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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

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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.

Keywords

aortic calcification; body mass index; body size; bone mineral density; obesity paradox; calcification paradox

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 events³.

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 tend 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 promote calcium deposition in bone tissue may prevent abnormal precipitation of calcium and phosphate salts in the vascular wall^{2,4,5}. Hence, as in other cardiovascular conditions⁶, 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.

METHODS

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.

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.

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/cm²).

Clinical variables and medications

BMI was calculated as body weight divided by squared height (kg/m²) 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 ≥1,000 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 m². 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 spectrometry¹⁷.

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 analogues (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.

Statistical analysis

Continuous variables are presented as mean±standard deviation and categorical variables as absolute and/or relative frequencies. Comparisons between the AC severity groups were drawn by one-way analysis of variance and chi-square tests, as appropriate.

Firstly, binary and ordered logistic regression models were used to assess the independent association of BMI with the presence and severity of AC, respectively. For ordered logistic models, the proportional odds assumption was tested and found to be acceptable in all cases. Variables known to potentially affect AC and/or showing significant univariate associations with it were entered in multivariable models. Race was combined into two categories (African Americans vs. non African Americans), according to previous literature showing lower prevalence of AC in the African Americans race group¹⁸. Since BMI is calculated from height and weight and these two measures may independently contribute to the relationship between BMI and AC, regression models were also constructed using body weight or body height in place of BMI.

We then added BMD to the model in order to examine i) the independent association of BMD with AC and ii) the mediator effect of BMD in the association between BMI and AC. Notably, mediation analysis in cross-sectional studies is considered a causal model that can suggest a direction of influence, based on pre-defined causal associations among the variables posited by the investigator (Figure 1). In brief, if the predictor and the mediator are correlated, and if the predictor and the mediator are also both correlated with the outcome, the existence of a causal path that links the three variables can be supposed, where the predictor causes the outcome “because” the predictor causes the mediator that causes the outcome¹⁹. Therefore, as part of the conditions necessary for mediation, we firstly confirmed the existence of a reciprocal association between the mediator (BMD), the predictor (BMI or body weight or body height) and the outcome (severity of AC) by estimating Spearman’s correlation coefficients between these variables. We then used a mediation pathway approach¹⁹ and calculate the percentage decrease of odds ratio for BMI after adjusting the model for BMD (see Figure 1 and its legend).

The interaction of each independent variable (BMI, body weight, body height, BMD) with age, gender and African American race was also included in the respective multivariate regression models, to test whether associations were consistent across race, gender and age groups. The variance inflation factor was 2 for all variables in each regression model, indicating no multi-collinearity.

All statistical analyses were performed using SAS package, version 9.2 (SAS Institute Inc., Cary, NC), and significance was set at $p = 0.05$.

RESULTS

Study population and univariate associations

Overall characteristics of the study population are presented in Table 1. Due to the high mean age of the sample (67 ± 13 years), 70% of participants included in the present analysis (229 women and 251 men) had evidence of calcification involving at least one aortic segment. In details, of the 214 individuals with AC score =1, 126 (59%) presented with apparent calcification of the aortic arch, 20 (9%) of the upper and 68 (32%) of the lower abdominal aorta. Of the 191 individuals with AC score =2, 36 (19%) had a calcification of both the aortic arch and upper abdominal aorta, 87 (45%) of both the lower and upper abdominal aorta and 68 (36%) of both the aortic arch and lower abdominal aorta.

Table 1 also presents the characteristics of study participants by severity of AC. As expected, age significantly increased across AC severity groups, as well as other cardiovascular risk factors such as systolic blood pressure and treated hypertension, smoking, and diabetes mellitus. The prevalence of male gender also tended to increase across AC severity groups, together with the number of participants of white ethnicity and the use of lipid-lowering drugs (mostly statins), bisphosphonate and vitamin D supplements. These latter were overall slightly more frequent in women than men (64% vs. 58%, $p=ns$). The more frequent use of vitamin D in older subjects with more comorbidities may be explained by participants receiving feedback on low vitamin D level at the end of each BLSA visits. Interestingly, both body weight and BMI significantly decreased with increasing severity of AC, as well as BMD. The trends of the variables presented in Table 1 did not significantly differ when considering women and men separately, although statistical significance was lost in some sub-analyses most likely due to the smaller sample size (see Supplemental Table S1).

