Osteoporosis International (2019) 30:1807–1815
https://doi.org/10.1007/s00198-019-05031-5

ORIGINAL ARTICLE

Bone mass density and bone metabolism marker are associated with progression of carotid and cardiac calcified plaque in Chinese elderly population

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Received: 30 October 2018 / Accepted: 22 May 2019 / Published online: 10 June 2019

Abstract

Summary Osteoporosis and cardiovascular diseases often coexist in the same elderly individuals. Does this suggest some potential correlation between the two diseases? Low bone mass and change of bone biomarker are associated with a higher risk of carotid and cardiac calcification plaques.

Introduction Bone mineral density (BMD) and bone metabolism marker may contribute to the progression of carotid and cardiac arterial calcifications. The aim of this study was to investigate whether low bone mass and the change of bone biomarker are associated with the prevalence of calcified atherosclerotic plaque in elderly Chinese.

Methods We conducted a five-year prospective study. BMD was measured by dual-energy X-ray absorptiometry scanning. Carotid and cardiac computed tomography angiography (CTA) was conducted using a 64-multidetector row scanner to assess carotid and cardiac arterial plaque at baseline and during follow-up.

Results Of 1571 community residents over 60 years of age, 184 (11.7%) subjects developed carotid calcified plaque, 510 (32.5%) subjects developed cardiac calcified plaque and 97 (6.2%) subjects developed co-existence calcified plaques in carotid and cardiac arteries. After adjustment for age and all relevant confounders, Q1, Q2 quartile of BMD, and osteoprotegerin (OPG), osteocalcin (OC), and C-terminal cross-linked telopeptide of type I collagen (CTX) were associated with increased risk of calcified plaques.

Conclusion This study suggested that lower BMD and change of bone metabolism biomarker were associated with a higher risk of carotid and cardiac calcified plaque development.

Keywords Bone metabolism marker · Bone mineral density · Calcified plaque · Cardiac artery · Carotid artery

Introduction

Osteoporosis and cardiovascular diseases are two common diseases that often coexist in the same elderly individuals, indicating that there may be some potential association between the pathogenesis of the two diseases.

As a systemic skeletal disease, osteoporosis is mainly characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. In prospective settings, low BMD was associated with relative risk of future cardiovascular events and related mortality [2, 3]. Vascular calcification has been proved to be an important pathological basis for cardiovascular diseases, its severity and extent reflect atherosclerotic plaque burden and independently predict the morbidity and mortality of cardiovascular diseases [4]. Furthermore, recent studies have shown that BMD reduction is associated with cardiovascular events, mainly due to vascular atherosclerosis, especially vascular calcification. There are many shared characteristics of the pathological process of vascular calcification and bone

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formation [5]. However, there are only a few reports on the association between lower BMD and coronary artery calcification. It is rare to study the relationship between lower BMD and carotid calcification.

In addition to reflecting the condition of bone metabolism and mineralization, recent clinical researches have confirmed that the biomarker of bone metabolism may also be associated with the progression of vascular calcification. Recently, prospective studies showed that osteoprotegerin (OPG) was an independent risk factor for the progression of carotid arteries calcification and incident cerebrovascular accidence and acute myocardial infarction [6, 7]. Clinical studies reported that osteocalcin (OC) was involved in atherosclerosis, and inversely related to carotid intima-media thickness [8], and the presence and severity of coronary artery disease [9]. C-terminal cross-linked telopeptide of type I collagen (CTX) is an important bone turnover marker. CTX was reported to be associated with carotid intima-media thickness [10]. Higher N-terminal propeptide of type I procollagen (PINP) levels predicted an increased risk of myocardial infarction [11]. However, it remains unclear the role of bone metabolism biomarkers in the association between the decrease of BMD and vascular calcification. The purpose of this study was to investigate whether low bone mass and change of bone biomarker were associated with the calcified atherosclerotic plaque.

