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Cross-sectional association of bone mineral density with coronary artery calcification in an international multi-ethnic population-based cohort of men aged 40–49: ERA JUMP study

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ABSTRACT

Introduction: Inverse associations of cardiovascular disease (CVD) and atherosclerosis with osteoporosis and bone mineral density (BMD) have been reported in post-menopausal women and elderly men. We aimed to investigate an association between vetebral bone density (VBD) and coronary artery cacification (CAC) in an international multi-ethnic cohort of middle-aged men in the EBCT and Risk Factor Assessment among Japanese and US Men in the Post-World-War-II birth cohort (ERA JUMP).

Methods: ERA JUMP examined 1134 men aged 40–49 (267 white, 84 black, and 242 Japanese Americans, 308 Japanese in Japan, and 233 Koreans in South Korea) free from CVD for CAC, and VBD, biomarkers of coronary atherosclerosis and BMD, respectively, with electron-beam computed tomography, and other risk factors. CAC was quantified with the Agatston method and VBD by computing the mean Hounsfield Unit (HU) value of the T12 to L3 vertebrae. To examine multivariable-adjusted associations of CAC with VBD, we used robust linear and logistic regressions.

Results: The mean VBD and median CAC were 175.4 HU (standard deviation: 36.3) and 0 (interquartile range: (0, 4.5)), respectively. The frequency of CAC was 19.0%. There was no significant interaction by race. VBD had a significant inverse association with CAC score ($\beta = -0.207$, p-value = 0.005), while a 10-unit increase in VBD was significantly associated with the frequency of CAC (odds ratio (95% confidence interval) = 0.929 (0.890–0.969)). Both associations remained significant after adjusting for covariates.

Conclusions: VBD had a significant inverse association with CAC in this international multi-ethnic cohort of men aged 40–49.

1. Introduction

Cardiovascular disease (CVD) and osteoporosis are two common diseases in the elderly and both are associated with significant morbidity, mortality and disability [1–4]. These two conditions have shared risk factors such as age, physical inactivity, smoking and unhealthy diet [5,6]. A recent systematic review reported that

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decreased bone mineral density (BMD) has a significant association with atherosclerosis, the major underlying cause of CVD, in post-menopausal women and elderly men aged 50 and over [7].

Coronary artery calcification (CAC) assessed by electron-beam or multi-detected computed tomography (CT) is a biomarker of coronary atherosclerosis and is a strong predictor of future CVD [8]. A recent guideline on the management of blood cholesterol by the American College of Cardiology/American Heart Association recommends CAC for screening among asymptomatic individuals with intermediate risk [9]. Many large studies (number of participants >1000) have reported an association of CAC with BMD [10–16]. To examine BMD and its association with CAC, some studies use dual-energy X-ray absorptiometry (DXA) [13–15,17–21], the gold standard [22] while other studies computed a surrogate for vertebrae bone density (VBD) of the thoracic and lumber vertebrae depicted on CT images that assess CAC [12,16,23,24]. Several of these studies reported a significant inverse association of CAC with BMD in post-menopausal women [11,16,18,19,23] and elderly men [11,25], similar to the results of the systematic review showing an association of BMD and fracture with CVD [7]. However, none of these studies have examined the association specifically in men aged 40–49 years. In addition, racial differences in BMD [2] and CAC [26] have been known, yet only a few studies have reported the association in multi-ethnic groups in one country [11,16,24] and none of these studies have reported the association in multi-ethnic groups in an international study.

In the current study, we aimed to investigate the cross-sectional association of CAC with BMD in an international multi-ethnic cohort of middle-aged men. We hypothesized that lower BMD would be significantly associated with higher CAC score and higher frequency of CAC in men (white, black and Japanese Americans in the US, Japanese in Japan, and Koreans in South Korea) aged 40–49 years in the EBCT and Risk Factor Assessment among Japanese and US Men in the Post-World-War-II birth cohort (ERA JUMP) study.

