mammograms using a novel densitometry method. BAC presence was defined as a BAC score greater than 0 mg, and severe BAC as a BAC score greater than 20 mg.

Results: Overall, 53% of women had osteopenia and 21% had osteoporosis. The prevalence of BAC greater than 0 mg was 29%, 30%, and 29% among women with normal BMD, osteopenia, and osteoporosis, respectively ($P = 0.98$). The prevalence of BAC greater than 20 mg was 5%, 3%, and 5% among women with normal BMD, osteopenia and osteoporosis, respectively ($P = .65$). The odds ratios (ORs) of BAC greater than 0 mg vs BAC = 0 mg after multivariable adjustment were 1.09 (95% CI, 0.81-1.48; $P = .54$) for osteopenia and 0.99 (95% CI, 0.69-1.48; $P = .98$) for osteoporosis. The adjusted ORs for BAC greater than 20 mg vs BAC 20 mg or less were 1.03 (95% CI, 0.52-2.01; $P = .93$) for osteopenia and 1.89 (95 CI, 0.81-4.47; $P = .14$) for osteoporosis.

Conclusion: Our findings do not support an association of either osteopenia or osteoporosis with BAC presence or severity among postmenopausal women.

Abbreviations: BAC, breast arterial calcification; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; MINERVA, MultIethNic study of brEast aRterial calcium gradation and cardioVAscular disease

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Numerous prior studies have shown that low bone mineral density (BMD) is related to greater level of calcification in coronary and extracoronary arteries in women [1-17], suggesting that bone and vascular calcifications may have shared biological pathways. However, the relationship between low BMD and breast arterial calcification (BAC) remains little studied and controversial, with 2 studies showing a statistically significant association [18, 19] and 2 showing no association [20, 21]. Important limitations of these prior studies assessing the relation between BMD and BAC include relatively small sample sizes (ranging from 88 to 567 women) and the recruitment of participants through tertiary centers rather than population-based settings. The aim of our study was to examine whether BMD status was related to presence and severity of BAC in a much larger sample of postmenopausal women identified from a population-based setting.

Methods

Cohort description

Details of recruitment, study procedures, and baseline characteristics of MINERVA (MultIethNic study of brEast aRterial calcium gradation and cardioVAscular disease) participants are published elsewhere [22]. In brief, eligible participants were female active members of Kaiser Permanente of Northern California (KPNC) between ages 60 and 79 years at the time of routine mammography screening at 1 of 9 KPNC facilities (Oakland, Richmond, Pleasanton, Antioch, Walnut Creek, San Francisco, Santa Clara, Campbell, and Mountain View) between October 24, 2012 and February 13, 2015. Mammography exams performed for diagnostic purposes were not included. Those with a prior history of myocardial infarction, coronary revascularization, stroke, heart failure, peripheral vascular disease, breast cancer, mastectomy or breast implants, dementia, chronic dialysis/renal transplant, or not having an assigned primary care provider were not eligible for the study. A total of 5145 women with available digital, uncompressed mammographic images were recruited into the study. Of those, 4425 (86%) attended a research clinic visit and completed the full questionnaire, and the remaining 720 (14%) completed an abbreviated version of the questionnaire administered over the phone and did not attend the research clinic visit. The study was approved by the KPNC Institutional Review Board and all participants signed an informed consent. The cohort sample included in the present analyses consisted of attendees to the research clinic visit who had available BMD scan data in centralized digital records as part of routine medical care in the 3 years preceding the clinic visit (n = 1535). Of those, 168 women were excluded for missing covariate information (although we retained in the analysis participants with missing data on breastfeeding history and with missing alcohol consumption), resulting in a final analytical sample of 1367. Compared with the full MINERVA cohort (n = 5145), the analytical subset used here was slightly older (66.5 ± 3.7 vs 65.7 ± 4.4 years), more likely to be white (67% vs 53%), and less likely to be African American (9% vs 16%), Hispanic/Latina (7% vs 13%), or Asian/Pacific Islander (17% vs 18%). Moreover, the participant sample used in the present analysis had a slightly higher education level (50% with at least some college and 30% with at least some graduate school vs 48% and 31%), and a higher prevalence of any BAC (30% vs 26%).

Study Procedures

Breast Arterial Calcification Assessment by Full-Field Digital Mammography

All images in this study were acquired using full-field digital mammography units (Senographe 2000D, General Electric Medical Systems or Selenia Hologic, Hologic Inc). Standard full-field digital mammograms were acquired from mediolateral oblique and craniocaudal projections. A new, validated densitometry method was used to estimate a continuous BAC mass (in milligrams [mg]) score using raw (uncompressed) digital mammograms [23, 24]. The 0th, 50th, 75th, 90th, 95th, and 100th percentile points of BAC mass (in mg) in the analytical sample of 1367 were 0, 0, 0.39, 5.68, 15.7, and 341.6. This distribution resembled the full cohort of 5145 women (data not shown).