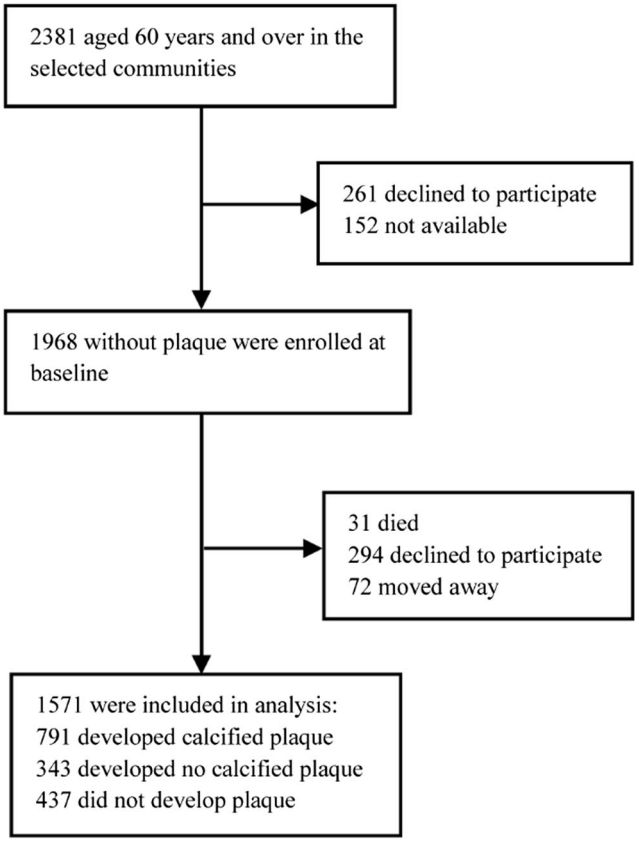

Fig. 1 Flowchart of an analysis of the selected sample

Materials and methods

Participants

The present study was performed from January 2010 through December 2010. Data were collected from 2381 subjects aged 60 and above who were enrolled as participants in our study and were examined by carotid and cardiac CTA. The common reasons used to perform CTA were (1) TIA or stroke; (2) coronary artery disease; (3) hypertension, diabetes mellitus, and hyperlipidemia; (4) following dizziness, syncope, vertigo, and peripheral artery disease. Four hundred thirteen subjects were excluded from the present study (152 were not available at the time of the screening because carotid or cardiac plaques were detected and 261 declined to participate). A total of 1968 without plaque were enrolled at baseline (Fig. 1). This study was approved by the institutional review board of Daping Hospital and all subjects provided informed consent.

Data collection

The following data were collected by formal questionnaire and neurologists. Procedures were administered by trained interviewers consisting of experienced neurologists and senior nurses.

Dual-energy X-ray absorptiometry (DEXA; QDR 4500 Elite Bone Densitometer; Hologic, Bedford, MA, USA) used to determine BMD. Lumbar spine (L1-L4) BMD was used as a measurement of global bone health. BMD was measured at baseline and 5 years after enrollment. Annual percent change (100 [BMD 1−BMD 2]/BMD 1 × length of follow-up in years) and absolute annual change in BMD during the 5-year follow-up period were calculated. BMD and percent change of BMD were categorized into quartiles. BMD: Q1: < 0.753, Q2: 0.754–0.883, Q3: 0.884–1.012, Q4: > 1.013.

The subjects' medical history was collected from medical records. Data included stroke, cardiac heart diseases, peripheral artery disease, malignant disease, febrile conditions, chronic obstructive pulmonary disease, chronic hepatitis, chronic renal insufficiency, hypertension, diabetes mellitus, and hyperlipidemia.

Blood pressure measurements and electrocardiography were performed on site. Fasting blood samples were collected to measure glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride, OPG, OC, CTX, PINP, BALP, DPD, and 25(OH) D. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The subjects with abnormalities implying potential diseases that were not previously diagnosed were introduced to Daping Hospital in Chongqing for further investigation.

Diagnosis of diseases including hypertension, diabetes mellitus, hyperlipidemia, stroke, cardiac heart diseases, atrial fibrillation, chronic renal insufficiency, and chronic hepatitis was based on codes from the International Classification of Diseases, Ninth Revision.

Calcified atherosclerotic plaque

The carotid CTA was conducted using a 64-multidetector row scanner (GE Healthcare, Milwaukee, WI). Collimation was 64 mm × 1.25 mm with tube rotation time of 500 ms. For carotid CTA, the contrast was injected at 5 ml/h for 4 s then 3 ml/s for 7 s, followed by saline injection at the rate 5 ml/s for 10 s. Total of 40 ml of contrast was used [12].

The cardiac CTA was conducted using a 64-multidetector row scanner (GE Healthcare, Milwaukee, WI). Collimation was 64 mm × 0.625 mm with tube rotation time of 350 ms. The tube current was 300–400 mA at 100–120 kV for subjects based on their body size. If individuals with baseline heart rates of > 65 beats/min, Metoprolol was used at 5 mg increments to a total possible dose of 25 mg to achieve a resting heart rate of < 65 beats/min.

CTA images were interpreted by experienced readers. All CTA images were evaluated on 3D image analysis workstation (GE Advantage Workstation, GE Healthcare, Milwaukee, WI). The CTA reader utilized any or all of available post-processing image reconstruction algorithms, including two-dimensional axial, or three-dimensional maximal intensity projection, multiplanar reformat, cross-sectional analysis, or volume rendered technique.

