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ORIGINAL ARTICLE

Association of volumetric bone mineral density with abdominal aortic calcification in African ancestry men

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Abstract
Summary We tested for association between cortical and trabecular volumetric bone mineral density (vBMD) with abdominal aortic calcification (AAC) prevalence in 278 Afro-Caribbean men. AAC was present in 68.3 % of the men. Greater cortical, but not trabecular, vBMD was associated with significantly decreased odds of AAC independent of traditional risk factors.
Introduction The aim of this study is to assess the prevalence and correlates of AAC in a sample of 278 Afro-Caribbean men (mean age 56) and to test for a largely unexplored association between cortical and trabecular vBMD with AAC prevalence.
Methods Men were recruited consecutively as part of an ongoing prospective cohort study of body composition in men aged 40+. For this analysis, AAC was assessed by computed tomography of the abdomen from L3 to S1. Aortic calcium was scored using the Agatston method, and prevalence was defined as a score ≥10 to rule out false positives. Men also had BMD assessed using peripheral quantitative computed tomography at 4 % (trabecular vBMD) and 33 % (cortical vBMD) of the radius and tibia.
Results Abdominal aortic calcification was present in 68.3 % of the men. Significant independent predictors of AAC prevalence were increased age, increased BMI, hypertension, and current smoking. Age was the strongest predictor, with each SD (7.8 year) increase in age conferring 2.7 times increased odds of having AAC ($P<0.0001$). A one SD greater cortical, but not trabecular, vBMD was associated with a significant decreased odds of AAC prevalence independent of other traditional risk factors (OR 0.65; 95 % CI 0.45–0.92).
Conclusions Cortical vBMD is inversely associated with AAC presence. This finding suggests that there may be shared physiology between cortical bone compartment remodeling and vascular calcification.

Keywords African ancestry · Aortic calcification · Computed tomography · Volumetric bone mineral density

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Introduction

Bone mineral density (BMD) has been inversely associated with subclinical and clinical cardiovascular disease (CVD), even after adjusting for potential confounding factors [1–6]. Arterial calcification is a marker of subclinical CVD that develops with age throughout the vasculature [7]. The presence and amount of arterial calcification significantly predicts CVD events and mortality [8–10]. While there have been many studies on the relationship between arterial calcification and areal BMD, they have predominately focused on patients with chronic kidney disease, or in population samples of Caucasians and Asians [11–15]. Less is known about this relationship in individuals of African ancestry, who are known

to have a lower prevalence of coronary arterial calcification than Caucasians [16–19], even though they are at greater risk of CVD events [20] and who have the greater peak BMD than other ethnic groups [21–23].

Most studies of arterial calcification and volumetric BMD have focused on the lumbar spine, which is mainly comprised of trabecular bone. To our knowledge, only four previous studies have examined the relationship between trabecular volumetric BMD (vBMD) and aortic arterial calcification (AAC) [6, 24–26], with results being inconclusive. No previous study, to our knowledge, has examined the association between AAC and cortical BMD. However, a study in rats with kidney failure suggests that cortical bone loss may be more strongly related to arterial calcification than trabecular bone [27], although the mechanisms driving this association remain unclear. In the present study, we assessed the association of AAC prevalence with cortical and trabecular vBMD in 278 Afro-Caribbean men.

Methods

Tobago CT cohort

The CT sample was designed as an ancillary study of the Tobago bone health study, a population-based prospective study of 2,652 community-dwelling men aged 40 years and older, who reside on the Caribbean Island of Tobago [23]. Men from Tobago are of homogeneous African ancestry with low European admixture (<6 %) [28]. Participants underwent a peripheral quantitative computed tomography (pQCT) scan of the tibia and radius to assess vBMD from 2004–2007. The CT sample consisted of 278 men who were recruited consecutively during a follow-up visit from 2011–2012. This ancillary CT study examined the differences in ectopic adiposity and arterial calcification in diabetics and nondiabetics. Written informed consent was obtained from each participant using forms and procedures approved by the University of Pittsburgh's institutional review board, the US Surgeon General's human use review board, and the Division of Health and Human Services institutional review board.