Bone Mineral Density and Covariates Assessment

BMD was measured as part of routine medical care using dual-energy X-ray absorptiometry (Hologic Inc). We identified the closest BMD assessment date within a 3-year window preceding the MINERVA baseline exam. The BMD T score was calculated according to standard guidelines (25) and participants were classified as having normal results, osteopenia, and osteoporosis based on the lowest BMD T score of the femoral neck, total hip, and lumbar spine, using recommended thresholds from the World Health Organization: normal BMD (T score ≥ -1.0; osteopenia $-1.0 >$ T score > -2.5; and osteoporosis T score ≤ -2.5) [25, 26]. In our analyses, site-specific classification as well as overall BMD classification based on the lowest T score of any of the 3 sites was examined.

Age, race/ethnicity, education level, reproductive history (menarche, menopausal hormone therapy, number of live births, and history of breastfeeding), smoking status, alcohol consumption, use of calcium supplements (dichotomized as no/yes), and use of osteoporosis drugs (dichotomized as no/yes) were ascertained with a self-administered questionnaire. Physical activity was measured with the Modified Baecke questionnaire for older adults [27], and we computed the total physical activity frequency (hours per week). Blood pressure was measured by standard procedure 3 times (with a 1-minute rest between assessments) in a seated position in the right arm using an automated blood pressure device (Welch Allyn model 5200) after 5 minutes of rest. The blood pressure cuff size was customized to the individual's arm circumference, and the average of the second and third readings were used in analysis. Weight was measured to the nearest 0.5 kg using a standard balance beam scale. Standing height was measured in centimeters to the nearest 0.5 cm with a standard generic wall-mounted stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Laboratory analyses were performed for a selected panel of blood analytes in a nonfasting state at a Clinical Laboratory Improvement Amendments–approved regional health plan laboratory. Nonfasting total cholesterol was measured with a Beckman AU5800 Chemistry Anayzer (Beckman Coulter, Inc). Hemoglobin A_{1c} was measured by immunoturbidimetric assay (Roche Diagnostics). Diabetes was defined as self-report of diabetes or use of antiglycemics in the questionnaire, hemoglobin A_{1c} greater than 6.5%, and by linkage with the KPNC Diabetes Registry (28). Hypertension was defined as self-report of hypertension, self-report of treatment for hypertension, systolic blood pressure greater than or equal to 140 mmHg, or diastolic blood pressure greater than or equal to 90 mmHg. Hypercholesterolemia was defined as self-report of high cholesterol, self-report of treatment for high cholesterol, or measured total cholesterol greater than 240 mg/dL. We obtained the most recent outpatient, nonemergency-department serum creatinine measurement within 1 year before the study visit and estimated glomerular filtration rates (eGFRs) using the Chronic Kidney Disease Epidemiology Collaboration equation [29].

Statistical methods

Group differences across BAC subgroups (BAC = 0 mg vs BAC > 0 mg) were ascertained using the t test for continuous variables and the chi-square test for categorical variables. To assess group differences across BAC severity groups (BAC = 0 mg, BAC > 0 mg but < 20 mg, BAC > 20 mg), we used analysis of variance and chi-square tests. To gauge the association

of BMD with any BAC, we performed logistic regression analysis with the outcome variable BAC greater than 0 mg (vs BAC = 0 mg) and the main independent variables osteopenia and osteoporosis (vs normal BMD, respectively). Four sets of separate logistic models were run, 1 for each site (hip, femoral neck, and spine) and another for overall osteopenia or osteoporosis defined using the lowest T score of any of the 3 sites. Each set of logistic models consisted of a minimally adjusted model (age and race/ethnicity as covariates) and a fully adjusted model that included (in addition to age and race/ethnicity) menopausal hormone therapy, breastfeeding, parity, eGFR, osteoporosis medications (in the full cohort analysis), hypertension, and calcium supplement use. We also performed logistic regression with BAC greater than 20 mg as the outcome and conducted sensitivity analyses of BAC greater than 0 mg and BAC greater than 20 mg excluding participants who self-reported taking osteoporosis drugs at baseline. To test for potential effect modification by age, we fitted 4 additional Models 1 (1 for each BMD predictor) adding the cross-product terms *osteopenia*age* and *osteoporosis*age*, with age specified as a continuous variable. In a separate set of interaction models, we added the cross-product terms *osteopenia* and *osteoporosis* for the Asian/Pacific Islander, African American, and Latina groups. None of the age or race/ethnicity interactions with either osteopenia or osteoporosis reached statistical significance after Bonferroni correction for multiple comparisons (8 age interactions plus 16 race/ethnicity interactions, $P = .05/24 = .002$). Results are thus not presented stratifying by either age or race/ethnicity. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc).