Plaque composition was measured. The plaque in each vascular segment was classified as non-calcified and calcified. Calcified plaque was plaque with a higher density. The presence of non-calcified plaque tissue was defined as any discernable structure in the artery wall with a CT density less than the contrast-enhanced artery lumen but greater than the surrounding connective tissue [13].

The model was used to assess carotid and cardiac arteries. Carotid arteries model was done based on a 6-segment model taking both right and left: common carotid and internal and external carotid arteries. A simplified 7 segment cardiac artery model was used which included the left main, left anterior descending artery, circumflex cardiac artery, right cardiac artery, and the three largest branches: diagonal, obtuse marginal, and posterior descending artery. The calcified plaques in both carotid and cardiac arteries were defined as co-existence arterial calcified plaques.

Follow-up

Subjects with carotid and coronary artery plaques were examined at baseline and during third and fifth year of follow-up.

Statistical analyses

We compared the characteristics of the subjects between non-calcified plaque and each calcified plaque group. We performed ANOVA test for independent normally distributed continuous data, chi-square test for categorical data, and Kruskal-Wallis test for ordinal and categorical variables that were not normally distributed. Cox proportional hazards models were used to assess associations between BMD or bone loss rate and risk of arterial plaque development with adjustment for potential confounders. Statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL).

Results

A total of 1968 subjects were followed-up. After 5 years, 31 (1.6%) died, 294 (14.9%) withdrew participation, and 72 (3.7%) moved away during the follow-up; thus, 1571 (79.8%) subjects completed the study (Fig. 1). Of the 1571 subjects in the study, 437 (27.8%) had no atherosclerotic plaque; 1134 (72.2%) had atherosclerotic plaque. Among 1134 subjects, 791 (69.8%) had calcified plaque, and 343 (30.2%) had no calcified plaque. Of the 791 subjects with calcified plaque, 184 (23.3%) developed carotid plaque, 510 (64.5%) developed cardiac plaque, and 97 (12.2%) developed co-existence calcified plaques in carotid and cardiac arteries. For 1571 subjects who completed the follow-up, 258 (16.4%) were in the Q1 quartile of BMD, 305 (19.4%) were in the Q2 quartile, 391 (24.9%) were in the Q3 quartile, and 617 (39.3%) were in the Q4 quartile, the average BMD was 0.89 ± 0.07. Among 791 subjects with calcified plaque, 206 (26.0%) subjects were in the Q1 quartile of BMD, 254 (32.1%) subjects were in the Q2 quartile, 181 (22.9%) subjects were in the Q3 quartile, and 150 (19.0%) subjects were in the Q4 quartile.

Clinical and biochemical characteristics of all subjects are presented in Table 1. Compared to the subjects without plaque, the subjects with calcified plaques had lower BMD, and more OPG, OC, CTX, hypertension, diabetes mellitus, and hyperlipidemia. There was no difference in serum level of creatinine, calcium, phosphate, 25(OH) D, PINP, BALP, total DPD, and free DPD in subjects with developing calcified plaque than the subjects without plaque.

All subjects were divided into four age groups. Prevalence rates of calcified plaque were 34.3% (148/431) for the subjects aged 60–65 years, 44.9% (184/410) for the subjects aged 66–70 years, 53.2% (206/387) for the subjects aged 71–75 years, and 73.8% (253/343) for the subjects aged > 75 years respectively. The prevalence of calcified plaque was found to increase with increasing age. In each age group, the subjects were further divided into three groups according to the type

Table 1 Baseline characteristics in subjects who did and did not develop calcified plaque