2. Methods

2.1. Study population

Participants were 1335 men enrolled the ERA-JUMP study. The study population and methods of the ERA JUMP study have previously been described in detail elsewhere [27,28]. Briefly, between 2002 and 2006 population-based samples of men aged 40–49 years were randomly selected and consisted of: (1) white and black American men from the voter registration list of Allegheny County, Pennsylvania., US, (2) Japanese American men from the list of offspring of Japanese American fathers who participated in the Kuakini Honolulu Heart Program in Honolulu, Hawaii, US, (3) Japanese men randomly selected from the Basic Residents' Register of Kusatsu City, Shiga, Japan, and (4) Korean men randomly selected from the Korean Health and Genomic Study in Ansan, Gyeonggi-do, South Korea.

All participants were without clinical CVD (*e.g.*, coronary heart disease and stroke) or other severe diseases. Among 1335 men who were enrolled in the study, 201 subjects were excluded due to missing data or fracture in the vertebrae (CT images of lumbar vertebra not included in the scan (n = 195), fracture in the vertebrae (n = 3), no CAC assessment (n = 2) and no lipid data (n = 1)). Our final sample was 1134 men (267 white Americans, 84 black Americans, 242 Japanese Americans, 308 Japanese, and 233 Koreans). The study was approved by the Institutional Review Boards of University of Pittsburgh, Pittsburgh, Pennsylvania, US; Kuakini Medical Center, Honolulu, Hawaii, US; Shiga University of Medical Science, Otsu, Shiga, Japan; and Korea University, Seoul, South Korea. All participants provided written informed consent.

2.2. Vertebral bone assessment

Non-contrast CT examinations were performed using electron-beam CT using GE-Imatron C150 EBT scanners (GE Medical Systems, South San Francisco, US) at the four centers using standardized protocols. Scanners were calibrated regularly by technicians during normal operation. The CT images were reconstructed using either the "sharp" or "normal" kernels at a 6.0 mm thickness and interval. Subjects were scanned from the aortic arch to the iliac bifurcation. A single trained reader manually outlined an ellipsoidal region of interest (ROI) on the central portion of the thoracic and lumbar vertebrae (T12 to L3) depicted on the CT images [29,30]. Cortical bone and calcification within the vertebrae were excluded. The VBD was computed as the mean Hounsfield unit (HU) value across the four vertebral ROIs as a surrogate for BMD. The reader was blinded to the subjects' characteristics. The vertebrae of 60 subjects were re-analyzed a minimum of 3 weeks after the initial assessment to evaluate intra-reader agreement. Intra-reader agreement between the first and second analyses was very high (concordance correlation coefficient of 0.996).

2.3. CAC measurement

CAC measurement has previously been reported in detail [27,31]. The Agatston method was used to quantify CAC score using AccuImage software (AccuImage Diagnostics, South San Francisco, CA, US) [32]. Subjects were scanned from the aortic root to the apex of the heart to evaluate CAC with contiguous images reconstructed at a 3.0 mm thickness and interval. A single experienced reader at the Cardiovascular Institute, University of Pittsburgh, Pennsylvania, read and assessed the coronary scans from all four centers. The reader was blinded to the subjects' characteristics. The reproducibility of CAC score was very high (intraclass correlation of 0.98) [27]. The cut-off point of CAC score $\geq$10 was used to define the presence of CAC, as we and others have previously reported [27,31].

2.4. Other measurements

Other measurements have been previously reported in detail elsewhere [27,31]. A self-administered questionnaire was used to obtain information from participants on demographic factors, smoking habits, alcohol use, medications (hypertension, dyslipidemia, and diabetes mellitus), and medical history. Current smoking was defined as smoking cigarettes over the past month. Alcohol use was defined as alcohol consumption at least two days per week. All the blood samples were collected after overnight fasting.