Results

The mean ± SD age of the cohort was 67 ± 4 years; 52% were white, 18% Asian/Pacific Islander, 15% African American, and 12% Latina. Thirty-one (2%) and 544 (40%) women had osteoporosis and osteopenia of the hip, respectively; 151 (11%) and 771 (56%) had osteoporosis and osteopenia of the femoral neck, respectively; and 200 (15%) and 513 (37%) had osteoporosis and osteopenia of the spine, respectively. Overall, 288 (21%) and 731 (53%) had osteoporosis and osteopenia, respectively. A total of 407 participants (30%) had BAC greater than 0 mg, and 55 (4%) had BAC greater than 20 mg.

The characteristics of the cohort by presence/absence of BAC are given in Table 1. Compared with women with no BAC, women with any BAC (ie, BAC > 0 mg) were slightly older, more likely to be white and Latina, and less likely to be Asian/Pacific Islander. Any presence of BAC was also significantly associated with lower use of menopausal hormone therapy, positive history of breastfeeding, increasing number of live births, lower eGFR, and hypertension. An association of borderline statistical significance ($P = .05$) existed between any BAC and self-report of osteoporosis treatment: Whereas 12% of women with no BAC were on osteoporosis drugs, 15% of women with BAC self-reported use of osteoporosis treatment. No meaningful differences by presence of BAC were noted for education level, age at menarche, smoking, alcohol consumption, physical activity, calcium supplements, BMI, diabetes, and hypercholesterolemia. Furthermore, no significant associations were found between BAC presence and T scores at any of the 3 sites or overall (all P values ≥ .12), or between BAC presence and site-specific or overall osteoporosis or osteopenia (all P values ≥ .28) (Table 1). BAC severity groups differed with respect to age, race, education, menopausal hormone therapy, history of breastfeeding, number of live births, eGFR, and hypertension (data not shown).

Fig. 1A depicts the prevalence of BAC greater than 0 mg and Fig. 1B shows BAC greater than 20 mg according to BMD status. Among women with normal BMD overall, the BAC prevalence was 29%, among those with osteopenia it was 30%, and among those with osteoporosis it was 30% ($P = .92$). No significant differences were noted in BAC prevalence in any of the BMD sites considered individually (all $P > .28$). No significant differences in prevalence of BAC greater than 20 mg were noted across BMD sites (all $P > .29$).

Table 1. Baseline cohort characteristics by breast arterial calcification (BAC) presence (n = 1367)

Baseline Cohort Characteristics	BAC = 0 mg n = 960 (70.2%)	BAC > 0 mg n = 407 (29.8%)	*P*[a]
Demographic factors			
Age, mean ± SD, y	66.5 ± 3.7	68.2 ± 4.3	< .001
Race, n (%)			.02
White	642 (66.9%)	296 (72.7%)	
African American	84 (8.7%)	35 (8.6%)	
Hispanic/Latina	71 (7.4%)	34 (8.4%)	
Asian/Pacific Islander	163 (17.0%)	42 (10.3%)	
Educational attainment, n (%)			.10
Less than high school	16 (1.7%)	8 (2.0%)	
High school or GED	144 (15.0%)	76 (18.7%)	
Associates degree or some college	157 (16.4%)	81 (19.9%)	
Bachelor degree	300 (31.3%)	120 (29.5%)	
Graduate school	343 (35.7%)	122 (30%)	
Reproductive history			
Menarche, n (%), y			.67
< 10	17 (1.8%)	6 (1.5%)	
10-11	169 (17.6%)	70 (17.2%)	
12-13	524 (54.6%)	221 (54.3%)	
14-15	201 (20.9%)	81 (19.9%)	
≥ 16	49 (5.1%)	29 (7.1%)	
Years into menopause, mean ± SD	16.9 ± 7.2	18.1 ± 8.1	.01
Currently on menopausal hormone therapy, n (%)			.04
No	843 (87.8%)	373 (91.7%)	
Yes	117 (12.2%)	34 (8.4%)	
History of breastfeeding, n (%)			.02
No	159 (16.6%)	72 (17.7%)	
Yes	517 (53.9%)	245 (60.2%)	
Unknown/missing	284 (29.6%)	90 (22.1%)	
Live births, n (%), No.			<.001
0	388 (40.4%)	142 (34.9%)	
1-2	413 (43.0%)	154 (37.8%)	
≥ 3	159 (16.6%)	111 (27.3%)	
Behavioral and anthropometric factors			
Smoking status, n (%)			.79
Never	565 (58.9%)	247 (60.7%)	
Former	363 (37.8%)	146 (35.9%)	
Current	32 (3.3%)	14 (3.4%)	
Alcohol consumption during past year, n (%)			
Wine			.37
Yes	572 (59.6%)	227 (55.8%)	
No	158 (16.5%)	69 (17.0%)	
Unknown/missing	230 (24.0%)	111 (27.3%)	
Beer			.28
Yes	156 (16.3%)	63 (15.5%)	
No	572 (59.6%)	229 (56.3%)	
Unknown/missing	232 (24.2%)	115 (28.3%)	
Liquor			.17
Yes	196 (20.4%)	88 (21.6%)	
No	534 (55.6%)	205(50.4%)	
Unknown/missing	230 (24.0%)	114 (28.0%)	
Total physical activity frequency, mean ± SD, h/wk	7.4 ± 4.4	7.1 ± 4.5	.25
Calcium supplements, n (%)			.31
No	317 (33.0%)	146 (35.9%)	
Yes	643 (67.0%)	261 (64.1%)	