Aortic calcification

Aortic calcification was assessed by central computed tomography using a dual slice high-speed NX/I scanner, with gantry speed 0.7 s (GE Medical Systems, Waukesha, WI). Scans captured images from cross-sectional slices in the abdomen from L3 to S1. Calcification measures included the summation of calcification in the abdominal aorta and common iliac arteries. Measurements were performed by experienced analysts using a computer workstation (TeraRecon San Mateo, CA), and the Agatston method [29] was used to score calcification, with presence defined by a score of >10 to rule out false-positive classification. A single reader at the Wake Forest University Department of Radiology read all scans, and in 153 blinded re-reads in a related study intra-reader, technical error was 6.4 % for AAC.

Volumetric bone mineral density

Volumetric BMD at the non-dominant forearm and left tibia was measured by pQCT using an XCT-2000 scanner (Stratec Medizintechnik, Pforzheim, Germany). Technicians followed stringent protocols for patient positioning and scanning. A scout view was obtained prior to the pQCT scan to define an anatomic reference line for the relative location of the subsequent scans (4 and 33 % of the total length) at the radius and tibia. Tibia length was measured from the medial malleolus to the medial condyle of the tibia, and forearm length was measured from the olecranon to the ulna styloid process. A single axial slice of 2.5-mm thickness with a voxel size of 0.5 mm and a speed of 20 mm/s was taken at all locations. Image processing was performed using the Stratec software package (version 5.5E). To determine the cortical volumetric BMD (in milligrams per cubic centimeter) at the 33 % site of the radius and tibia, identical parameters were mode 2, threshold=169 mg/cm^3 and cortmode 1, threshold=710 mg/cm^3. To determine the trabecular volumetric BMD (in milligrams per cubic centimeter) at the 4 % site of the radius and tibia, identical parameters for contour finding and separation of trabecular and cortical bone were contour mode 2, threshold=169 mg/cm^3 and peel mode 1, area=45 %. The short-term in vivo precision of the pQCT measurements for 15 subjects ranged from 0.65 % (for cortical density at the tibia) to 2.1 % (for trabecular density at the tibia).

Other characteristics

Demographic, health history, and anthropomorphic characteristics were assessed by trained staff using interview and clinical exams. Body weight was measured to the nearest 0.1 kg on a balance beam scale, and standing height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, both without participants wearing shoes. BMI was calculated as weight in kilograms divided by standing height in meters squared. Smoking status was classified as either current or not, and participants reporting smoking <100 cigarettes in their lifetime were considered nonsmokers. Alcohol consumption is limited in this sample and was, therefore, coded as consuming ≥4 drinks per week (yes/no) to identify individuals with greater than average alcohol intake. Physical activity was assessed by the number of minutes walked per week for exercise, and participants were classified as "active" if they reported walking more than 1 h per week. Men reporting less walking were classified as "not active". Diabetes was defined as a fasting serum glucose level ≥126 mg/dl or current use of

diabetes medication. Blood pressure was measured three times while seated, and the average of the second and third reading was used in this analysis. Hypertension was defined as a SBP ≥140 mmHg, DBP ≥90 mmHg, and/or current use of antihypertensive medication. In a subset of 224 men, lipoproteins were measured in fasting serum samples. HDL-c was determined using the selective heparin/manganese chloride precipitation method. LDL-c was calculated by the Friedewald equation. Triglycerides were determined enzymatically using the procedure of Bucolo and David [30].

Statistical analysis

All variables were assessed for non-normality and transformed as necessary. Outliers, defined as ≥4 SD from the mean, were removed for each measure; no more than one observation was removed from any measure. Differences in means or frequencies by diabetic status were tested by chi-squared test or *T*-test, as appropriate. Logistic regression was used to identify the significant predictors of aortic calcification after adjustment for other cofactors. Models of volumetric BMD predicting AAC were developed by sequentially adding covariates to assess the strength and independence of the associations. Covariates included (in order of their addition) are as follows: age, BMI, smoking, alcohol intake, physical activity, diabetes, and hypertension. Odds ratios were expressed as the effect of a 1 SD or unit increase in covariate or BMD in multivariable adjusted models.

