

Volumetric BMD and Vascular Calcification in Middle-Aged Women: The Study of Women's Health Across the Nation

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ABSTRACT: The association of spine vBMD with AC and CAC was studied in a biracial cohort of 490 middle-aged women in the Study of Women's Health Across the Nation. Lower vBMD was related to high AC, but not to CAC, independent of age and shared risk factors between osteoporosis and cardiovascular disease.

Introduction: This analysis studied the association of spine volumetric BMD (vBMD) with aortic (AC) and coronary artery (CAC) calcification in middle-aged women and evaluated whether such associations were independent of age and shared risk factors between osteoporosis and cardiovascular disease (CVD) or explained by endogenous estradiol levels.

Materials and Methods: Vascular calcification and trabecular vBMD of the spine were measured using electron-beam CT in 490 women free from clinical CVD in the Study of Women's Health Across the Nation. Women were 45–58 years of age, 61% were white, and 64% were perimenopausal. Calcification scores were categorized into three levels (no AC, $N = 146$; moderate AC, scores = 1–74, $N = 221$; high AC, $N = 123$; no CAC, $N = 256$; moderate CAC, score = 1–7.54, $N = 111$; high CAC, $N = 123$). The highest categories were set at the 75th percentiles. Multinomial logistic regression was used to assess the association between vBMD (per SD) and the AC and CAC levels, with no calcification as the reference group.

Results: AC and CAC were detected in 70% and 48% of the population, respectively. Mean vBMD was 161.6 ± 37.2 (SD) mg/ml. vBMD was associated with high AC in unadjusted, age-adjusted, and risk factor-adjusted analysis. Per 1 SD decrease in vBMD, the adjusted odds of high AC compared with no AC was significantly increased by 68% (95% CI, 1.06–2.68). Estradiol did not influence this association. vBMD was related to high CAC in unadjusted (OR = 1.35; 95% CI, 1.08–1.70) but not adjusted models. No associations of vBMD with moderate AC or CAC were observed.

Conclusion: Lower vBMD was related to high AC, but not to CAC, in a biracial cohort of healthy middle-aged women independent of age and shared risk factors between osteoporosis and CVD. Further research should study possible pathophysiological links between the two conditions and the potential for common preventive and therapeutic interventions.

J Bone Miner Res 2006;21:1839–1846. Published online on September 11, 2006; doi: 10.1359/JBMR.060903

Key words: volumetric BMD, aortic calcification, coronary artery calcification, estradiol, Study of Women's Health Across the Nation

INTRODUCTION

CARDIOVASCULAR DISEASE (CVD) and osteoporosis are common age-related conditions. Mounting biological^(1–6) and epidemiologic evidence supports a link between the two diseases. In both cross-sectional and longitudinal

epidemiologic studies, low bone mass has been related to increased cardiovascular mortality,^(7–11) cardiovascular morbidity,^(12–19) and subclinical markers of atherosclerosis, including vascular calcification.^(20–31) Cross-sectionally, a negative association was observed between BMD and calcification of the aorta (AC)^(20,21,23) and coronary arteries (CAC).⁽²⁴⁾ Similarly, the presence of AC was associated with a higher prevalence and number of vertebral and hip fractures.⁽²⁰⁾ The progression of aortic calcification was also linked to trabecular BMD loss at the spine in white postmenopausal women⁽²⁰⁾ and to metacarpal bone loss in women in the Framingham study⁽²²⁾ and in a Dutch population-based longitudinal study.⁽²³⁾

Several hypotheses have been proposed to explain the association between CVD and osteoporosis including (1)

An abstract from this paper was presented at the American Heart Association 45th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, April 29 to May 2, 2005, Washington, DC.

Dr Cauley receives research funding from Merck & Co., Eli Lilly & Co., Pfizer Pharmaceuticals, and Novartis Pharmaceuticals. She also receives honorarium from Merck & Co. and Novartis in addition to serving on the Speakers' Bureau for Merck & Co.. All other authors state that they have no conflict of interest.