Table 1. Continued

Baseline Cohort Characteristics	BAC = 0 mg n = 960 (70.2%)	BAC > 0 mg n = 407 (29.8%)	*P*[a]
Self-report of treatment for osteoporosis, n (%)			.05
No	848 (88.3%)	344 (84.5%)	
Yes	112 (11.7%)	63 (15.5%)	
BMI (kg/m^2), mean ± SD	26.7 ± 5.5	27.2 ± 5.3	.13
Renal function[b]			
Estimated GFR, mean ± SD, mL/min/1.73 m^2	79.9 ± 12.7	77.8 ± 12.6	.004
Estimated GFR, categories, n (%), mL/min/1.73 m^2			.08
< 60	66 (6.9%)	38 (9.3%)	
60-90	661 (68.9%)	289 (71.0%)	
> 90	233 (24.3%)	80 (19.7%)	
Diabetes[c]			.98
No	833 (86.8%)	353 (88.7%)	
Yes	127 (13.2%)	54 (13.3%)	
Hypertension[d]			.01
No	538 (56.0%)	199 (48.9%)	
Yes	422 (44.0%)	208 (51.1%)	
Hypercholesterolemia,[e] n (%)			.67
No	401 (41.8%)	175 (43.0%)	
Yes	559 (58.2%)	232 (57.0%)	
Bone mineral density			
Hip T score, mean ± SD	–0.75 ± 1.0	–0.66 ± 1.0	.12
Osteoporosis (T score < –2.5), n (%)	22 (2.3%)	9 (2.2%)	.28
Osteopenia (T score –2.5 to –1.0), n (%)	395 (41.2%)	149 (36.6%)	
Normal (T score > –1.0), n (%)	543 (56.6%)	249 (61.2%)	
Femoral neck T score, mean ± SD	–1.38 ± 1.0	–1.30 ± 1.0	.17
Osteoporosis (T score < –2.5), n (%)	109 (11.4%)	42 (10.3%)	.54
Osteopenia (T score –2.5 to –1.0), n (%)	547 (57.0%)	224 (55.0%)	
Normal (T score > –1.0), n (%)	304 (31.7%)	141 (34.6%)	
Spine T score, mean ± SD	–0.95 ±1.5	–0.88 ±1.6	.44
Osteoporosis (T score < –2.5), n (%)	144 (15.0%)	56 (13.8%)	.64
Osteopenia (T score –2.5 to –1.0), n (%)	353 (36.8%)	160 (39.3%)	
Normal (T score > –1.0), n (%)	463 (48.2%)	191 (46.9%)	
Overall T score, mean ± SD	–1.65 ± 1.0	–1.59 ± 1.0	.35
Overall osteoporosis (T score < –2.5), n (%)	204 (21.3%)	84 (20.4%)	.92
Overall osteopenia (T score –2.5 to –1.0), n (%)	510 (53.1%)	221 (54.3%)	
Overall normal (T score > –1.0), n (%)	246 (25.6%)	102 (25.1%)	

Abbreviations: BMI, body mass index; GED, General Educational Development; GFR, glomerular filtration rate.
[a]T test for continuous variables; chi-square tests for categorical variables.
[b]By Chronic Kidney Disease Epidemiology Collaboration equations.
[c]Self-report of diagnosis or self-report of treatment for diabetes or hemoglobin A_{1c} greater than 6.5% or in Kaiser Permanente of Northern California diabetes registry.
[d]Self-report of hypertension or self-report of treatment for hypertension or systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than 90 mmHg.
[e]Self-report of high cholesterol, treatment for high cholesterol, or measured total cholesterol greater than 240 mg/dL.

Table 2 summarizes the results of the logistic regression models predicting presence vs absence of BAC. In age- and race-adjusted models, neither osteopenia nor osteoporosis at any site (hip, femoral neck, spine, or overall) were associated with likelihood of BAC. Further adjustment for covariables in Model 2 did not appreciably alter the odds ratio estimates, although a statistically significant inverse association between hip osteopenia and presence of BAC emerged. When the analyses were repeated excluding women self-reporting use of osteoporosis drugs, the null findings persisted (data not shown). Table 3 shows the results