Univariate correlation coefficients between predictors, mediator and outcome of the predefined mediation pathway are shown in Figure 1. Both BMI and body weight showed a significant inverse correlation with AC and a positive correlation with BMD. BMD was also inversely correlated with AC. Body height did not show a significant correlation with AC, but only with BMD.

Independent inverse association between BMI and AC

In multivariate ordered logistic analysis (Table 2, Model 1), independent predictors of severity of AC were lower BMI (OR 0.96, 95%CI 0.92–0.99, $p=0.01$), older age (OR 1.12, 95%CI 1.10–1.14, $p<.0001$), higher systolic blood pressure (OR 1.012, 95%CI 1.003–1.022,

$p<.01$), use of lipid-lowering drugs (OR 1.43, 95%CI 1.05–1.95, $p=0.02$) and smoking (OR 1.76, 95%CI 1.30–2.37, $p<.001$). The same results were obtained in binary model predicting the presence of aortic calcification (data not shown), and when substituting body weight for BMI (Supplemental Table S2). On the contrary, height did not show an independent association with AC (Supplemental Table S3). No significant interaction was found between BMI and age, gender and African American race (Table 2).

Because of the nonlinear trend of BMI and obesity across AC severity groups (Table 1), a BMI-squared term was entered into Model 1 and a significant nonlinear relationship between BMI and AC severity was observed ($p=0.026$). To better understand the meaning of this quadratic relationship, Model 1 was run separately for participants with BMI ≤ 25 kg/m² (normal), BMI 25–30 kg/m² (overweight) and BMI >30 kg/m² (obesity)⁶. As shown in Figure 2, both normal (OR: 1.76; 95%CI 1.24–2.50, $p=0.0015$) and obese (OR: 1.23; 95%CI 0.84–1.80, $p=0.295$) participants had higher AC severity than the intermediate overweight group. Results did not differ when the analysis was stratified by BMI tertiles (thresholds 24.8 and 28.6 kg/m², respectively, data not shown). The extreme BMI categories of malnutrition (<18.5 kg/m²) and severe obesity (>35 kg/m²) were not considered, because of the very low number of participants falling into these groups (5 and 41, respectively).

Independent association of BMD with AC and its potential role as a mediator of the inverse association between BMI and AC

When BMD was added to Model 1 of Table 2, it was significantly and inversely associated with AC severity (OR 0.82, 95%CI 0.069–0.96, $p=0.01$), namely for any 10 g/cm² increase in BMD there was a 18% decrease in the probability of having a higher AC score. Interestingly, in this BMD-adjusted model, the size of the odds ratio for BMI associated with lower AC was reduced by about 14% and was no longer statistically significant (OR 0.967, 95%CI 0.932–1.003, $p=0.0729$). Results were consistent even after accounting for variables with significant univariate associations with AC and known to potentially affect vascular calcification and bone density, including physical activity, blood levels of vitamin D and calcium, use of vitamin D supplements and bisphosphonates (Table 2, Model 3). No significant interaction was found between BMD and either age, gender or African American race in Model 3. However, there was a borderline interaction between BMD and age ($p=0.07$) and analyses stratified by median age suggested a stronger relationship between BMD and AC in participants older than 68 years old (OR 0.76, 95%CI 0.60–0.97, $p=0.03$) as compared to the younger ones (OR 0.82, 95%CI 0.62–1.07, $p=0.15$).

DISCUSSION

The present study demonstrated an independent inverse relationship between body size and severity of AC in a normative aging population. This relationship was mediated, at least in part, by BMD.

Inverse relationship between body size and vascular calcification

We found a negative relationship between BMI and the severity of AC, which was accounted for by body weight but not height. A more in-depth analysis also showed