Body-mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure (BP) was measured in the right arm of the seated participant after the participant sat quietly for five minutes, using an appropriate-sized cuff, with an automated sphygmomanometer (BP-8800, Omron Health Care Co. Ltd, Tokyo, Japan). The average of 2 measurements was used to determine BP. Hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or use of anti-hypertensive medication. Diabetes mellitus was defined as a fasting blood glucose $\geq$126 mg/dl or use of anti-diabetic medication. Total cholesterol and triglycerides were measured using enzymatic assays, and high-density lipoprotein cholesterol (HDL-C) was measured using a direct method. Low-density lipoprotein cholesterol (LDL-C) was estimated using Friedewald's formula [33]. When triglycerides exceeded 400 mg/dl, we did not estimate LDL-C and measured LDL-C directly. Lipid measurements were standardized

according to the protocol for the US Centers for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network. Hyperlipidemia was defined as triglycerides ≥150 mg/dl, HDL-C <40 mg/dl, LDL-C ≥140 mg/dl, or use of anti-hyperlipidemia medication [34].

2.5. Statistical analyses

Participant characteristics were reported as means and standard deviations (SDs) for continuous variables with normal distributions, medians and interquartile ranges (IQRs) for continuous variables with skewed distributions, and frequencies and percentages for categorical variables. CAC scores were analyzed as both continuous and binary variables (CAC score <10 or ≥10). To examine the differences of the CAC score and the frequency of CAC ≥ 10 among VBD quartiles, a nonparametric test for trend was used across ordered groups. To examine multivariable-adjusted associations of CAC with VBD, we used robust linear and logistic regressions because of the highly skewed distribution of the CAC score. For multivariable adjustments in robust linear and logistic regressions, we first adjusted for age, race, and BMI (Model 1), then further adjusted for hypertension, diabetes, and hyperlipidemia (Model 2). In Model 3, we additionally adjusted for alcohol use and smoking status (current, past, or never smokers) [35,36]. There were no significant interactions by race, thus race-specific analysis was not performed. Two-tailed p-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with STATA software (version 14, Stata Corporation, College Station, Texas).

3. Results

The mean (SD) of age and BMI were 45.2 (2.8) and 25.9 (4.1), respectively (Table 1). Frequency of hypertension, diabetes, and hyperlipidemia was 22.4%, 7.1%, and 68.9%, respectively. Frequency for never, former, and current smokers was 45.2%, 27.7%, and 27.2%, respectively. The median CAC score (IQR) was 0 (0, 4.5), and frequency of CAC was 19.0%. The mean (SD) of VBD was 175.4 (36.3) HU (Table 1).

Table 1
Characteristics of the participants (n = 1134).

Age (years)	45.2 ± 2.8
BMI (kg/m^2)	25.9 ± 4.1
Race	
White American, n (%)	267 (23.5)
Black American, n (%)	84 (7.4)
Japanese American, n (%)	242 (21.3)
Japanese, n (%)	308 (27.2)
Korean, n (%)	233 (20.6)
Smoking status	
Never, n (%)	512 (45.2)
Former, n (%)	314 (27.7)
Current, n (%)	308 (27.2)
Alcohol use, n (%)	556 (49.0)
Systolic blood pressure (mmHg)	124.0 ± 14.0
Medications for hypertension, n (%)	111 (9.8)
Hypertension, n (%)	254 (22.4)
Glucose (mg/dl)	105.1 ± 18.1
Medications for diabetes, n (%)	21 (1.9)
Diabetes, n (%)	80 (7.1)
LDL-C (mg/dl)	127.1 ± 34.9
HDL-C (mg/dl)	50.2 ± 13.5
Total cholesterol (mg/dl)	207.9 ± 37.9
Triglycerides (mg/dl)	131.5 (95.0, 190.0)
Medications for hyperlipidemia, n (%)	105 (9.3)
Hyperlipidemia, n (%)	781 (68.9)
CAC score	0 (0, 4.5)
CAC score ≥10, n (%)	215 (19.0)
VBD (HU)	175.4 ± 36.3

The mean ± standard deviation is shown unless otherwise mentioned. The median (interquartile range) is shown in triglyceride and the CAC score. BMI = body-mass index; CAC = coronary artery calcification; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; VBD = vertebrae bone density.