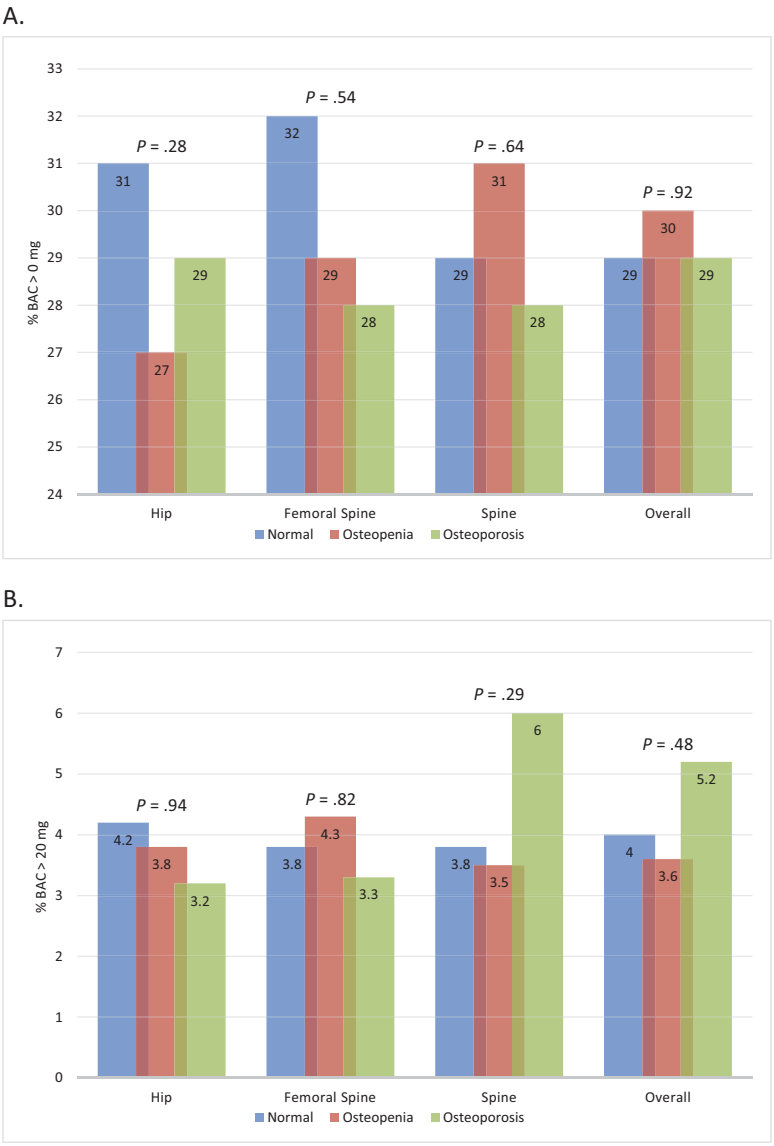

Figure 1. Prevalence of A, breast arterial calcification (BAC) greater than 0 mg, and B, BAC greater than 20 mg, by bone mineral density status by site and overall.

of the logistic models predicting BAC greater than 20 mg vs BAC of 20 mg or less. Similar to the presence vs absence analyses, no significant associations were found between any of the osteopenia and osteoporosis sites and higher severity of BAC. We found similar results for a threshold of BAC greater than 10 mg (data not shown). In the fully adjusted model that included overall osteopenia and osteoporosis, self-report of osteoporosis treatment had an association with any presence of BAC that approached the level of statistical significance (OR = 1.43; 95% CI, 0.98-2.08; $P = .06$). The corresponding OR for BAC greater than 20 mg was 1.72 (95% CI, 0.78-3.79; $P = .17$).

Discussion

In our sample of postmenopausal women, the prevalence of osteopenia overall was 53% and the prevalence of osteoporosis was 21%. Osteoporosis was more common at the lumbar spine (15% of women), followed by the femoral neck (11%), and least common in the total

Table 2. Odds ratios (ORs) of breast arterial calcification (BAC) greater than 0 mg vs BAC equal to 0 mg as a function of bone mineral density status (n = 1367)

BMD Site and Model	Full Cohort (n = 1367)		Excluding 175 Who Self-Reported Osteoporosis Drugs (n = 1192)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hip osteopenia				
Model 1	0.78 (0.61-1.01)	.06	0.78 (0.59-1.03)	.08
Model 2	0.76 (0.58-0.99)	.04	0.79 (0.60-1.05)	.10
Hip osteoporosis				
Model 1	0.93 (0.41-2.11)	.87	0.59 (0.19-1.84)	.37
Model 2	0.91 (0.39-2.11)	.83	0.66 (0.21-2.07)	.47
Femoral neck osteopenia				
Model 1	0.89 (0.68-1.16)	.38	0.87 (0.66-1.14)	.31
Model 2	0.88 (0.67-1.18)	.39	0.88 (0.66-1.16)	.36
Femoral neck osteoporosis				
Model 1	0.83 (0.55-1.27)	.40	0.95 (0.57-1.58)	.85
Model 2	0.78 (0.49-1.23)	.29	0.98 (0.58-1.64)	.94
Spine osteopenia				
Model 1	1.15 (0.89-1.49)	.28	1.21 (0.92-1.59)	.16
Model 2	1.18 (0.91-1.55)	.21	1.26 (0.95-1.67)	.11
Spine osteoporosis				
Model 1	1.06 (0.73-1.52)	.77	1.08 (0.69-1.68)	.73
Model 2	0.98 (0.66-1.47)	.95	1.12 (0.71-1.78)	.62
Overall osteopenia[a]				
Model 1	1.05 (0.78-1.40)	.75	1.06 (0.78-1.43)	.70
Model 2	1.09 (0.81-1.48)	.54	1.09 (0.80-1.49)	.56
Overall osteoporosis[a]				
Model 1	1.04 (0.73-1.50)	.79	1.05 (0.69-1.60)	.70
Model 2	0.99 (0.69-1.48)	.98	1.10 (0.71-1.70)	.65