decreased AC severity among overweight participants compared with lean and obese ones. An “obesity paradox” has been described for several cardiovascular diseases, including hypertension^{20, 21}, stroke²², coronary artery disease⁶, acute coronary syndromes²³ and heart failure²⁴. In all these settings, investigators have found either a negative or J-shaped relationship between the severity of the disease and BMI, meaning excess risk/mortality at lower BMI or at both extremes of BMI, respectively. Evidence in the same direction is also available for patients with peripheral arterial disease²⁵ and vascular calcification^{7, 8}. In a large cohort of 9993 patients with coronary artery disease who underwent percutaneous coronary intervention, Kovacic and colleagues identified an inverse association between BMI and an index of calcification of the coronary arteries⁸. Interestingly, they showed that overweight and obese patients had respectively a 17% and 30% decreased probability of severe coronary calcification as compared to patients with normal BMI⁸. These data were recently confirmed using coronary intravascular ultrasound²⁶. Reduction in body weight with aging is primarily due to skeletal muscle loss and functional decline²⁷, and this has been proposed as potential reason for the so-called “obesity paradox” in elderly patients with heart failure and other cardiovascular diseases²⁸. With regard to vascular calcification, a small study demonstrated that the negative association between body weight and AC was explained by peripheral lean body mass, and in multivariate analysis it found that elderly men with reduced lean mass had increased severity of AC⁷. Excess cardiovascular risk in lean individuals has also been attributed to deleterious lifestyles, particularly smoking and excess alcohol intake, contributing to both leanness and risk of death^{25, 29}. Remarkably, in our study, as in others^{25, 30}, former and current smoking was an independent predictor of the severity of AC, but no significant interaction was found between smoking and BMI or body weight, and the prevalence of smokers was comparable in normal weight, overweight and obese study participants (43%, 49% and 40%, respectively). On the other hand, one may emphasize the role of vascular calcification as a marker of advanced atherosclerosis, thus able to identify patients with higher chance of developing cardiovascular diseases such as ischemic heart disease³¹ and heart failure³². In this view, weight loss could be considered secondary to AC, meaning that more prevalent cardiovascular diseases in patients with severe AC might determine a reduction in daily physical activity and food intake which ultimately lead to a lean and frail phenotype³³.

The association of body size with aortic calcification may be mediated by bone mineral density

We confirmed the inverse relationship between BMD and AC reported in previous studies (reviewed by Persy and colleagues¹). This association was independent of several potential confounders, including age, blood pressure, renal function, diabetes and smoking. More importantly, the strength of the association between BMI and AC severity was reduced and was no longer significant after the analysis was adjusted for BMD, suggesting a mediation effect of BMD, as depicted in Figure 1 and previously proposed by Kovacic and colleagues⁸. Indeed, our findings support the hypothesis that decreased body weight determines a reduction in BMD, which in turn determines an increase in vascular calcification. This information could not be gained from previous studies, most of which used BMI as one covariate among others, without reporting its estimate in multivariate models^{12, 34–39}. We instead purposely constructed our models adding BMD after BMI, in

order to explore the effect of BMD on the association between BMI and AC. We found that the beta estimate of BMI was reduced of about 14% after accounting for BMD. Though limited by the cross-sectional nature of the analysis, this methodology and the reduction in beta estimate we found in our cohort suggest possible causal pathways between variables¹⁹. This process may particularly apply to the elderly, who are more likely to suffer from weight loss, bone demineralization and vascular calcification^{40, 41}. In accordance with this concept, we found a borderline interaction between BMD and age ($p=0.07$), and after appropriate stratification the role of BMD was confirmed only for individuals older than 68 years of age. However, this finding may have been due to the presence of more severe AC in the older age group, and the hypothesis that BMD mediates the association of BMI with AC needs to be further tested in specifically selected populations.

The present study was not designed to identify potential mechanisms by which the cross-talk between the bone and the vasculature occurs. It has been proposed that circulating factors involved in bone resorption, such as osteopontin, fibroblast growth factor 23, phosphate, and parathyroid hormone might promote the conversion of vascular cells (particularly smooth muscle cells) to bone-like cells that express a number of bone-related proteins and ultimately differentiate into osteoblasts^{1, 2, 5}. In particular, alterations in the receptor activator of nuclear factor κ B (RANK)/RANK ligand/osteoprotegerin axis may contribute to both bone loss and vascular calcification⁴². By binding to RANK, RANK ligand stimulates osteoclast differentiation and activation and, thereby, bone resorption; this effect is antagonized by osteoprotegerin, which acts as a decoy receptor for RANK ligand⁴³. Of note, mice knockout for the osteoprotegerin gene exhibit early-onset osteoporosis and aortic and renal artery calcification⁴⁴ and the RANK ligand/osteoprotegerin ratio is altered in human vascular calcification^{45, 46}.