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their age-related independent progression, (2) the presence of shared risk factors (such as smoking and physical inactivity), (3) the presence of common pathophysiological mechanisms that could lead to the development of both conditions and that may involve endogenous hormones or inflammatory cytokines, and (4) a cause-effect relationship whereby one condition may be leading to the other. For instance, atherosclerosis, by reducing blood flow to the lower extremities, could alter bone metabolism in the hip and result in osteoporosis.

Although several lines of evidence suggest a link between CVD and osteoporosis, the nature of this link and the mechanisms involved are still not clearly elucidated. Reports on this association focused mostly on white postmenopausal women and less is known about the presence of such relationships in younger women and in other ethnic groups. Furthermore, the majority of previous studies did not use state-of-the-art assessments of vascular calcification and BMD, such as CT technology. CT allows for a graded quantification of vascular calcification, and a 3D volumetric determination of BMD that adjusts for bone size and is unaffected by the presence of extraosseous calcification. Additionally, although estrogen deficiency was suggested as a common denominator in the association between osteoporosis and CVD,^(22–24,32) to our knowledge, no study has actually explored the role of endogenous estrogen.

The aims of this analysis were to evaluate the association of spine volumetric BMD (vBMD) with vascular calcification of the aorta and coronary arteries, all determined using electron-beam CT (EBCT), in a biracial cohort of middle-aged women and to study whether such associations were (1) independent of age, (2) independent of shared risk factors between osteoporosis and CVD, or (3) explained by endogenous estradiol levels.

MATERIALS AND METHODS

Subjects

This analysis used data from the baseline assessment of an ancillary study of subclinical atherosclerosis in the Study of Women's Health Across the Nation (SWAN). SWAN is a multicenter, multiethnic, longitudinal study designed to characterize the biological and psychosocial changes that occur during the menopausal transition in a community-based cohort. Details of the study design and recruitment have been previously published.⁽³³⁾ Briefly, SWAN is being conducted at seven sites: Boston, MA, Chicago, IL, Detroit, MI, Los Angeles, CA, Newark, NJ, Pittsburgh, PA, and Oakland, CA. A total of 3302 women 42–52 years of age were enrolled from 1996 to 1997. At the time of enrollment, women had an intact uterus and at least one ovary and were not pregnant or breast feeding. All participants were still menstruating, and women who used oral contraceptives or hormone replacement in the prior 3 months were excluded. Women were followed up annually and evaluated for a wide array of physiologic, physical, behavioral, and psychological measures.

The subclinical disease evaluation (SWAN Heart) was performed at the Pittsburgh and Chicago study sites.

SWAN participants at their fourth, fifth, sixth, or seventh follow-up visits were eligible for this ancillary study if they had a carotid ultrasound scan in conjunction with a previous SWAN visit. If they did not have a baseline carotid scan, women were eligible if they had no history of CVD (including angina, myocardial infarction, congestive heart failure, stroke, transient ischemic attacks, coronary revascularization, peripheral vascular surgery, or endarterectomy), were not taking exogenous hormones in the past 3 months, were not taking medications for diabetes at the time of screening, and had no hysterectomy and/or bilateral oophorectomy. A total of 608 women were enrolled in this ancillary study. They underwent a battery of measures to identify subclinical cardiovascular disease including vascular calcification of the aorta and coronary arteries, in addition to an evaluation of volumetric BMD of the spine.

This analysis included 490 women (189 black and 301 white). Women were excluded for one or more of the following conditions: had history of clinical CVD ($N = 2$), were hormone users ($N = 69$), had surgical menopause ($N = 11$), or did not have vBMD or vascular calcification measures ($N = 41$). None of the women had treated diabetes.

The SWAN study was approved by the institutional review boards of the participating institutions and all women signed informed consent before participation.