	Without plaque ($n = 437$)	Without calcified plaque ($n = 343$)	With calcified plaque ($n = 791$)
Age (y), ± SD	63.9 ± 10.2	65.1 ± 9.4	68.6 ± 9.7**
Female, *n* (%)	224 (51.3)	170 (49.6)	386 (48.8)
BMI (kg/m^2), mean ± SD	21.8 ± 3.4	22.7 ± 3.1	23.2 ± 2.6
BMD (g/cm^3), mean ± SD	0.94 ± 0.06	0.91 ± 0.07	0.78 ± 0.05**
Creatinine (μmol/L), mean ± SD	65.3 ± 11.8	65.4 ± 10.6	65.7 ± 10.6
Calcium (mmol/L), mean ± SD	2.23 ± 0.09	2.25 ± 0.15	2.26 ± 0.12
Phosphate (mmol/L), mean ± SD	1.16 ± 0.21	1.18 ± 0.13	1.19 ± 0.15
25(OH)D (ng/L), mean ± SD	14.2 ± 6.5	13.7 ± 5.8	13.4 ± 6.1
Vascular risk factors			
Current smoking, *n* (%)	56 (12.8)	54 (15.6)*	137 (17.3)*
Current drinking, *n* (%)	34 (7.7)	29 (8.4)	76 (9.6)
Hypertension, *n* (%)	141 (32.3)	121 (35.5)*	299 (37.8)*
Diabetes mellitus, *n* (%)	80 (18.4)	85 (21.8)*	211 (23.7)*
Hyperlipidemia, *n* (%)	127 (29.1)	107 (31.2)*	256 (32.4)*
Previous myocardial infarction, *n* (%)	18 (4.2)	19 (5.6)	62 (7.9)*
Previous stroke, *n* (%)	9 (2.1)	13 (3.8)	42 (5.3)*
Bone biomarkers			
OPG (pmol/l), mean ± SD	6.24 ± 0.35	7.37 ± 0.28	9.86 ± 0.23**
OC (μg/ml), mean ± SD	17.2 ± 12.6	18.3 ± 11.8	20.8 ± 13.1*
CTX (μg/L)	0.34 ± 0.19	0.35 ± 0.16	0.37 ± 0.18*
PINP (ng/mL)	36.4 ± 15.3	37.8 ± 15.1	38.5 ± 16.4
BALP (U/L, ± SD)	16.5 ± 7.4	17.6 ± 8.3	18.1 ± 7.9
Total DPD (nmol/mmol creat)	6.45 ± 2.31	7.17 ± 2.06	7.48 ± 2.15
Free DPD (nmol/mmol creat)	3.16 ± 1.03	3.42 ± 1.35	3.69 ± 1.17

BMI body mass index, *BMD* bone mineral density, *OPG* osteoprotegerin, *OC* osteocalcin, *CTX* type I collagen cross-linked C-telopeptide, *PINP* N-terminal propeptide of type I collagen, *BALP* bone alkaline phosphatase, DPD deoxypyridinoline

P value for comparison between subjects with plaque (calcified or without calcified) and subjects without plaque

*$p < 0.05$

**$p < 0.01$ vs. without plaque

of plaque (carotid calcified plaque, cardiac calcified plaque, co-existence calcified plaques). Figure 2 shows the prevalence of calcified plaque of three types in four age groups. As the age increased, the proportion of co-existence calcified plaques increased and the proportion of carotid increased ($P < 0.05$).

We established Cox proportional hazards models to obtain insights into the independent predictors of plaques risk and the results are shown in Table 2. Low BMD was inversely associated with the risk of calcified plaque in unadjusted analyses. A fully adjusted model accounting for age and other potential confounders showed significant inverse associations between BMD and calcified plaque. Additionally, serum OPG, OC, and CTX level were associated with increased risk of calcified plaque. Hypertension, diabetes mellitus, and hyperlipidemia were also associated with increased risk of calcified plaque.

The association between bone metabolism biomarker and the calcified plaques in different BMD stratification are shown in Table 3. In the Q1 quartile, serum levels of Ca, 25(OH) D, OPG, OC, CTX, PINP, and BALP were significantly associated with the risk of calcified plaque. In the Q2 quartile, serum levels of 25(OH) D, OPG, OC, and CTX were significantly associated with the risk of calcified plaques. In the Q3 quartile, serum levels of OPG and OC significantly increased the risk of calcific plaques. In addition, only serum levels of OPG was significantly associated with the calcified plaque in the Q4 quartile.

Table 4 summarizes the association between BMD and prevalence of calcified plaques in different vascular beds. Low BMD was associated with increased risk of carotid and cardiac calcified plaques in unadjusted and fully adjusted for age and all relevant confounders, severe bone loss increased the risk of calcified plaques in the carotid and coronary arteries by 2.68 and 3.01 times, respectively. A significant inverse correlation was indicated. Furthermore, low BMD was more highly associated with co-existence calcified plaques than carotid or cardiac calcified plaque in unadjusted and adjusted for age and other confounders.