Model 1: age, race/ethnicity.
Model 2: Model 1 covariates + menopausal hormone therapy, breastfeeding, parity, glomerular filtration rate, osteoporosis medications (in the full cohort analysis), hypertension, and calcium supplement use.
[a]Defined by the lowest T score at any of the 3 sites and using separate models for assessing overall osteopenia and overall osteoporosis.

hip (2%). In turn, osteopenia was highest at the femoral neck (56%), followed by the hip (39%) and lumbar spine (37%). Our data are consistent with estimates from the 2005-2010 National Health and Nutrition Examination Survey, in which the prevalence of osteoporosis and low bone mineral mass at the femur neck or lumbar spine in adults age 65 to 79 were 21% and 52%, respectively [30]. BAC was present in 30% of the women and was associated with older age, race\ethnicity (driven by lower BAC prevalence among Asian/Pacific Islander participants), use of menopausal hormone therapy (protective relation), history of breastfeeding, higher parity, reduced eGFR, and hypertension.

The findings of our study, conducted in more than 1200 postmenopausal women undergoing routine mammography, contribute to an increasing body of literature suggesting there is no association between BMD status and BAC in postmenopausal women. Previous studies have been limited by small sample size and inconsistent findings, with some reporting an association [18, 19] and others reporting no association [20, 21] of osteoporosis with BAC. The first study by Reddy et al in 2008 reported an independent cross-sectional association of overall osteopenia and osteoporosis with BAC presence in a sample of 228 women (55% Hispanic, 45% white) who underwent screening mammography and BMD evaluation between 2001 and 2003 [18]. Several differences between this study and ours should be pointed out that may explain the different results. First, Reddy and colleagues included whites and Hispanic women (whereas we included all 4 major ethnicities in the United States) and women older than 40 years (whereas MINERVA included women ages 60 to 79 years). Second, as recognized

Table 3. Odds ratios (ORs) of breast arterial calcification (BAC) greater than 20 mg vs BAC less than or equal to 20 mg as a function of bone mineral density status and according to self-report of osteoporosis treatment (n = 1367)

	Full Cohort (n = 1367)		Excluding 175 Women With Self-Report of Osteoporosis Treatment (n = 1192)	
BMD Site and Model	**OR (95% CI)**	*P*	**OR (95% CI)**	*P*
Hip osteopenia				
Model 1	0.94 (0.53-1.69)	.85	0.73 (0.37-1.44)	.36
Model 2	0.94 (0.50-1.77)	.58	0.75 (0.37-1.53)	.43
Hip osteoporosis				
Model 1	1.19 (0.15-9.33)	.87	1.86 (0.23-15.1)	.56
Model 2	1.36 (0.16-11.7)	.85	2.55 (0.28-22.9)	.40
Femoral neck osteopenia				
Model 1	1.15 (0.62-2.14)	.66	0.84 (0.43-1.65)	.62
Model 2	1.18 (0.61-2.29)	.77	0.88 (0.44-1.78)	.73
Femoral neck osteoporosis				
Model 1	0.94 (0.33-2.68)	.91	1.63 (0.56-4.74)	.37
Model 2	1.02 (0.32-3.21)	.97	1.77 (0.58-5.39)	.31
Spine osteopenia				
Model 1	0.91 (0.48-1.71)	.76	1.00 (0.51-1.95)	.99
Model 2	1.03 (0.52-2.01)	.93	1.09 (0.54-2.19)	.79
Spine osteoporosis				
Model 1	1.85 (0.88-3.88)	.10	1.31 (0.47-3.58)	.60
Model 2	1.89 (0.81-4.47)	.14	1.41 (0.49-4.06)	.52
Overall osteopenia[a]				
Model 1	0.84 (0.42-1.67)	.61	0.76 (0.37-1.54)	.45
Model 2	0.96 (0.46-1.99)	.90	0.82 (0.38-1.74)	.61
Overall osteoporosis[a]				
Model 1	1.42 (0.65-3.12)	.80	1.20 (0.47-3.02)	.45
Model 2	1.53 (0.62-3.78)	.35	1.27 (0.47-3.38)	.63

Model 1: age, race/ethnicity.
Model 2: Model 1 covariates + menopausal hormone therapy, breastfeeding, parity, glomerular filtration rate, osteoporosis medications (in the full cohort analysis), hypertension, and calcium supplement use.
[a]Defined by the lowest T score at any of the 3 sites and using separate models for assessing overall osteopenia and overall osteoporosis.