Aortic and coronary calcification

Subjects underwent EBCT for quantification of calcification in the coronary arteries and aorta. An Imatron C-150 Ultrafast CT Scanner (Imatron, San Francisco, CA, USA) was used. Three scans were performed. The first was a scout pass that allowed an evaluation of the patient's anatomy so that landmarks for the coronary and aortic scans could be identified. The second scan was for the coronary arteries in which 30–40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. Images were obtained during a maximal breath hold using ECG triggering so that each 100-ms exposure was obtained during the same phase of the cardiac cycle (60% of R-R interval). The third scan was for the aortic evaluation. The scanner was set to acquire images from the aortic arch to the iliac bifurcation and cross-sectional 6-mm images were taken with a 300-ms exposure time. All scan data were saved to an optical disc. The radiation exposure was 0.783 rads for the coronary scan and 2.45 rads for the aortic scan. Readings of coronary and aortic calcification were done centrally in Pittsburgh using a DICOM workstation and software by AcuImage (South San Francisco, CA, USA). This software program implements the widely accepted Agatston scoring method. Coronary artery and aortic calcium lesions were considered to be present when three contiguous pixels >130 Hounsfield units were detected overlying the vessels of interest. Scoring resulted in a total calcium score as well as a total number of calcifications. The coronary calcification score was obtained from the sum of the individual scores for the four major epicardial coronary arteries. Aortic calcification produced one score. Image analysis was performed by a single physician trained in EBCT to guarantee consistency.

Volumetric BMD

Trabecular volumetric BMD of the spine was determined from the aortic CT scan using an Imatron C-150 Ultrafast CT Scanner (Imatron, San Francisco, CA, USA) and Mindways data acquisition software, calibration phantom, and patient phantom (Mindways Software, Austin, TX, USA). BMD measurements (mg/ml) were acquired from single-slice cross-sectional images at the level of L₃, L₄, and L₅ vertebral bodies. An average of the three BMD values was obtained. Quality control measures were performed at both study sites including weekly scanning of the calibration phantom and the use of identical scan protocols for all participants. BMD readings were done centrally at the University of Pittsburgh.

Potential confounders

Covariates were obtained from the SWAN follow-up visit that corresponds to the SWAN Heart baseline assessment (i.e., fourth, fifth, sixth, or seventh follow-up visits). Variables such as lipids, glucose, and insulin levels and physical activity were obtained from the baseline SWAN visit because they were not available for all follow-up SWAN visits that concurred with the baseline SWAN Heart assessment. Sociodemographic factors (age, race, study site, education), smoking history, alcohol consumption, and physical activity were determined using either an interview-administered or a self-administered questionnaire. Physical activity was assessed using an adaptation of the Baecke questionnaire.⁽³⁴⁾ This self-reported instrument assesses physical activity in different domains including sports, household, and daily routine on the basis of frequency, intensity, and duration of the activity. Scores for each domain were calculated as the average responses to questions about various activities and ranged from 1 (lowest) to 5 (highest). A total physical activity score was calculated as the sum of the individual scores. Menopause status was determined using self-reported bleeding patterns and categorized as premenopause (a menstrual period within the past 3 months with no change in regularity), early perimenopause (a menstrual period within the past 3 months but with a self-reported change in cycles), late perimenopause (no menstrual bleeding for at least 3 months but no more than 12 months), and postmenopause (no menstrual bleeding for at least 12 months). Blood pressure was measured in the right arm using a standard mercury sphygmomanometer, with the participant seated after at least 5 minutes of rest. Three sequential blood pressure values were completed, and the final two were averaged. Weight and height were measured without shoes and with participants wearing light clothing. Portable scales were calibrated weekly, and stationary clinic devices were calibrated monthly. Body mass index was calculated as weight (kg) divided by height squared (m²). Hypertension was defined based on a self-report of a physician's diagnosis of the condition. Standard cardiovascular risk factors were assayed at the Medical Research Laboratories (Lexington, KY, USA), which is certified by the National Heart Lung and Blood Institute, Centers for Disease Control Part III program. Lipids were analyzed on EDTA-treated plasma.