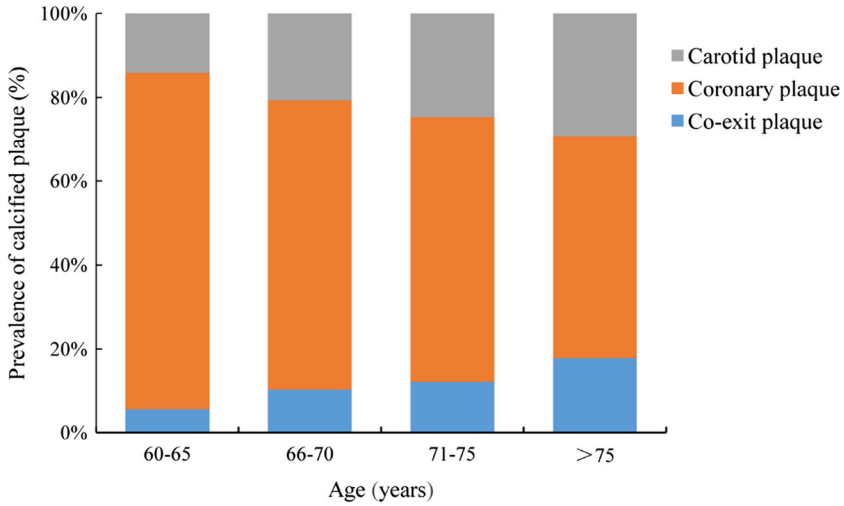

Fig. 2 The prevalence of calcified plaque increased with age in carotid calcified plaque group ($n = 184$), cardiac calcified plaque group ($n = 510$), and co-existence calcified plaques group ($n = 97$). The prevalence of arterial calcified plaques was divided into four groups according to age. With the increase of age, the proportion of co-existence calcified plaques increased and the proportion of carotid increased ($P < 0.05$)

The association between BMD and the risk of calcified plaque in women and men are presented in Table 5. Compared with BMD in the highest quartile (Q4), women with BMD values in the lowest quartile (Q1) had a HR of 3.26 (95% CI 2.21–5.03). The association remained statistically significant after adjustment with age, smoking, vascular risk factors, OPG, OC, and CTX (HR 3.21, 95% CI 2.15–5.02). Similarly, men with BMD values in the lowest quartile (Q1) had an unadjusted HR of 3.04 (95% CI 1.46–4.15) and adjusted HR of 3.01 (95% CI 1.42–3.98) relative to men with BMD values in the highest quartile (Q4). These results suggest that the lower BMD is associated with increased risk of calcified plaque in both women and men.

Discussion

Previous studies have mainly reported the relationship between lower BMD and the prevalence of cardiac calcified plaque [14, 15]. In this study, the result suggested for the first time that lower BMD was inversely associated with carotid and cardiac calcified plaques. In particular, the study showed that co-existence calcified plaques were more strongly related to BMD than carotid or cardiac calcified plaque. Meanwhile, this was the first prospective study to report the correlation between bone metabolism biomarkers and the risk of developing calcified atherosclerotic plaque.

In previous studies, BMD has been shown to be related to the prevalence of atherosclerotic calcified plaque, but the

Table 2 Association between BMD and calcified plaque in Cox proportional hazards models

	Hazard ratio for plaques unadjusted	Hazard ratio for plaques adjusted *
BMD		
Q1	3.22 (1.69–5.35)	3.18 (1.62–5.14)
Q2	2.24 (1.36–3.78)	2.15 (1.15–3.74)
Q3	1.43 (0.87–3.39)	1.37 (0.85–3.31)
Q4	1	1
Current smoking	1.36 (1.05–2.19)	1.34 (1.03–2.02)
Hypertension	1.78 (1.42–2.71)	1.75 (1.33–2.63)
Diabetes mellitus	1.39 (1.18–2.26)	1.37 (1.12–2.18)
Hyperlipidemia	1.45 (1.23–1.81)	1.42 (1.16–1.75)
OPG	2.12 (1.49–3.94)	2.06 (1.35–3.71)
OC	1.78 (1.36–2.82)	1.74 (1.31–2.67)
CTX	1.57 (1.24–2.45)	1.53 (1.17–2.34)

BMD: Q1: < 0.753, Q2: 0.754–0.883, Q3: 0.884–1.012, Q4: > 1.013

BMD bone mineral density, *OPG* osteoprotegerin, *OC* osteocalcin, *CTX* type I collagen cross-linked C-telopeptide

*Adjusted for age, gender, current smoking, hypertension, diabetes mellitus and hyperlipidemia, previous myocardial infarction, previous stroke, OPG, OC, and CTX

Table 3 Association between bone metabolism biomarkers and calcified plaques in different BMDs