Results

Sample characteristics

Out of the 278 men studied, 190 (68.3 %) had aortic calcification (Table 1). Median calcium score in those with AAC was 414.5 and ranged from 10.3–13,061.5. The men were aged 56.3 years on average, and those with AAC were about 6 years older than those without AAC ($P<0.0001$). Men with AAC had greater BMI than those without AAC ($P=0.003$). The prevalence of smoking, intake of four or more alcoholic drinks per week, and walking for more than 1 h per week for exercise did not differ between men with and without AAC. Prevalence of diabetes was greater in those with AAC than those without (29 vs. 15 %, $P=0.01$). Hypertension also differed by AAC status ($P=0.0003$). Measures of cortical BMD were lower in those with AAC than without ($P<0.0001$ for both radius and tibia), but trabecular BMD did not differ by AAC status.

Predictors of aortic calcification

A 7.8-year (1 SD) greater age was associated with 2.7 times greater odds of AAC (Table 2). BMI and hypertension were significantly related to AAC after adjustment for age ($P<0.05$ for both). Each 4.6 kg/m^2 increase in BMI was associated with 60 % greater age-adjusted odds of AAC. Hypertensives were 2.0 times more likely to have AAC than non-hypertensives. Diabetes was not significantly associated with AAC after

Table 1 Characteristics of Afro-Caribbean men by presence of aortic calcification

Trait	All men ($N=278$)	No calcification ($N=88$)	Calcification ($N=190$)
Aortic calcium score*	414.5 (97.2–1142.1)	–	414.5 (97.2–1,142.1)
Age (years)	56.3±7.8	**52.1±6.0**	**58.3±7.8**
BMI (kg/m^2)	27.9±4.6	**26.7±3.9**	**28.4±4.8**
Current smoking (%)	10.1	9.1	10.5
Drink ≥4 alcoholic drinks/week (%)	9.4	5.7	11.1
Walk ≥1 h/week (%)	55.0	58.0	53.7
Diabetes (%)	24.5	**14.8**	**29.0**
Hypertension (%)	45.3	**29.6**	**52.6**
Cortical BMD (mg/cm3)			
Tibia	1,178±27	**1,186±21**	**1,173±28**
Radius	1,213±25	**1,222±18**	**1,209±26**
Trabecular BMD (mg/cm3)			
Tibia	236±37	232±35	238±38
Radius	210±48	209±42	210±50

Characteristics are shown as Mean±SD or frequency

BOLD indicates significant difference by calcification status ($P\leq0.05$)

*Aortic calcification score is shown in those with calcification as median (IQR)

Table 2 Odds of aortic calcification in Afro-Caribbean men

Variable	Unit	Age-adjusted OR (95 % CI)	Multivariate-adjusted* OR (95 % CI)
Age (years)	7.8	**2.7 (1.9–3.7)**	**2.7 (1.9–3.9)**
BMI (kg/m^2)	4.6	**1.6 (1.1–2.1)**	**1.4 (1.0–2.0)**
Current smoking (%)	1	2.0 (0.8–5.0)	**2.6 (1.0–6.6)**
Walk ≥1 h/week (%)	1	1.0 (0.6–1.7)	–
Drink ≥4 drinks/week (%)	1	2.8 (1.0–8.0)	–
Diabetes (%)	1	1.9 (0.9–3.8)	–
Hypertension (%)	1	**2.3 (1.3–4.0)**	**2.0 (1.1–3.7)**

Odds ratios (95 % CI) are for 1SD or 1 unit increase in variable as shown. **BOLD**: $P \leq 0.05$

*Multivariate ORs are adjusted for all covariates in model

adjustment for age. The multivariate model containing only significant predictors of AAC included age, BMI, hypertension, and smoking ($P \leq 0.05$ for all; Table 2).