Total cholesterol and triglyceride levels were analyzed by enzymatic methods on a Hitachi747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). High-density lipoprotein (HDL) was isolated using heparin-2M manganese chloride. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.⁽³⁵⁾ Serum insulin was measured using a radioimmunoassay (RIA; DPC Coat-a-count, Los Angeles, CA, USA) procedure. Glucose was measured using a hexokinase-coupled reaction (Boehringer Mannheim Diagnostics). The estradiol (E2) assay was conducted at the University of Michigan SWAN Endocrine Laboratory with an ACS-180 automated analyzer (Bayer Diagnostics Corp., Tarrytown, NY, USA) using a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, anti-ligand antibody, and competitive ligand labeled with dimethylacridinium ester (DMAE). E2 concentrations were measured with a modified rabbit anti-E2-6 ACS-180 immunoassay with increased sensitivity and a lower limit of detection of 1.0 pg/ml. Duplicate E2 assays were conducted with results reported as the arithmetic mean for each subject, with a CV of 3–12%.

Data analysis

In this analysis, AC and CAC measures were treated as categorical rather than continuous variables because of their skewness and the large proportion of zero scores (29.8% and 52.2% of the population had zero scores for AC and CAC, respectively). Aortic calcification (range: 0–2810, median = 13) was categorized into three levels as follows: no AC (0 score), moderate AC (scores between 1 and 74), and high AC (scores \geq 75). Similarly, coronary calcification (range: 0–311.4, median = 0) was categorized into no CAC (0 score), moderate CAC (1–7.54), and high CAC (\geq 7.55). The highest categories for both AC and CAC were set at the 75th percentile of the variable. Baseline characteristics of women in the different AC groups were compared using χ^2 test for categorical variables and either ANOVA or Kruskal-Wallis test for continuous data. The difference in mean vBMD among the three AC groups was tested using ANOVA, and a test for linear trend was performed. Multinomial logistic regression was used to assess the association between vBMD, expressed as SD scores (calculated as the deviation from the mean of vBMD divided by the SD of vBMD), and the three AC groups. No AC was considered the reference group. This regression approach was used instead of ordinal logistic regression because the assumption of proportional odds was not met. Unadjusted, age-adjusted, and risk factor-adjusted models were performed. Covariates were selected for entry into the multiple regression model if they were associated with both vBMD and AC in univariate analyses, using a 0.15 level of significance. The effect of estradiol on the association between vBMD and AC was tested by introducing this variable into the adjusted regression model. Potential racial differences in the relationship of vBMD with AC were tested by entering a product term for race and vBMD in the multiple multinomial logistic regression model. Associations between vBMD and AC levels were presented as unadjusted, age-

TABLE 1. PARTICIPANTS CHARACTERISTICS [% , MEAN \pm SD, OR MEDIAN (IQR)] BY AC LEVELS, THE SWAN STUDY

	No AC (score = 0) (N = 146)	Moderate AC (score = 1–74) (N = 221)	High AC (score \geq 75) (N = 123)	p
Age (years)	49.3 \pm 2.6	50.1 \pm 2.9	50.7 \pm 2.8	<0.0001
Percent black	30	44	39	0.03
Menopause status				0.10
Percent premenopause	9.9	12.0	6.6	
Percent early perimenopause	62.1	49.0	49.1	
Percent late perimenopause	6.8	13.0	13.2	
Percent postmenopause	21.2	26.0	31.1	
Percent current smoker	10.2	11.6	29.7	<0.0001
Percent hypertensive	8.3	13.2	18.8	0.04
Physical activity score	8.4 (7.3, 9.6)	7.9 (6.8, 9.2)	7.6 (6.7, 8.8)	0.008
Weight (kg)	65.6 \pm 8.5	81.9 \pm 14.4	87.9 \pm 23.0	<0.0001
Height (cm)	162.5 \pm 5.8	164.1 \pm 6.4	164.7 \pm 5.7	0.005
Cholesterol (mg/dl)	179.2 \pm 29.9	194.3 \pm 32.9	205.0 \pm 37.4	<0.0001
LDL (mg/dl)	102.4 \pm 27.0	118.9 \pm 28.8	127.2 \pm 34.1	<0.0001
HDL (mg/dl)	60.0 \pm 14.4	54.2 \pm 12.9	52.5 \pm 14.3	<0.0001
Triglyceride (mg/dl)*	76.5 (59.5, 98.0)	91.5 (66.0, 125.0)	105.5 (78.0, 154.0)	<0.0001
Glucose (mg/dl)*	88.0 (83.5, 93.0)	91.0 (86.0, 99.0)	92.0 (86.0, 100.0)	<0.0001
Insulin (uIU/ml)*	6.8 (5.4, 9.3)	8.8 (6.8, 14.0)	11.0 (7.7, 16.1)	<0.0001
DBP (mmHg)	74.1 \pm 9.6	76.6 \pm 9.7	77.0 \pm 10.4	0.02
SBP (mmHg)	114.5 \pm 14.8	119.9 \pm 15.5	124.0 \pm 18.1	<0.0001
Estradiol level (pg/ml)*	35.1 (17.5, 106.9)	30.2 (15.8, 67.0)	27.3 (17.8, 68.6)	0.34
vBMD (mg/ml)	167.2 \pm 37.0	165.2 \pm 37.2	148.6 \pm 34.7	<0.0001
BMD T score	-0.05 \pm 1.42	-0.12 \pm 1.43	-0.76 \pm 1.34	<0.0001

