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Role of bone mineral density in the inverse relationship between body size and aortic calcification: Results from the Baltimore Longitudinal Study of Aging

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ABSTRACT

Objective: There is a J-shaped relationship between body mass index (BMI) and cardiovascular outcomes in elderly patients (obesity paradox). Whether low BMI correlates with aortic calcification (AC) and whether this association is accounted for by bone demineralization is uncertain.
Methods: Presence of AC was evaluated in 687 community-dwelling individuals (49% male, mean age 67 ± 13 years) using CT images of the thoracic, upper and lower abdominal aorta, and scored from 0 to 3 according to number of sites that showed any calcification. Whole-body bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry. Predictors of AC were assessed by logistic regression, and the role of BMD using mediation analysis.
Results: Age and cardiovascular risk factors were positively associated while both BMI ($r = -0.11$, $p < 0.01$) and BMD ($r = -0.17$, $p < 0.0001$) were negatively associated with AC severity. In multivariate models, lower BMI (OR 0.96, 95%CI 0.92–0.99, $p = 0.01$), older age, higher systolic blood pressure, use of lipid-lowering drugs and smoking were independent predictors of AC. A nonlinear relationship between BMI and AC was noticed ($p = 0.03$), with decreased AC severity among overweight participants. After adjusting for BMD, the coefficient relating BMI to AC was reduced by 14% and was no longer significant, whereas BMD remained negatively associated with AC (OR 0.82, 95%CI 0.069–0.96, $p = 0.01$), with a trend for a stronger relationship in older participants.
Conclusion: Low BMI is associated with increased AC, possibly through calcium mobilization from bone, resulting in low BMD. Prevention of weight loss and bone demineralization with aging may help reducing AC.

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1. Introduction

Aortic calcification (AC) occurs in the tunica media of the arteries as a result of senile degeneration, or in the tunica intima as results of atherosclerotic plaques calcification [1,2]. Regardless of its localization and origin, AC is an independent risk factor for cardiovascular events [3].

Cross-sectional and longitudinal studies have shown that AC tends to be associated with low bone mineral density (BMD), suggesting the existence of a “calcification paradox”, whereby low calcium deposition in the bone tends to be associated with higher calcium deposition in the arterial wall [1,4]. Although the mechanisms of this association are unknown, it has been suggested that high body mass index (BMI) by stimulating bone mechanoreceptor that promotes calcium deposition in bone tissue may prevent abnormal precipitation of calcium and phosphate salts in the

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vascular wall [2,4,5]. Hence, as in other cardiovascular conditions [6], studies have suggested that low BMI may be associated with an increased risk of AC, particularly in elderly populations [7,8]. If the negative association between BMI and AC is confirmed, it may be worth considering interventions that reduce AC in older patients who are losing weight because of dietary restriction or pathologic causes. Nevertheless, information on the dynamic interplay between body size, bone mineralization and vascular calcification is still limited. We sought to examine the independent association between BMI and AC in a population of community-dwelling older adults participating in the Baltimore Longitudinal Study of Aging (BLSA), and to evaluate the potential contribution of BMD as a mediator of this association.

2. Methods

2.1. Study population

This research project used data from the BLSA, an ongoing prospective study of normative aging in community-dwelling volunteers living primarily in the Baltimore–Washington area (USA) [9]. Participants are enrolled if they are healthy at baseline, but remain in the study if any disease develops. Once enrolled in the study, they undergo approximately 3–4 days of medical examinations at regular intervals throughout their lifespan.

Participants included in the present analysis were those with measures of pulse wave velocity, dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT) images of the body trunk and abdomen collected at the same visit [10]. From the original cohort of 711 individuals who met these criteria, 23 subjects were excluded because of missing covariates and 1 subject because of the presence of aortic and iliac intraluminal prostheses, leaving a final sample of 687 individuals, 351 women (mean age 66 ± 12 years, range 31–95) and 336 men (mean age 68 ± 13 years, range 28–94).

The BLSA study protocol was approved by the Intramural Research Program of the National Institute on Aging and the Institutional Review Board of the MedStar Health Research Institute (Baltimore, MD). All participants provided informed participation consent at each visit.