The frequency of CAC was significantly lower across higher quartiles of VBD: the frequency of CAC for the quartiles was 25.2%, 19.0%, 15.6%, and 16.2%, respectively (p-value for trend = 0.004) (Table 2). The 25th, 50th, 75th, and 90th percentiles of the CAC score were 0, 0, 10.3, and 51.4 in quartile 1, 0, 0, 4.1, and 42.2 in quartile 2, 0, 0, 4.4, and 30.1 in quartile 3, and 0, 0, 3.8, and 27.1 in quartile 4, respectively. The ranges of VBD (HU) in quartiles 1 through 4 were 61.4–151.6, 151.6–175.35, 175.35–196.9, and 196.9–325.8, respectively.

VBD was significantly and inversely associated with CAC score in the unadjusted model using robust linear regression (β = −0.2 07, p-value = 0.005) (Table 3). The significant association remained after adjusting for age, race and BMI (Model 1), additionally adjusting for hypertension, hyperlipidemia, and diabetes (Model 2), and further adjusting for alcohol use and smoking (Model 3).

The odds ratio (OR) of the presence of CAC for a 10-unit increase in VBD was 0.929 (95% CI: 0.890–0.969, p-value = 0.001) in the unadjusted model using logistic regression (Table 4). The significant inverse association persisted after adjusting for age, race and BMI (Model 1), additionally adjusting for hypertension, hyperlipidemia, and diabetes (Model 2), and further adjusting for alcohol use and smoking (Model 3).

4. Discussion

The current population-based cross-sectional study demonstrated a significant inverse association of VBD with coronary atherosclerosis in middle-aged men without CVD. The study is the first to document the association in an international multiethnic cohort of 1134 men aged 40–49 years. Previous systematic review and meta-analysis reported a significant inverse association of BMD with atherosclerosis in post-menopausal women and elderly men aged ≥50 years [7]. Our finding is consistent with the results of the systematic review and extends the association to men in their 40s.

Several [10–12,16,18,19,23,25] but not all studies [13,14,17,20,21,37,38] have reported a significant association of BMD with CAC. These studies are population- or volunteer-based studies with various sample sizes. Four large population-based studies (number of participants >1000) examined cross-sectional associations of BMD with CAC, with mixed results [10,12,13,16]. The Copenhagen General Population Study reported a significant inverse association of T7 to T9 VBD with the presence of CAC in 1548 men and women (mean (SD) age of 61 years (10)) [10]. The Framingham Offspring Study (FOS) examined the association of L3 VBD with CAC score in 1327 men and women (mean (SD) age of 60 years (9)) and reported a significant association only in women [12]. The Rotterdam Study reported no significant association of BMD by DXA with CAC score in 1274 men and women (mean age of 64 years) [13]. The Multi-Ethnic Study of Atherosclerosis (MESA) examined 1909 men and women without CVD (mean age of 65 years for men and 64 years for women) for L2 to L4 VBD and CAC and reported a significant association only in women [16]. Although neither FOS or MESA documented any significant association of BMD with CAC in men, both studies documented a significant association of BMD with aortic calcification by electron-beam or multi-detector CT. Thus, collectively, the results of these large population-based studies support a significant inverse association of BMD with vascular calcification in the general adult population.

Table 2
Association of quartiles of vertebra bone density with coronary artery calcification score and the presence of coronary artery calcification.

Quartile of vertebra bone density	Q1 (n = 282)	Q2 (n = 285)	Q3 (n = 283)	Q4 (n = 284)	p-value for trend
CAC score, median (75th and 90th percentile)	0 (10.3, 51.4)	0 (4.1, 42.2)	0 (4.4, 30.1)	0 (3.8, 27.1)	0.534
Presence of CAC (%)	25.2	19.0	15.6	16.2	0.004

Quartile of vertebra bone density is based on Hounsfield Unit (HU). Range of HU was 61.4–151.6 for Q1, 151.6–175.35 for Q2, 175.35–196.9 for Q3 and 196.9–325.8 for Q4.
Presence of CAC was defined as coronary calcification score ≥10.
CAC: coronary artery calcification.

Table 3
Difference in CAC score per 1-unit increase in VBD.