* Medians, IQR, and *p* value from Kruskal-Wallis test are reported because of the skewed distribution of the variable.

adjusted, and risk factors–adjusted ORs and 95% CIs per 1 SD decrease in vBMD. The same analytical approach was followed for CAC. In both AC and CAC models, no significant interactions between race and BMD were observed; therefore, no race-specific analyses were performed. Data were analyzed using SAS version 8.01 (SAS Institute, Cary, NC, USA). Multinomial regression models were fitted using the CATMOD procedure in SAS.

RESULTS

Participant characteristics

Seventy percent (*N* = 344) of the population (66% of white and 77% of black women) had AC, defined as an aortic calcium score > 0, whereas 48% (*N* = 234) had CAC (41.9% of whites and 57.1% of blacks), defined as a total coronary calcium score > 0. Calcification of the aorta and coronary arteries occurred concurrently in 60% of the women (42% of those with AC had CAC and 88% of women with CAC had AC). The average BMD was 161.6 \pm 37.2 (SD) mg/ml, and the mean T score was 0.26 \pm 1.43. By WHO criteria, 4.7% of the cohort had osteoporosis (T score < -2.5), and 26.3% had low bone mass (T score between -2.5 and -1). Participants with high AC were older, heavier, less physically active, and more likely to be postmenopausal, smokers, and hypertensive compared with those with moderate or no AC. A significant decrease in HDL and increase in cholesterol, triglyceride, LDL, glucose, insulin, and systolic and diastolic blood pressure were observed with increasing AC levels (Table 1).

Similarly, participants with high CAC were older, heavi-

er, and more likely to be hypertensive than those with moderate or no CAC. A significant increase in lipid levels, blood pressure, glucose, and insulin and a decrease in HDL and estradiol were observed with increasing CAC levels (Table 2).

AC and vBMD

There was a significant trend for decreasing vBMD with increasing AC levels (*p* for trend < 0.0001). In unadjusted logistic regression analysis, lower vBMD was found to be associated with increased odds for high AC. Per 1 SD decrease in vBMD, the odds of high AC compared with no AC was significantly increased by 73% (OR = 1.73; 95% CI, 1.33–2.25). This association remained significant after adjusting for age (OR = 1.54, 95% CI, 1.17–2.03) and shared covariates between vBMD and AC (OR = 1.68; 95% CI, 1.06–2.68). On the other hand, no significant relationship was observed between vBMD and moderate AC in unadjusted or adjusted analyses (Table 3).

We tested the effect of estradiol on the association between BMD and high AC. Estradiol did not show a significant association with AC (Table 1) but was positively and significantly associated with vBMD (Spearman correlation = 0.26; *p* < 0.0001). When estradiol was included in the model, the adjusted OR for high AC per 1 SD decrease in vBMD was only slightly reduced from 1.67 (95% CI, 1.05–2.67, based on a sample of 347 women with nonmissing estradiol levels; *p* = 0.03) to 1.62 (95% CI, 1.00–2.61; *N* = 347).