Biochemical markers	Q1 Adjusted HR for calcified plaques (95% CI)	*P*	Q2 Adjusted HR for calcified plaques (95% CI)	*P*	Q3 Adjusted HR for calcified plaques (95% CI)	*P*	Q4 Adjusted HR for calcified plaques (95% CI)	*P*
Calcium (mmol/L)	1.45 (1.21–1.76)	< 0.05	1.23 (0.85–1.42)	> 0.05	1.19 (0.87–1.38)	> 0.05	1.17 (0.95–1.35)	> 0.05
Phosphate (mmol/L)	1.12 (0.77–1.34)	> 0.05	1.09 (0.71–1.25)	> 0.05	1.04 (0.69–1.21)	> 0.05	1.02 (0.74–1.17)	> 0.05
25(OH)D (ng/L)	1.59 (1.27–1.78)	< 0.01	1.32 (1.13–1.66)	< 0.05	1.16 (0.75–1.32)	> 0.05	1.14 (0.83–1.26)	> 0.05
OPG (pmol/l)	2.31 (1.64–2.75)	< 0.01	1.78 (1.35–2.04)	< 0.01	1.57 (1.33–1.86)	< 0.01	1.32 (1.24–1.73)	< 0.05
OC (μg/ml)	2.07 (1.49–2.51)	< 0.01	1.59 (1.27–1.88)	< 0.01	1.35 (1.29–1.69)	< 0.05	1.12 (0.86–1.27)	> 0.05
CTX (μg/L)	1.71 (1.35–1.96)	< 0.01	1.37 (1.33–1.74)	< 0.05	1.23 (0.88–1.35)	> 0.05	1.19 (0.92–1.31)	> 0.05
PINP (ng/mL)	1.36 (1.27–1.68)	< 0.05	1.13 (0.72–1.36)	> 0.05	1.07 (0.74–1.30)	> 0.05	1.04 (0.77–1.28)	> 0.05
BALP (U/L)	1.39 (1.32–1.70)	< 0.05	1.16 (0.76–1.32)	> 0.05	1.09 (0.83–1.27)	> 0.05	1.06 (0.81–1.21)	> 0.05
Total DPD (nmol/mmol creat)	1.12 (0.76–1.31)	> 0.05	1.08 (0.84–1.29)	> 0.05	1.05 (0.81–1.22)	> 0.05	1.03 (0.79–1.16)	> 0.05
Free DPD (nmol/mmol creat)	1.16 (0.94–1.33)	> 0.05	1.12 (0.87–1.30)	> 0.05	1.08 (0.83–1.25)	> 0.05	1.05 (0.80–1.22)	> 0.05

BMD: Q1: < 0.753, Q2: 0.754–0.883, Q3: 0.884–1.012, Q4: > 1.013

HR hazard ratio, *BMD* bone mineral density, *OPG* osteoprotegerin, *OC* osteocalcin, *CTX* type I collagen cross-linked C-telopeptide, *PINP* N-terminal propeptide of type I collagen, *BALP* bone alkaline phosphatase, *DPD* deoxypyridinoline

*Adjusted for age, gender, current smoking, hypertension, diabetes mellitus and hyperlipidemia, previous myocardial infarction, previous stroke, OPG, OC, CTX, PINP, BALP, total DPD, and free DPD

subjects in these reports were type 2 diabetic patients and were examined by cross-sectional methods. The purpose of the present study was to determine the relationships between BMD and calcified atherosclerotic plaques, including calcified plaque in the coronary arteries, carotid bifurcation, and abdominal aorta that were measured using computed tomography in 1023 subjects [14]. Significant inverse relationships between calcified plaque and BMD were observed in European American men and African American women after adjusting for age and other covariates. Another report examined relationships between BMD and calcified atherosclerotic plaque in 753 African-Americans [15]. The analyses were performed to assess cross-sectional relationships between vertebral BMD and calcified plaque in the coronary and carotid arteries and aorta. Significant inverse associations were seen between BMD and calcified plaque in all three vascular beds in African-American men and women. In this study, we also found that subjects with calcified plaque had lower BMD compared with those without plaque in the univariate analysis ($p < 0.01$).

Few studies have confirmed that BMD is negatively correlated with the prevalence of carotid calcified plaque. In a 1994–1995 cross-sectional, population-based study of 2543 men and 2726 postmenopausal women aged 55–74 years in Norway, the authors assessed a possible relation between BMD and the prevalence of carotid artery plaques, the study indicated that low bone mass was associated with an increased risk of echogenic calcified atherosclerotic plaques but not with a risk of echolucent plaques [16]. In 2006, the association of low bone mass with atherosclerosis was examined. The study

Table 4 Association between BMD and risk of developing calcified plaque in three groups