	β	95%CI	p-Value	R2
Unadjusted	−0.207	(−0.351, −0.063)	0.005	0.0083
Model 1	−0.220	(−0.368, −0.072)	0.004	0.0468
Model 2	−0.219	(−0.367, −0.070)	0.004	0.0499
Model 3	−0.185	(−0.327, −0.043)	0.011	0.0602

Model 1 adjusted for vertebral bone attenuation, age, race, and body mass index.
Model 2 adjusted for Model 1 + hypertension, hyperlipidemia, and diabetes.
Model 3 adjusted for Model 2 + alcohol drinking and smoking.
CAC = coronary artery calcification; VBD = Vertebral bone density.

Table 4
Odds ratio of prevalent CAC for 10-unit increase in VBD.

	OR for 10-unit	95%CI	p-Value	Pseudo R2
Unadjusted	0.929	(0.890, 0.969)	0.001	0.0108
Model 1	0.940	(0.897, 0.985)	0.010	0.1099
Model 2	0.939	(0.895, 0.985)	0.010	0.1248
Model 3	0.951	(0.906, 0.999)	0.045	0.1428

Model 1 adjusted for vertebral bone attenuation, age, race, and body mass index.
Model 2 adjusted for Model 1 + hypertension, hyperlipidemia, and diabetes.
Model 3 adjusted for Model 2 + alcohol drinking and smoking.
Prevalent CAC was defined as CAC score 10 or greater. CAC = coronary artery calcification; VBD = Vertebral bone density; OR = odds ratio; CI = confidence interval.

Many previous studies reported the association in a single racial group (whites [10,12,21,23,25,37], Chinese [17,18] and Koreans [14,15,19]) while only three multi-ethnic studies have reported an association of BMD with CAC. Ahmadi et al. examined 5590 consecutive men and women of white, black, Hispanic, and Asian Americans without CVD and showed a significant inverse association of VBD with CAC score in all participants as well as in each racial group [11]. MESA examined a population-based sample of 1909 men and women of white, black, Hispanic and Asian Americans and showed a significant inverse association of VBD with both CAC score and presence of CAC only in women [16]. The Study of Women's Health Across the Nation (SWAN) examined 490 middle-aged women of white and black Americans and showed a significant inverse association of VBD with CAC which was attenuated and became non-significant after adjusting for risk factors [24]. None of these studies showed interaction by race. Our observation of no significant interaction by race is consistent with the results of these previous studies.

CAC is a well-established biomarker of coronary atherosclerosis [8] and CAC score has a very high correlation to the amount of atheromatous burden of the coronary arteries [39]. Frequency of CAC increases with age and male sex [26,40,41]. Many studies reported a significant association of BMD with CAC in women, especially in post-menopausal women [10–12,16,18,19,23]. However, SWAN, which examined predominantly pre-menopausal women did not show a significant association [24]. One likely explanation for this non-significant association is that frequency of CAC was too low in pre-menopausal women to detect a significant association. In fact, SWAN has shown a significant inverse association of BMD with aortic calcification, which has much higher frequency than of CAC in pre-menopausal women [24]. Our study showed a significant association of BMD with CAC in men aged 40–49 years. We believe the significant association is unlikely to be observed in women aged 40–49 or men in younger age groups due to low frequency of CAC in these age groups.

Inflammation and oxidative stress are considered as biological mechanisms linking BMD and vascular calcification. Higher serum levels of inflammatory markers, such as C-reactive protein (CRP), interleukin (IL)-6, and tumor-necrotizing factor α (TNF-α), and oxidative stress are associated with higher severity of atherosclerosis and vascular calcification [42–44]. IL-6 and TNFα are produced in the vessel wall by the endothelial cells, smooth muscle cells, and macrophages, which leads to recruitment of macrophages and monocytes to form vascular calcifications [43]. Inflammation and oxidative stress also play an important role in osteoclast function, bone turnover, and bone remodelling by stimulating osteoclast differentiation and the progression of osteoporosis [45–47]. Among studies that reported a significant inverse cross-sectional association of BMD with CAC [10–12,16,18,19,23,25], MESA is the only study that considered a marker of inflammation (*i.e.*, CRP) as a covariate [16]. MESA showed that the significant association in women did not attenuate and remained significant after adjusting for CRP. The current study also showed that after adjusting for CRP, the association of BMD with CAC did not attenuate and remained significant in a subsample of 899 subjects (Supplemental Tables 1 and 2). The sample size is smaller because we analysed CRP in white, black and Japanese Americans and Japanese in Japan, but not in Koreans. These results