The validity of our data was substantiated by the fact that traditional risk factors associated with AC such as age, smoking and systolic blood pressure were highly predictive of increase severity of AC. While the effects of statins on vascular calcification remain controversial^{1, 2}, our findings of an independent positive relationship between the use of statins and the severity of AC are echoed by a recent subanalysis of the Veterans Affairs Diabetes Trial, demonstrating an accelerated progression of vascular calcification in more frequent statin users⁴⁷. Further research work is necessary to pinpoint the influence of treatment with statins on vascular calcifications.

Study limitations

The present study has some limitations. First, the study is cross-sectional in nature making it impossible to draw any conclusion about cause-effect relationships. The suggestion of a possible role for BMD as mediator should also be interpreted with some caution. Longitudinal research may shed some light on temporal relationships between BMI, BMD, and AC, whereas experimental studies may gain insight into the causal mechanisms by which a reduction in body size may increase AC, for instance through mobilization of bone calcium. Second, CT scout images have a lower sensitivity than axial CT images for the detection of AC. However, whereas several previous studies adjudicated the presence and severity of AC from plain thoracic or lumbar radiographs^{7, 12, 34–36, 38, 48}, we used a

combination of CT scout images of the chest and CT slices of the upper and lower abdomen to generate a comprehensive severity score of AC. The risk associated with radiation exposure did not allow obtaining volumetric quantification of AC in our study participants. In addition, radiographic modalities used in most epidemiological studies, including ours, do not allow distinguishing between intimal and medial AC. Third, due to the low prevalence of participants using bisphosphonate medications (n=74, 56 women and 18 men) and women younger than 50 years of age (n=36, 10.3%), we were not able to performed specific subanalyses and test the effects of these class of drugs and menopause in our associations. However, results did not differ after performing sensitivity analysis excluding these 110 participants (see Supplemental Table S4). Finally, our aim of exploring the contribution of BMD to the association between BMI and AC led us to use whole-body BMD and not BMD derived from any particular part of the body. Nevertheless, analyses were also performed using femoral BMD in place of total BMD, and results did not substantially change.

In conclusion, our current findings indicate that low body size is associated with AC, possibly through the mediation of calcium released from the bone and precipitating in the arterial wall. Thus, our data provide a potential link between the so-called “calcification paradox” and “obesity paradox”^{1, 49}. Our findings also have important implications for body weight management in the elderly²⁷. Classical interpretation of obesity indexes may have limitations when applied to elderly individuals, in whom excess body weight may confer some protective effects on cardiovascular morbidity and mortality⁴⁹. Our findings extend this observation and suggest that the same hypothesis applies to AC. Avoidance of weight loss is of particular importance together with physical activity for preservation of bone health through life. Further prospective studies are encouraged in order to test whether such interventions may help preventing not only bone demineralization but also vascular calcification that happen with aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We studied determinants of aortic calcification in elderly participants of the Baltimore Longitudinal Study of Aging
- We confirmed an inverse relationship between bone mineral density and aortic calcification (calcification paradox)
- We also demonstrated an inverse relationship between body mass index and aortic calcification (obesity paradox)
- This relationship was partially explained by the reduction in bone mineral density in subjects with decreased body weight
- Decreased body weight determines a reduction in bone mineral density, which in turn may increase aortic calcification

Figure 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.

Figure 2. Nonlinear relationship between body mass index and aortic calcification

The graph shows that the probability of increased aortic calcification severity decreased in participants with overweight as compared to those with normal weight or obesity. Odds ratios (OR) and 95% confidence intervals are adjusted for age, gender, race, systolic blood pressure, antihypertensive medications, LDL cholesterol, lipid-lowering medications, glomerular filtration rate, diabetes and smoke.

Table 1

Characteristics of study population overall and by number of aortic segments with apparent calcification.