	Carotid calcified plaque		Coronary calcified plaque		Co-existence calcified plaques	
BMD quartile	Hazard ratio unadjusted	Hazard ratio adjusted*	Hazard ratio unadjusted	Hazard ratio adjusted*	Hazard ratio unadjusted	Hazard ratio adjusted*
Q1	2.74 (1.54–4.13)	2.68 (1.52–3.98)	3.05 (1.89–4.37)	3.01 (1.73–4.25)	3.37 (2.27–5.13)	3.34 (2.12–5.06)
Q2	2.19 (1.67–3.21)	2.11 (1.61–3.04)	2.25 (1.72–3.55)	2.17 (1.64–3.56)	2.46 (1.89–3.64)	2.31 (1.87–3.57)
Q3	1.25 (0.53–2.64)	1.23 (0.62–2.58)	1.37 (0.69–2.74)	1.32 (0.72–2.69)	1.55 (0.77–3.25)	1.48 (0.82–3.13)
Q4	1	1	1	1	1	1

BMD: Q1: < 0.753, Q2: 0.754–0.883, Q3: 0.884–1.012, Q4: > 1.013

BMD bone mineral density

*Adjusted for age, gender, current smoking, hypertension, diabetes mellitus and hyperlipidemia, previous myocardial infarction, previous stroke, OPG, OC, and CTX

Table 5 Association between BMD and the risk of developing calcified plaque in women and men

BMD quartile	Women Hazard ratio unadjusted	Hazard ratio adjusted*	Men Hazard ratio unadjusted	Hazard ratio adjusted*
Q1	3.26 (2.21–5.03)	3.21 (2.15–5.02)	3.04 (1.46–4.15)	3.01 (1.42–3.98)
Q2	2.19 (1.53–3.38)	2.16 (1.47–3.35)	1.97 (1.39–3.18)	1.93 (1.35–3.17)
Q3	1.54 (0.82–3.16)	1.48 (0.79–3.12)	1.17 (0.76–2.63)	1.13 (0.72–2.59)
Q4	1	1	1	1

BMD bone mineral density. BMD: Q1: < 0.753, Q2: 0.754–0.883, Q3: 0.884–1.012, Q4: > 1.013

*Adjusted with age, current smoking, hypertension, diabetes mellitus and hyperlipidemia, previous myocardial infarction, previous stroke, OPG, OC, and CTX

conducted a 10-year follow-up survey and analyzed 609 women ≥ 50 years old in Japanese postmenopausal women [17]. The results found low bone mass might be associated with carotid atherosclerosis in the first 10 years of postmenopausal women.

Between 2002 and 2005, 936 individuals (mean age of 64 years) were assessed for spine BMD and coronary artery calcification [18]. The inverse association of BMD with coronary artery calcification was stronger in women without dyslipidemia. In contrast, no consistent association was observed between BMD and coronary artery calcification in men. In 2011, 661 subjects with at least one cardiac risk factor but without known coronary heart disease were included in the study [19]. The study demonstrated that the association between low BMD and the presence of subclinical coronary calcification among middle-aged participants was not significant after controlling for age and other risk factors for coronary heart disease and osteoporosis. However, these results suggested that Q1 and Q2 quartile of BMD were significantly associated with calcified plaques of the carotid and cardiac arteries. The inconsistencies in clinical findings may be due to differences in population and methods, as well as in the selection of anatomical locations to assess BMD and arterial calcification. The different populations and methods may partially explain some of the conflicting findings in the literature.

In this study, serum OPG, OC, and CTX levels were found to be independently associated with increased risk of atherosclerotic calcified plaque. OPG may play a role in the relationship between osteoporosis and vascular calcification. The epidemiological data in subjects with cardiovascular diseases (CVD) indicated that OPG was associated with increased risk of CVD [20, 21]. More recently, other studies in vitro, as well as in vivo, indicated that OPG was a major regulator of bone remodeling by blocking receptor activator NF-κB ligand (RANKL), resulting in the inhibition of osteoclast formation [22]. The serum OPG level was a stable marker for vascular calcification and the progression of atherosclerosis [23]. Indeed, the experimental data in animal models strongly suggested that OPG was sufficient to reduce lesion size and inhibits calcium deposition [24]. The increase of OPG level may be an adaptive response to inhibit the harmful effects of RANKL and TNF-related apoptotic inducing ligand (TRAIL). In this study, we also demonstrated that higher level of serum OPG was associated with calcified plaque in different quartiles of BMD. Previous studies have indicated that OC is one of the most abundant non-collagenous proteins in the mineralized matrix of bone, expanding the endocrine function of the skeleton with far-reaching extra-osseous effects [25]. The serum OC level was negatively correlated with fasting blood glucose level, fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR) index, and obesity [26], and positively correlated with serum adiponectin level and insulin secretion [27]. However, contradictory results have also been reported. For example, a decrease in circulating OC caused by anti-bone resorption agents had no effect on glucose metabolism in postmenopausal women, suggesting a more limited role of OC in glucose and energy metabolism in humans [28]. Moreover, Ling et al. also reported that OC had no significant effect on CAD and coronary atherosclerosis [29]. In this study, there was a significant positive association between OC and calcified plaque in vascular beds. The potential reasons for discrepancies may include the method of OC measurement and variability in population characteristics and ethnicity, gender, and method of measuring calcification or atherosclerosis. Large-scale longitudinal studies are needed to further understand the clinical relevance of OC in vascular calcification and atherosclerosis. As a degradation marker of type I collagen, CTX was shown in areas of intimal hyperplasia and in advanced plaque [30]. However, CTX was only associated with coronary and co-existence calcified plaque in this study.