indicate that CRP is an unlikely mediator between bone and vascular calcification, although the results do not deny inflammation as a mechanistic link between BMD and vascular calcification.

Limitations of the study warrant discussion. First, the current study was cross-sectional and we cannot establish causality. However, unlike traditional risk factors such as high blood pressure and lipids, which are one-time point measurement of these risk factors, both CAC and BMD represent cumulative exposure to risk factors in the past. A recent meta-analysis of 28 longitudinal epidemiological studies reports that BMD at baseline has a significant association with future CVD events [48]. Second, the study was observational which cannot exclude the possibility of unmeasured and residual confounding. Third, we did not assess physical inactivity or dietary factors that are associated with both BMD and CAC [5,6]. However, among studies that reported a significant inverse cross-sectional association of BMD with CAC [10–12,16,18,19,23,25], few studies have considered physical inactivity [10,12,16]. or dietary factors (i.e., dietary intake of calcium, blood levels of vitamin D, calcium and phosphate [16,23,25]) as covariates. Fourth, of the 1335 subjects enrolled in ERA JUMP, 201 subjects (15.1%) were excluded due to missing data or fracture in the vertebrae, which might introduce selection bias. Comparing subjects who were included and excluded in the current study, age, smoking status and frequency of hyperlipidemia were not statistically different but frequency of hypertension, diabetes and CAC were significantly higher in subjects who were excluded (data not shown). Therefore, exclusion of these subjects would weaken rather than strengthen the association of CAC with BMD. Finally, we used x-ray attenuation, which is represented in CT image pixel HU values as computed attenuation of four lower vertebrae as a surrogate for overall BMD. Although, x-ray attenuation is a reasonable surrogate for density, we only evaluated a small section of the skeletal anatomy, albeit a critical anatomical region related to BMD.

In conclusion, we examined an international multi-ethnic cohort of American, Japanese and Korean men aged 40–49 years without CVD for CAC and VBD, adjusted for cardiovascular risk and other factors. We observed a significant inverse cross-sectional association between BMD and CAC, which remained significant after considering various covariates. Our results support the hypothesis that a direct association between bone loss and subclinical atherosclerosis exists in men as early as in their 40 s. Further research is warranted to investigate pathological mechanisms that underlie the association of bone loss and atherosclerosis.

CRediT authorship contribution statement

Chikako Nakama: Conceptualization, Data Collection, Data analysis, Draft the paper. **Takashi Kadowaki:** Data Collection, Critically revise the paper. **Jina Choo:** Data Collection, Critically revise the paper. **Aiman El-Saed:** Data Collection, Critically revise the paper. **Aya Kadota:** Data Collection, Critically revise the paper. **Bradley J. Willcox:** Data Collection, Critically revise the paper. **Akira Fujiyoshi:** Data Collection, Critically revise the paper. **Chol Shin:** Data Collection, Critically revise the paper, Obtained the funds. **Joseph K. Leader:** Conceptualization, Data Collection, Critically revise the paper. **Katsuyuki Miura:** Data Collection, Critically revise the paper. **Kamal Masaki:** Data Collection, Critically revise the paper. **Hirotsugu Ueshima:** Data Collection, Critically revise the paper, Obtained the funds. **Lewis H. Kuller:** Conceptualization, Critically revise the paper. **Jessica Bon:** Conceptualization, Critically revise the paper. **Akira Sekikawa:** Conceptualization, Data Collection, Data analysis, Draft the paper, Critically revise the paper, Obtained the funds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100618.

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