2.2. Assessment of aortic calcification

CT images of the chest and abdomen were reviewed for the presence of apparent calcification of the aortic walls. All images were acquired using a Somatom Sensation CT scanner (Siemens, Malvern, PA). AC was assessed at three different levels: thoracic aorta, upper abdominal aorta and lower abdominal aorta. More precisely, lateral radiographs of the chest obtained from sagittal CT scout images of the body trunk were used to assess the presence or absence of aortic arch calcification, as previously described [7,11,12]. A 10-mm axial slice obtained at the level between the first and the second lumbar vertebra (L1–L2) and an analogous slice obtained between the fourth and the fifth lumbar vertebra (L4–L5) were used to assess the presence or absence of calcification of the upper and lower abdominal aorta, respectively. An AC severity score ranging from 0 to 3 was then calculated, by assigning a value of 1 to each aortic segment (arch, upper and lower abdomen) where the presence of calcification was detected.

2.3. Assessment of bone mineral density

Whole-body BMD was measured by DEXA using the Lunar Prodigy Scanner with version 10.51.006 software (General Electric, Madison, WI) [13]. BMD was also measured at both femoral necks and averaged, and used for sensitivity analysis (femoral BMD). BMD was expressed as grams per square centimeter (g/cm^2).

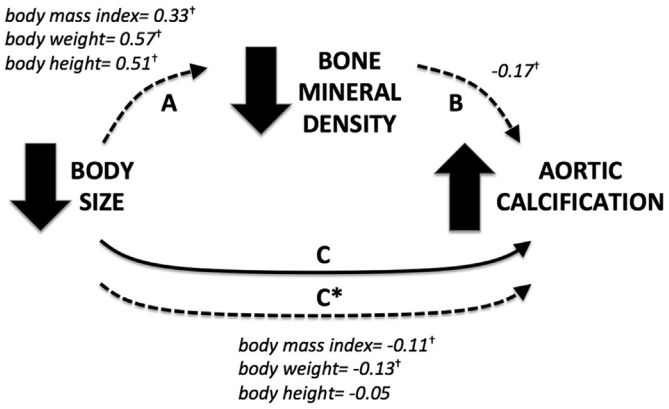

Fig. 1. Putative mediation pathway for the relationship between body size, bone mineral density and aortic calcification. A mediator is conceptualized as being within the causal pathway of the predictor and the outcome of interest (A & B above: decreased body size determines a reduction in bone mineral density, which in turn increases aortic calcification). If one ignores the mediator (bone mineral density), one will observe a relationship between the predictor (body size) and the outcome variable (aortic calcification) (C). Adjusting for the mediator results in an attenuation or elimination of the relationship between the predictor and the outcome variable (C*). Numbers in italic represent Spearman correlation coefficients between different body size measures (body mass index, body weight and body height), bone mineral density and aortic calcification severity score. † = p value <0.01.

2.4. Clinical variables and medications

BMI was calculated as body weight divided by squared height (kg/m^2) and a BMI ≥ 30 defined obesity. Brachial blood pressure was measured at rest in triplicate using an appropriately sized cuff, and the average of three systolic blood pressure measurements was used in analyses. Smoking was ascertained by a questionnaire and participants who had never smoked >100 cigarettes were considered as non-smokers. Physical activity was quantified by converting the time spent walking, climbing stairs, or in any moderate to vigorous activity, as assessed by questionnaires, into calories expended per week, as previously reported [14]. Participants were classified as active if reporting ≥1000 kcal/week of exercise activity [15]. Diabetes mellitus was diagnosed according to the 2011 American Diabetes Association criteria [16] or use of diabetes medications. The glomerular filtration rate (GFR) was calculated by the simplified modification of diet in renal disease (MDRD) formula and expressed as mL/min/1.73 m^2. Fasting serum samples were drawn to assay plasma lipoprotein, and low-density lipoprotein cholesterol concentrations were estimated by using the Friedewald formula. Automated chemical analysis was used to measure serum calcium, and 25-hydroxyvitamin D concentrations were measured by liquid chromatography–mass spectrometry [17].

Use of medications was determined at each study visit according to the Anatomical Therapeutic Chemical classification system recommended by the World Health Organization. Antihypertensive medications included vasodilators (C01D, C03 and C04), diuretics (C03), beta blockers (C07), calcium channel blockers (C08) and agents acting on the renin–angiotensin system (C09). Participants taking vitamin D and analogs (A11CC), vitamin D and A in combination (A11CB), and vitamin D with other vitamins (A11A, A11B, A11H, A11JC) were considered as taking vitamin D supplementation. Lipid-lowering medications included statins (C10AA) and their combination with other lipid-lowering agents (C10BA and C10BX). Bisphosphonates included codes M05BA and M05BB.