TABLE 2. PARTICIPANTS CHARACTERISTICS [% , MEAN ± SD, OR MEDIAN (IQR)] BY CAC LEVELS, THE SWAN STUDY

	No CAC (score = 0) (N = 256)	Moderate CAC (score = 1–7.54) (N = 111)	High CAC (score ≥ 7.55) (N = 123)	p
Age (years)	49.6 ± 2.7	50.2 ± 3.1	50.9 ± 2.6	<0.0001
Percent black	31.6	46.0	46.3	0.004
Menopause status				0.11
Percent premenopause	11.1	10.9	7.2	
Percent early perimenopause	55.6	55.4	45.0	
Percent late perimenopause	9.8	13.9	11.7	
Percent postmenopause	23.5	19.8	36.0	
Percent current smoker	17.3	11.2	16.8	0.36
Percent hypertensive	7.0	16.7	22.3	0.0001
Physical activity score	8.3 (7.2, 9.5)	7.6 (6.9, 9.0)	7.7 (6.6, 8.9)	0.01
Weight (kg)	68.7 ± 11.2	85.2 ± 14.4	93.0 ± 20.0	<0.0001
Height (cm)	163.2 ± 6.0	163.8 ± 6.3	164.9 ± 6.0	0.02
Cholesterol (mg/dl)	185.9 ± 30.1	193.4 ± 36.7	205.5 ± 37.8	<0.0001
LDL (mg/dl)	109.6 ± 27.9	118.0 ± 33.0	127.5 ± 32.6	<0.0001
HDL (mg/dl)	58.0 ± 14.5	53.3 ± 13.5	52.2 ± 12.6	0.0002
Triglyceride (mg/dl)*	79.0 (61.0, 108.0)	92.0 (68.0, 127.0)	107.0 (78.0, 164.0)	<0.0001
Glucose (mg/dl)*	88.0 (84.0, 94.0)	92.0 (87.0, 99.0)	94.0 (88.0, 101.0)	<0.0001
Insulin (uIU/ml)*	6.9 (5.3, 9.4)	10.3 (7.7, 13.6)	11.6 (7.8, 17.3)	<0.0001
DBP (mmHg)	73.3 ± 9.0	78.1 ± 9.9	79.6 ± 10.2	<0.0001
SBP (mmHg)	114.4 ± 13.6	123.1 ± 16.0	126.3 ± 18.5	<0.0001
Estradiol level (pg/ml)*	42.4 (17.5, 102.6)	27.6 (16.4, 63.0)	23.1 (14.4, 41.9)	0.0007
vBMD (mg/ml)	163.8 ± 37.1	166.1 ± 37.3	153.1 ± 36.4	0.01
BMD T score	-0.18 ± 1.43	-0.09 ± 1.43	-0.59 ± 1.4	0.009

* Medians, IQR, and p value from Kruskal-Wallis test are reported because of the skewed distribution of the variable.

CAC and vBMD

Participants with high CAC had the lowest vBMD (p for trend = 0.009). In unadjusted regression analysis, vBMD was significantly associated with high CAC (OR = 1.35; 95% CI, 1.08–1.70). However, controlling for age reduced the strength of this association and rendered it nonsignificant (OR = 1.19; 95% CI, 0.94–1.51). Additional adjustment for shared covariates between BMD and CAC did not affect the strength or significance of the relationship (OR = 1.19; 95% CI, 0.81–1.74). No association between

BMD and moderate CAC was observed in unadjusted, age-adjusted, or risk factor-adjusted models (Table 3).

Lower estradiol was found to be significantly associated with higher CAC levels in univariate (Table 2) but not in adjusted analysis. The addition of estradiol to the model had no effect on the association between vBMD and CAC levels. For instance, the adjusted OR for high CAC per 1 SD decrease in vBMD changed from 1.24 (95% CI, 0.83–1.86, based on a sample of 375 women with nonmissing estradiol levels) to 1.21 (95% CI, 0.81–1.82; N = 375).