in their discussion, BMD in their cohort was driven by clinical indication (which could have induced collider bias and false-positive results) [31] and therefore the prevalence of osteoporosis was higher than in MINERVA (29% vs 21%) despite being a younger cohort. In addition, Reddy et al did not include recognized risk factors for BAC (parity and breastfeeding) nor did they consider osteoporosis medications and hormone replacement therapy in the analysis. A second study among 211 postmenopausal women in Brazil found, similar to ours, no association of low bone mass and osteoporosis with BAC [21]. A third cross-sectional study among 567 Turkish postmenopausal women reported a significant relationship between BAC and osteoporosis [19]. These authors however did not perform multivariable modeling and reported also that osteopenia was more common among women with no BAC. Supporting our negative findings, a fourth recent study among 88 postmenopausal women in Iran found no significant relationship between BMD and BAC [20].

A noteworthy finding in our study was that self-report use of osteoporosis drugs was associated with greater presence of BAC, although this relationship became borderline significant after multivariable adjustment. Although nitrogen-containing bisphosphonates (NCBPs, including ibandronate, alendronate, risedronate, and zoledronate) have been shown to reduce aortic calcification in animal models [32, 33], evidence of an effect on humans is sparse and inconsistent. For example, in the MESA cohort (n = 3636 women) NCBPs were

associated with a decreased prevalence of calcification in either the coronaries, aortic valve, aortic valve ring, mitral annulus, or in the thoracic aorta among women age 65 years or older, whereas calcification outcomes were more prevalent in NCBP users among women younger than 65 years [34]. Additional studies are required to further clarify the potential role of type, dose, duration of treatment, and administration route of NCBPs in human vascular calcification.

This study has several strengths. Our cohort of 1273 women is one of the largest populations to date in which the association of BMD and vascular calcification has been examined, focusing specifically on postmenopausal women with diverse representation from all 4 major ethnicities in the United States. We had extensive, rigorously obtained phenotypic information on known risk factors for BAC, including reproductive history, as well as information on intake of calcium supplements. Moreover, MINERVA is the first large cohort of postmenopausal women with a continuous measure of BAC by densitometry. We recognize several important limitations in our study. Because the cohort is insured, findings may not generalize to uninsured populations. Because we focused on women age 60 and older, we could not assess the association between BMD and BAC among younger women. We also recognize that the analyses presented here are cross-sectional.

In conclusion, low bone mass and osteoporosis did not appear to be associated with BAC or BAC gradation among postmenopausal women. A trend toward increased BAC presence in women self-reporting osteoporosis treatment deserves further investigation.

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References and Notes

1. Avramovski P, Avramovska M, Lazarevski M, Sikole A. Femoral neck and spine bone mineral density—surrogate marker of aortic calcification in postmenopausal women. *Anatol J Cardiol*. 2016;**16**(3):202–209.
2. Campos-Obando N, Kavousi M, Roeters van Lennep JE, et al. Bone health and coronary artery calcification: the Rotterdam Study. *Atherosclerosis*. 2015;**241**(1):278–283.
3. Chan JJ, Cupples LA, Kiel DP, O'Donnell CJ, Hoffmann U, Samelson EJ. QCT volumetric bone mineral density and vascular and valvular calcification: the Framingham Study. *J Bone Miner Res*. 2015;**30**(10):1767–1774.
4. Chen Z, Qureshi AR, Ripsweden J, et al. Vertebral bone density associates with coronary artery calcification and is an independent predictor of poor outcome in end-stage renal disease patients. *Bone*. 2016;**92**:50–57.
5. Chen Z, Sun J, Haarhaus M, et al. Bone mineral density of extremities is associated with coronary calcification and biopsy-verified vascular calcification in living-donor renal transplant recipients. *J Bone Miner Metab*. 2017;**35**(5):536–543.