Vitamin D is a secosteroid hormone, synthesized mainly in the skin upon ultraviolet-B (UVB) radiation [31]. Its storage form is 25-hydroxyvitamin-D (25(OH) D) which has an approximate half-life of 2 to 3 weeks [32]. The assessment of the vitamin D status is therefore based on the measurement of 25(OH) D [31]. Currently, the effect of 25 (OH) D on atherosclerosis or calcified plaque remains much debated. In a population-based study of healthy middle-aged men, vitamin D deficiency (defined as 25(OH) D < 20 ng/mL) had a

significant positive association with the presence of coronary artery calcification [33]. However, Kamycheva et al. established that increased serum 25(OH) D level might predict subclinical atherosclerosis in nonsmokers [34]. In this study, no important association between serum 25(OH) D level and calcified plaques were found in vascular beds, the findings are consistent with other recent reports [29, 35]. In the subgroup analysis, the positive association between 25(OH) D and calcified plaques were only based on the severe loss of bone mass. The results implied that low BMD might be a confounding factor in the association of 25(OH) D with calcified plaques.

Although the relationship between low bone mass and aortic valve calcification has not been explored in this study, some studies have shown that low bone mass and age are related not only to the coronary artery and carotid artery calcification but also to aortic valve calcification. Aksoy Y et al. found that BMD was negatively correlated with aortic valve calcification in the elderly [36]. The researchers evaluated BMD in 49 patients with aortic valve calcification and 65 patients without aortic valve calcification and found that BMD in the patients with aortic valve calcification was significantly lower than that in patients without aortic valve calcification. Another study found that there was a close relationship between bone turnover and aortic valve calcification [37]. Aortic valve calcification was mediated by many processes that promote bone formation. A cross-sectional study of 1068 elderly people aged ≥ 65 from Spain showed that the prevalence of calcific aortic valve disease (CVAD) was about 3% [38]. Further analysis of elderly people aged ≥ 85 showed that the prevalence of CVAD was 7.4%. The result showed that CVAD was closely related to age.

This study has some limitations. Firstly, this study only discussed the relationship between bone mass loss and carotid artery and coronary artery calcification plaque, but no relationship between osteoporotic fracture and atherosclerotic plaque. Osteoporotic fracture is the most serious complication of low BMD. The study of the relationship between the fracture and atherosclerotic plaque may be more helpful to reveal the effect of low BMD in the formation of atherosclerotic plaque. Secondly, the present study did not evaluate the relationship between BMD reduction and myocardial infarction, stroke, and mortality. The calcified plaques of the coronary artery and carotid artery are the pathological basis of myocardial infarction and stroke in the elderly population. It is of great importance to prevent the occurrence of myocardial infarction and stroke by studying the relationship between low BMD and the adverse events of calcified plaques such as myocardial infarction and stroke. Thirdly, the present study only investigated the association of bone metabolism markers with the progression of calcified plaques, the effect of changes in bone markers on calcified plaques has not been assessed. Due to the lack of assessment of changes in bone markers, our results may exist biased. Finally, this study did not carry out the research of the related pathogenesis. The data of animal experiments are necessary to elucidate the mechanism of bone mass loss and bone markers on the progression of calcified plaques.

In conclusion, this finding showed that the subjects with low bone mass had more advanced calcified atherosclerotic plaque than those with a normal bone mass. Thus, the elderly population with low bone mass would be considered to be a targeted population to prevent cardiovascular events. Further study is needed to explore the mechanism linking bone mass and calcified atherosclerotic plaque.

Funding This study was supported by grants from the National Natural Science Foundation of China (8160090461) and the Excellent Youth Fund of Third Military Medical University (2017YQRC-04).

Compliance with ethical standards

Conflict of interest None.

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