TABLE 3. RESULTS OF THE MULTINOMIAL LOGISTIC REGRESSION MODELS FOR AC AND CAC. UNADJUSTED, AGE-ADJUSTED, AND RISK FACTOR-ADJUSTED ORS (95% CI) PER 1 SD* DECREASE IN vBMD

	AC level			CAC level		
	No AC (0)	Moderate AC (1–74)	High AC (≥75)	No CAC (0)	Moderate CAC (1–7.54)	High CAC (≥7.55)
vBMD (unadjusted)	1.00	1.05 (0.86, 1.30)	1.73 [‡] (1.33, 2.25)	1.00	0.94 (0.75, 1.17)	1.35 [§] (1.08, 1.70)
	146	221	123	256	111	123
vBMD (adjusted for age)	1.00	0.98 (0.78, 1.22)	1.54 [§] (1.17, 2.03)	1.00	0.88 (0.70, 1.10)	1.19 (0.94, 1.51)
	146	221	123	256	111	123
vBMD (adjusted for age + shared risk factors) [†]	1.00	1.33 (0.93, 1.90)	1.68 [¶] (1.06, 2.68)	1.00	1.09 (0.77, 1.53)	1.19 (0.81, 1.74)
	109	171	84	211	91	98

Values are ORs and N or ORs (95% CI) and N.

* vBMD SD = 37.2 mg/ml.

[†] AC model: adjusted for age, race, study site, menopause status, educational level, smoking status, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level. CAC model: adjusted for age, race, study site, menopause status, alcohol drinking, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level.

[‡] p < 0.0001.

[§] p < 0.01.

[¶] p < 0.05.

DISCUSSION

In this cross-sectional analysis performed in a biracial cohort of women during the menopause transition, lower trabecular BMD of the spine was significantly associated with higher AC levels. This association was not age related, was independent of shared risk factors between BMD and AC, and was not influenced by estradiol. Additionally, lower vBMD was associated with high CAC levels; however, this relationship was not significant after adjusting for age.

Our results on the association of BMD with AC confirm prior cross-sectional and longitudinal findings and extend them to a younger cohort of white and African-American women who were predominantly peri- or premenopausal. Schulz et al.⁽²⁰⁾ observed that the presence of EBCT-determined AC was associated with lower BMD and higher prevalence of vertebral and hip fractures in white postmenopausal women. In a cohort of Danish postmenopausal women, Tanko et al.⁽²¹⁾ reported a negative correlation between hip BMD and radiographically determined AC, which was independent of age and common risk factors. Other longitudinal studies associated the progression of AC to a higher degree of bone loss.^(20,22,23) On the other hand, other reports failed to observe an association between BMD and AC.^(36–38)

Traditionally, osteoporosis and atherosclerosis were considered unrelated, and their coexistence was attributed to independent age-related processes.^(36–38) Mounting biological observations^(1–6) and epidemiologic evidence from this study and others^(7–31) suggest a link between the two conditions that is independent of age. Laboratory studies indicate that atherosclerotic calcification and bone calcification share a number of common features. It is now considered that the arterial tissue is calcified in a highly regulated and organized process by mechanisms similar to those involved in bone mineralization.^(1,39) Hydroxyapatite, a mineral that is present in bones, is also found in calcium deposits of atherosclerotic plaques.⁽⁴⁾ In addition, calcified plaques express several bone matrix proteins such as GLA protein, bone morphogenetic protein-2, osteopontin, osteocalcin, and collagen I.^(2,3,5,6)