6. Cirillo C, Bilancio G, Natale F, et al. Cardiovascular calcification and subcortical bone demineralization in hypertension. *Hypertens Res.* 2017;**40**(9):825–830.
7. Idoate F, Cadore EL, Casas-Herrero A, et al. Noncoronary vascular calcification, bone mineral density, and muscle mass in institutionalized frail nonagenarians. *Rejuvenation Res.* 2017;**20**(4):298–308.
8. Kim KJ, Kim KM, Park KH, et al. Aortic calcification and bone metabolism: the relationship between aortic calcification, BMD, vertebral fracture, 25-hydroxyvitamin D, and osteocalcin. *Calcif Tissue Int.* 2012;**91**(6):370–378.
9. Lee SH, Park SJ, Kim KN, Cho DY, Kim YS, Kim BT. Coronary calcification is reversely related with bone and hair calcium: the relationship among different calcium pools in body. *J Bone Metab.* 2016;**23**(4):191–197.
10. Paccou J, Edwards MH, Patsch JM, et al. Lower leg arterial calcification assessed by high-resolution peripheral quantitative computed tomography is associated with bone microstructure abnormalities in women. *Osteoporos Int.* 2016;**27**(11):3279–3287.
11. Rodríguez AJ, Scott D, Hodge A, English DR, Giles GG, Ebeling PR. Associations between hip bone mineral density, aortic calcification and cardiac workload in community-dwelling older Australians. *Osteoporos Int.* 2017;**28**(7):2239–2245.
12. Värri M, Tuomainen TP, Honkanen R, et al. Carotid intima-media thickness and calcification in relation to bone mineral density in postmenopausal women—the OSTPRE-BBA study. *Maturitas.* 2014;**78**(4):304–309.
13. Xu R, Yang HN, Li YQ, et al. Association of coronary artery calcium with bone mineral density in postmenopausal women. *Coron Artery Dis.* 2016;**27**(7):586–591.
14. Ye C, Xu M, Wang S, et al. Decreased bone mineral density is an independent predictor for the development of atherosclerosis: a systematic review and meta-analysis. *PloS One.* 2016;**11**(5):e0154740.
15. Zhang Y, Feng B. Systematic review and meta-analysis for the association of bone mineral density and osteoporosis/osteopenia with vascular calcification in women. *Int J Rheum Dis.* 2017;**20**(2):154–160.
16. Lewis JR, Eggermont CJ, Schousboe JT, et al. Association between abdominal aortic calcification, bone mineral density, and fracture in older women. *J Bone Miner Res.* 2019;**34**(11):2052–2060.
17. Rodríguez AJ, Leow K, Szulc P, et al. Abdominal aortic calcification, bone mineral density and fractures: a systematic review and meta-analysis protocol. *BMJ Open.* 2019;**9**(4):e026232.
18. Reddy J, Bilezikian JP, Smith SJ, Mosca L. Reduced bone mineral density is associated with breast arterial calcification. *J Clin Endocrinol Metab.* 2008;**93**(1):208–211.
19. Atci N, Elverici E, Kurt RK, Ozen D, Unlu E, Araz L. Association of breast arterial calcification and osteoporosis in Turkish women. *Pak J Med Sci.* 2015;**31**(2):444–447.
20. Adibi A, Rabani F, Hovsepian S. Bone density in postmenopausal women with or without breast arterial calcification. *Adv Biomed Res.* 2017;**6**:36.
21. Nasser EJ, Iglésias ER, Ferreira JA, Fernandes CE, Pompei LM. Association of breast vascular calcifications with low bone mass in postmenopausal women. *Climacteric.* 2014;**17**(4):486–491.
22. Iribarren C, Sanchez G, Husson G, et al. MultIethNic Study of BrEast ARterial Calcium Gradation and CardioVAscular Disease: cohort recruitment and baseline characteristics. *Ann Epidemiol.* 2018;**28**(1):41–47.e12.
23. Molloi S, Mehraien T, Iribarren C, Smith C, Ducote JL, Feig SA. Reproducibility of breast arterial calcium mass quantification using digital mammography. *Acad Radiol.* 2009;**16**(3):275–282.
24. Molloi S, Xu T, Ducote J, Iribarren C. Quantification of breast arterial calcification using full field digital mammography. *Med Phys.* 2008;**35**(4):1428–1439.
25. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. *J Clin Densitom.* 2013;**16**(4):455–466.
26. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ III, Khaltaev N. A reference standard for the description of osteoporosis. *Bone.* 2008;**42**(3):467–475.
27. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc.* 1991;**23**(8):974–979.
28. Moffet HH, Adler N, Schillinger D, et al. Cohort profile: the Diabetes Study of Northern California (DISTANCE)—objectives and design of a survey follow-up study of social health disparities in a managed care population. *Int J Epidemiol.* 2009;**38**:38–47.
29. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;**150**:604–612.

30. Looker AC, Frenk SM. Percentage of adults aged 65 and over with osteoporosis or low bone mass at the femur neck or lumbar spine: United States, 2005-2010. Centers for Disease Control and Prevention Division of Health and Nutrition Examination Surveys website. https://www.cdc.gov/nchs/data/hestat/osteoporsis/osteoporosis2005_2010.pdf). August 2015. Accessed May 8, 2019.
31. Sackett DL. Bias in analytic research. *J Chronic Dis*. 1979;**32**:51–63.
32. Lomashvili KA, Monier-Faugere MC, Wang X, Malluche HH, O'Neill WC. Effect of bisphosphonates on vascular calcification and bone metabolism in experimental renal failure. *Kidney Int*. 2009;**75**(6):617–625.
33. Synetos A, Toutouzas K, Benetos G, et al. Catheter based inhibition of arterial calcification by bisphosphonates in an experimental atherosclerotic rabbit animal model. *Int J Cardiol*. 2014;**176**(1):177–181.
34. Elmariah S, Delaney JA, O'Brien KD, et al. Bisphosphonate use and prevalence of valvular and vascular calcification in women MESA (the Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2010;**56**:1752–1759.