Association of volumetric bone mineral density and aortic calcification

In unadjusted models, a 1 SD greater cortical BMD at the radius or tibia was associated with reduced odds of AAC (OR 0.50; 95 % CI 0.36–0.70 and OR 0.51; 95 % CI 0.36–0.71, respectively; Table 3). However, there was no association between trabecular BMD at the radius or tibia and AAC (OR 1.00; 95 % CI 0.78–1.29 and OR 1.18; 95 % CI 0.92–1.53, respectively). The association between cortical BMD and AAC persisted even after adjustment for age, BMI, lifestyle factors, diabetes, and hypertension. A 1 SD greater cortical BMD at the radius or tibia was associated with one-third lower odds of having AAC (OR 0.64; 95 % CI 0.45–0.92 and OR 0.67; 95 % CI 0.46–0.97, respectively) in the fully-adjusted model. There was no association between trabecular BMD at the radius or tibia and AAC in multivariable analysis.

Discussion

To our knowledge, this is the first report of aortic calcification in Afro-Caribbean men. Aortic calcification was present in 68.3 % of these men. The main correlates of aortic calcification were older age, higher BMI, hypertension, and smoking. We also found that cortical, but not trabecular, vBMD was associated with AAC prevalence.

To our knowledge, this is the first report of a differential association of cortical and trabecular vBMD with AAC in humans. Results were identical at the radius and tibia; thus, weight-bearing does not appear to influence this association. There have been three previous studies that investigated the association of trabecular vBMD and AAC [6, 24, 25]. Only two previous studies included men, and only one of these included African-Americans [6]. The study that included African-Americans found that spine vBMD, a mostly trabecular site, was inversely associated with abdominal calcified plaque in European-American men, but not in African-American men or in women of either ethnicity [6]. The other study found no association between spine or hip vBMD and AAC score in White men or women [24]. However, a study conducted in both White and African-American menopausal women found an association of trabecular vBMD with AAC, but did not report ethnicity-stratified results [25]. The inconsistency in the results by study may be indicative of true sex- and/or ethnicity-specific differences in the relationship of trabecular vBMD with AAC.

Our study suggests a differential association of cortical bone with aortic calcification that may not have been revealed in previous studies that focused solely on trabecular bone. This finding is in agreement with a study of medial calcification

Table 3 Odds of aortic calcification by volumetric bone mineral density in Afro-Caribbean men

Model covariates	Cortical BMD		Trabecular BMD	
	Radius	Tibia	Radius	Tibia
Unadjusted	0.50 (0.36–0.70)	0.51 (0.36–0.71)	1.00 (0.78–1.29)	1.18 (0.92–1.53)
Age	0.62 (0.44–0.87)	0.63 (0.44–0.89)	1.08 (0.82–1.42)	1.22 (0.91–1.62)
+BMI	0.67 (0.48–0.94)	0.68 (0.48–0.98)	1.04 (0.78–1.38)	1.13 (0.84–1.52)
+Lifestyle Factors*	0.69 (0.49–0.96)	0.68 (0.48–0.98)	1.06 (0.79–1.41)	1.14 (0.85–1.54)
+Diabetes	0.64 (0.45–0.92)	0.66 (0.46–0.96)	1.04 (0.78–1.39)	1.14 (0.84–1.53)
+Hypertension	0.64 (0.45–0.92)	0.67 (0.46–0.97)	1.03 (0.77–1.38)	1.12 (0.82–1.51)

Odds ratios (95 % CI) are for 1 SD increase in volumetric BMD

*Lifestyle factors included smoking, walking, and alcohol intake

in rats with chronic renal failure [27], which observed a strong inverse correlation between cortical but not trabecular BMD and aortic calcification (all r>−0.60, $P<0.05$ for all) [27]. Measures of kidney function were available in 273 of our men. This sample had good kidney function overall (mean eGFR, 83.8 ml/min/1.73 m^2). Within this subset, eGFR was not associated with AAC in univariate analyses, and adding eGFR to the models did not explain the association of cortical vBMD and AAC (data not shown).