Several hypotheses have been proposed to explain the link between osteoporosis and atherosclerosis. The coexistence of the two conditions was attributed to their shared etiological factors (such as smoking, physical inactivity, alcohol intake, hypertension, etc.), which may simultaneously promote atherosclerosis and bone demineralization. In our analysis, the observed inverse association between vBMD and AC, a marker of subclinical atherosclerosis, was present after controlling for age, ethnicity, and other common etiological factors such as weight, physical inactivity, blood pressure, and lipids. Estrogen deficiency was implicated in the progression of the two conditions. It has been identified as the major determinant of age-related bone loss in women and men.^(40,41) Despite recent evidence from randomized, placebo-controlled trials on the adverse effects or lack of effects of hormone replacement therapy (HRT) on CVD outcomes,^(42,43) endogenous estrogen is known to have protective effects on the cardiovascular system in women,⁽⁴⁴⁾

either directly or through the modulation of other factors including cytokines, oxidized lipids, and endothelial NO synthase (eNOS).^(32,44) A beneficial effect of estrogen use on arterial calcification has also been suggested by some studies.^(36,45) In our analysis, estradiol was positively correlated with vBMD; however, it was not associated with the extent of AC. Adding estradiol to the model minimally reduced the strength of the association between BMD and AC. This suggests that estrogen deficiency was not a major player in this association. Other factors including inflammatory markers,^(13,23) oxidized lipids,⁽⁴⁶⁾ imbalances in the calciferol endocrine system,⁽⁴⁷⁾ vitamin K deficiency,⁽⁴⁸⁾ or genetic factors⁽⁴⁹⁾ may be involved in this relationship.

We observed an association between BMD and CAC in unadjusted analysis; however, this association became not significant after controlling for age. These results are consistent with those reported by Sinnott et al.⁽⁵⁰⁾ in a population of postmenopausal women. However, in another population of white postmenopausal women free from CAD, a negative correlation between CAC and BMD of the hip was observed, and women with lumbar spine osteoporosis had a significantly higher CAC score than controls.⁽²⁴⁾ The extent of CAC in our population was lower than that reported in other studies. Only 2.4% ($N = 12$) of this cohort had CAC scores ≥ 100 (which correlate with moderate to severe plaque burden⁽⁵¹⁾) compared with 12.4% in the Healthy Women Study.⁽⁵²⁾ Therefore, it is possible that we did not observe an association between BMD and CAC owing to the fact that our young cohort has not yet developed extensive CAC.

Our study has several strengths. The associations were studied in a well-characterized biracial cohort of middle-aged women who were free from clinical CVD, and they were adjusted for a comprehensive set of shared risk factors for osteoporosis and vascular calcification. We also used CT to simultaneously assess BMD and vascular calcification of the aorta and coronary arteries. CT technology allows for a 3D volumetric determination of BMD, an assessment of purely trabecular bone, and a graded quantification of vascular calcification. In the existing literature, vascular calcification was mostly assessed using conventional radiography,^(21–23,36–38) with low sensitivity for the detection of small calcium deposits. Similarly, in a large number of studies, bone mass was determined using radiographic techniques, single X-ray absorptiometry, and single-photon or dual-photon absorptiometry.^(8–10,16,18,22,23,28,30,38) Some studies have used DXA in bone determination^(7,11,13–15,17,19,21,25–27,29,31,36,37); however, this projectional technique is limited by its 2D areal assessment of BMD, which does not adjust for bone size. DXA is also affected by the presence of extraosseous calcification such as aortic calcification and degenerative osteoarthritic changes.

The main limitation of this study is its cross-sectional nature, which does not allow the evaluation of a causal association between vascular calcification and low BMD and the elucidation of common mechanisms involved in the pathogenesis of both conditions. Additionally, our cohort included healthy middle-aged women, which may limit the generalizability of the results to other populations.

In conclusion, our results provide further evidence for an association between BMD and AC in women that is independent of age and shared risk factors. However, establishing a link between bone demineralization and vascular calcification requires more longitudinal evidence and further study into common pathophysiological mechanisms for the two conditions. Once confirmed, such association may lead to the early identification of subjects at risk for CVD and/or osteoporosis and to the potential for common preventive and therapeutic interventions that target both conditions.

ACKNOWLEDGMENTS

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health, DHHS, through the National Institute on Aging, the National Institute of Nursing Research and the NIH Office of Research on Women's Health (Grants NR004061, AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). The SWAN Heart Ancillary Study is supported by National Heart, Lung, and Blood Institute Grants HL65581 and HL65591.

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Received in original form May 2, 2006; revised form July 31, 2006; accepted September 7, 2006.