	Overall	Number of aortic segments with apparent calcification				P value
		0	1	2	3	
	n=687	n=207	n=214	n=191	n=75	
Age, years	67±13	57±11	65±10	74±9	80±8	<.0001
Male gender	49%	41%	51%	53%	53%	0.055
Race						0.02
White	66%	59%	63%	71%	80%	
African American	28%	35%	30%	24%	17%	
Others	6%	6%	7%	5%	3%	
Systolic blood pressure, mmHg	124±17	119±15	124±16	128±18	126±18	<.0001
LDL cholesterol, mg/dL	112±34	115±33	113±32	106±35	115±36	0.08
Body weight, kg	78±15	80±16	78±16	77±14	73±13	<.001
Height, cm	169±9	169±9	170±10	168±10	167±9	0.13
Body mass index, kg/m ²	27±5	28±5	26.9±4.7	27.1±4.3	25.9±3.7	0.002
Obesity (≥ 30 kg/m ²)	24%	28%	22%	26%	16%	0.17
Glomerular filtration rate, ml/min/1.73m ²	77±18	83±16	79±17	73±18	70±18	<.0001
Ever smoking	45%	32%	40%	59%	61%	<.0001
Diabetes mellitus	22%	18%	18%	27%	29%	0.03
Antihypertensive medications	42%	27%	42%	55%	52%	<.0001
Lipid-lowering drugs	42%	30%	44%	51%	48%	<.0001
Whole-body BMD, g/cm ²	1.19±0.12	1.22±0.11	1.19±0.11	1.18±0.12	1.13±0.11	<.0001
Femoral neck BMD, g/cm ²	0.92±0.15	0.97±0.14	0.92±0.14	0.90±0.14	0.84±0.13	<.0001
Physically active, 1000 kcal/week	58%	59%	58%	59%	52%	0.75
Vitamin D supplementation	61%	53%	61%	66%	68%	0.025
25-hydroxyvitamin D, mg/dL	33±11	31±12	33±12	34±11	34±10	0.04
Calcium levels, mg/dL	9.3±0.4	9.2±0.4	9.3±0.5	9.3±0.5	9.2±0.4	0.20
Bisphosphonate medications	11%	6%	11%	15%	13%	0.05

Table 2

Ordered logistic regression predicting severity of aortic calcification.

	Model 1			Model 2			Model 3					
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P			
BMI, kg/m ²	0.956	0.922	0.990	0.0129	0.967	0.932	1.003	0.0729	0.974	0.936	1.014	0.1952
BMD, 10 g/m ²					0.815	0.693	0.960	0.0142	0.767	0.641	0.918	0.0038
Age, year	1.117	1.099	1.136	<.0001	1.114	1.095	1.132	<.0001	1.121	1.101	1.141	<.0001
Male gender	1.061	0.779	1.445	0.7092	1.375	0.951	1.986	0.0903	1.591	1.065	2.377	0.0233
African American	0.877	0.617	1.245	0.4630	0.968	0.675	1.387	0.8582	1.012	0.682	1.501	0.9542
Systolic blood pressure, mmHg	1.012	1.003	1.022	0.0098	1.012	1.003	1.021	0.0126	1.010	1.000	1.020	0.0451
Antihypertensive drugs	1.209	0.871	1.678	0.2565	1.202	0.866	1.669	0.2714	1.153	0.812	1.635	0.4261
LDL cholesterol, mg/dL	1.003	0.999	1.008	0.1419	1.003	0.999	1.008	0.1861	1.003	0.998	1.008	0.2672
Lipid-lowering drugs	1.431	1.048	1.954	0.0243	1.438	1.052	1.965	0.0225	1.294	0.922	1.817	0.1367
Glomerular filtration rate, ml/min/1.73m ²	1.003	0.994	1.013	0.4688	1.003	0.994	1.013	0.4638	1.003	0.993	1.012	0.6081
Diabetes	1.265	0.875	1.828	0.2118	1.300	0.898	1.882	0.1641	1.261	0.853	1.864	0.2451
Ever smoking	1.758	1.302	2.373	0.0002	1.790	1.325	2.419	0.0002	1.851	1.344	2.549	0.0002
Physical activity									1.145	0.828	1.584	0.4115
Vitamin D supplements									0.930	0.660	1.310	0.6774
25-hydroxyvitamin D, mg/dL									0.999	0.984	1.015	0.8999
Bisphosphonate drugs									0.805	0.477	1.359	0.4167
Serum calcium, mg/dL									1.421	0.976	2.070	0.0669

OR=odds ratio; CI=confidence interval; BMI=body mass index; BMD=bone mineral density. Maximal variance inflation factor in model 1,2 and 3 was 1.41, 1.70 and 1.80, respectively. In model 1, p values for interactions with BMI: *age=0.60; *gender=0.08; *race=0.61. In model 3, p values for interactions with BMD: *age=0.07; *gender=0.32; *race=0.82.