The mechanisms underlying an association of AAC with cortical but not trabecular bone is unknown, and our study was not designed to determine the potential mechanisms for the association. However, cortical and trabecular bone are known to have different turnover rates and age-related patterns [31] and have different epidemiologic correlates [22]. Thus, it is not surprising that there may be a differential association between cortical and trabecular bone with AAC. Further studies are needed to confirm our findings and to better understand the potential mechanisms for compartment-specific bone associations.

The presence of aortic calcification has been reported in many studies of similar-aged men with differing ethnic backgrounds (Table 4) [1, 17, 18, 32, 33]. Prevalence of AAC in these studies was generally 60–70 %, without a strong pattern by ethnicity, except for the Japanese men aged 40–49 who had 36 % AAC prevalence [33]. There is inconclusive evidence on the presence of an ethnic difference in AAC prevalence. One previous study of multiple ethnicities reported significantly greater AAC in Whites than Blacks [18]. However, another study reported very similar AAC prevalence between the Whites and African-Americans, although no formal test of ethnicity and AAC alone was performed [17]. The Afro-Caribbean men from our Tobago study had a prevalence of 68 %, which is consistent with previous reports in White and African-American samples (Table 4).

The strongest predictors of AAC prevalence include greater age, male sex, smoking, higher BMI or waist circumference, hypertension, dyslipidemia, and diabetes [1, 17, 18, 32–35]. In the current study, the only independent significant correlates of AAC were age, BMI, hypertension, and smoking. We did not have measures of lipids and lipoproteins in the entire set of men with CT; therefore, we were unable to thoroughly assess the association of these measures with AAC prevalence. In the subset of men with LDL-c, HDL-c, and triglycerides ($N=224$), lipid levels were not independently associated with AAC (data not shown). Diabetes was not associated with AAC in the age- or multivariate-adjusted models. We included diabetes into our analyses of AAC and BMD and found similar results. In previous studies, smoking has been associated with three to four times increased odds of AAC [18, 34, 35]. Smoking was associated with 2.6 times greater odds of AAC in our final multivariate model ($P=0.05$). Age, BMI, and hypertension were also significantly associated with AAC and replicate effects in previous studies [1, 17, 18, 32–35]. Alcohol intake was limited in this sample, and we were likely underpowered to assess the association of alcohol consumption with AAC.

The prevalence of abdominal aortic calcification was similar to values in other populations of White and African ancestry men of similar age. The strongest correlate of AAC was age, followed by hypertension, BMI, and current smoking. We also found an association between cortical bone and aortic calcification. Additional research is needed to determine the shared pathways underlying cortical bone metabolism and aortic calcification.

Table 4 Aortic arterial calcification in Afro-Caribbean men compared to previous reports in men of various ethnic backgrounds

Study	Description	Ethnicity	N	Mean Age (range)	AAC (%)
Tobago Bone Health Study	Population-sample in Tobago	Afro-Caribbean	278	56 (40–90)	68.3
Multi-Ethnic Study of Atherosclerosis (18)	Population-sample across USA	African-American	409	63 (45–84)	63.0*
		Non-Hispanic White	782	65 (45–84)	82.0[R]
		Chinese	258	65 (45–84)	76.0*
NHLBI Family Heart Study (17)	Family sample enriched for CVD across USA	African-American	201	52 (25+)	71.8
		Non-Hispanic White	1,099	55 (25+)	71.0[#]
ERA-JUMP (33)	Population-sample in Pittsburgh, PA (1) and Hawaii (2), USA; Japan (3)	Non-Hispanic White (1)	301	45 (40–49)	68.8[R]
		Japanese-American (2)	292	45 (40–49)	62.3
		Japanese (3)	310	45 (40–49)	35.8*
Jackson Heart Study (32)	Population-sample in Jackson, MS, USA	African-American	489	58 (35–84)	65.0
Framingham Heart Study (1)	Population-sample in Framingham, MA, USA	Primarily Non-Hispanic White	1,046	60 (47–80)	67.5

*Significant ($P<0.05$) difference in AAC prevalence by ethnicity compared to *R* reference group

[#] Test for racial difference in AAC prevalence not performed

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Conflicts of interest None

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