Associations between bone mineral density and coronary artery calcification: a systematic review and meta-analysis

Peiyu Zhang*, Liu Yang*, Qingwen Xu, Yidi Zeng, Yipin Yu, Qinghua Peng and Hao Liang

Abstract

Background: The studies about the correlation between bone mineral density (BMD) and coronary arterial calcification (CAC) were still controversial. The aim of this study was to conduct a meta-analysis to evaluate the association between BMD and CAC.

Methods: We systematically searched PubMed, Embase, Google scholar and Cochrane library for observational studies. We pooled odds ratio (OR) or correlation coefficient, and 95% confidence interval (CI) of the studies. Continuous data were pooled by mean difference (MD). Sub-group analysis was applied to investigate sources of heterogeneity. Funnel plots for publication bias was also performed.

Results: Seventeen studies met the inclusion criteria. Pooled ORs for the prevalence of CAC in patients with low BMD versus patients with normal BMD was 2.11 (95% CI: 1.11 - 4.02, p=0.000). The pooled ORs for comparing CAC score of low BMD and normal BMD patients is 33.77 (95% CI: 23.77 - 43.77, p=0.02). The data pooled for comparing CAC score of low BMD and normal BMD patients is 33.77 (95% CI: 23.77 - 43.77, p=0.000). The pooled ORs of multivariate logistic regression to predict the association were 1.00 (95% CI: 0.92 - 1.10, p=0.95, age-adjusted), and 0.95 (95% CI: 0.86 - 1.05, p=0.33, multivariable-adjusted). Cohort category and BMD assessment method were the main sources of heterogeneity.

Conclusions: Low BMD is associated with higher prevalence and severity of CAC, especially in postmenopausal women. But the relation is not significant after adjusting age and other confounding variables. Low BMD and CAC may be two independent processes with aging. More large-scale studies with high-quality design are still needed to increase the understanding of them.

Keywords: bone mineral density, coronary artery calcification, meta-analysis

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between -1 and -2.5 SD, and osteoporosis as T-score less than -2.5 SD.4

The mechanism of low BMD and artery calcification share similar pathways. It has been shown that arterial calcification is an active process involving protein molecules. Leopold5 have found that microRNAs (miRs) is a key factor in vascular calcification, it affects vascular calcification mainly by regulating gene recombination of smooth muscle cells, and another study reported the receptor activator of nuclear factor-kappaB ligand/osteoprotegrin pathway may be a link between osteoporosis and CAC.6 Moreover, atheroma plaque calcification involves cytokines and growth factors including proinflammatory cytokines (IL-6 and TNF-α), osteoprotegerin, sclerostin, matrix GLA protein, and FGF-23, which also play a role in bone turnover.7

Epidemiology study showed that the incidence of CAC is age-dependent and gender-dependent with CAC occurring in more than 90% of men and 67% of women over the age of 70.8,9 However, it’s still conflicting on whether CAC and BMD are related or not. The Copenhagen General Population Study reported that BMD and CAC were inversely related in both men and postmenopausal women, supporting the hypothesis that a direct relation between bone loss and development of atherosclerosis exists irrespective of gender.10 Xu et al.11 investigated the association between BMD and CAC in postmenopausal women, suggesting that women with low BMD were at a high risk for CAC. However, the Chinese study showed that there was no direct relationship between osteoporosis and CAC in elderly men after adjusting for age and other factors.12

Though previous studies have explored the correlation between BMD and CAC, the results were inconsistent, and some of the studies did not exclude age and gender confounders. Thus, it is still unknown whether they are independently related or not. The aim of the study was to perform a meta-analysis to investigate the pooled results of associations between BMD and CAC and whether the correlation is different adjusted by sex, age, or bone region.

Methods
We performed a systematic review and meta-analysis of the existing literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.13 This study was a part of the work registered in PROSPERO (No. CRD42019124663). All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

Search strategy
We searched the following electronic databases for English literature (up to December 31 of 2020): PubMed, Embase, Google scholar and Cochrane library. The fewer key-words or corresponding Medical Subject Headings (MeSH) were used for searching to avoid article omission headings ((bone (Title/Abstract) AND density (Title/Abstract). Our literature search process is shown in Figure 1. We retained 51 articles after reading the titles and abstracts of 846 literatures. By reading the full text, we excluded 34 studies for the reasons: data unavailable; the content is not relevant (the association between BMD and other vascular calcification; intervention research). Finally, seventeen articles were included in the quality assessment and meta-analysis.

Selection criteria
Inclusion criteria were the following:

- observational studies concerning association between BMD and CAC;
- CAC score was calculated according to the Agaston method based on CT scanning of coronary arteries;
- BMD was measured by DXA or quantitative computed tomography (QCT), and the definition of osteopenia and osteoporosis was based on the WHO criteria: T-score based on the WHO criteria: the participants were regarded as normal (T-score > -1 SD), osteopenic (-2.5 SD < T < -1 SD), and osteoporotic (T-score < -2.5 SD).

Exclusion criteria were the following:

- animal studies, reviews, letters, abstracts, or case reports;
- studies on CAC patients afflicted with other diseases, such as diabetes and kidney disease;
studies that provide insufficient data on BMD values (no descriptions of bone location, measurement method or device);
• duplicate reports.

Data extraction and quality assessment
The data were extracted by three reviewers independently and recorded in Excel file, and we discussed and resolved the inconsistencies. The first author’s name, year of publication, country, gender and age of participants, sample size, BMD value and location, number of people with low BMD (osteopenia and osteoporosis) and coronary artery calcification score (CAC score) were extracted from each study. We used a six-item table tailored from Newcastle Ottawa Scale (NOS)\textsuperscript{14} for quality assessment. The quality assessment graphs are generated by Review Manager (RevMan, version 5.3. Copenhagen: the Nordic Cochrane Center, the Cochrane Collaboration, 2014).

Publication bias
Funnel plots for publication bias were performed, when the meta-analysis contained more than 5 studies. Publication bias is confirmed if the plot is asymmetrical.

Statistical analysis
We used RevMan to pool the categorical data of odds ratio (OR) with 95\% confidence interval.
(CI) and continuous data by mean difference (MD). We used GetData Graph Digitizer Version 2.26 to extract the data from the studies with only graph displaying results. We combined the sample’s mean and standard deviation by the method of Altman DG et al. Some continuous variables were transformed by the methods of Luo D et al. and Wan X et al. Correlation coefficients of BMD and CAC score were pooled using Medcalc (ver. 19.0) software. When $I^2 \geq 50\%$ or $p \leq 0.05$ (significant heterogeneity), random-effects model was used to combine HRs, or else fixed-effects model was applied. Sub-group analysis was applied to investigate sources of heterogeneity. $p$-value $<0.05$ was considered statistically significant.

**Results**

**Study characteristics**

Seventeen studies published from March 1998 to October 2020 were included in our meta-analysis (S_Table 1), and the articles were all published in English. The studies were conducted in the United States (7 studies, 41.2%), China (3 studies, 17.6%), Korea (4 studies, 23.5%), Turkey (1 study, 5.9%), Denmark (1 study, 5.9%) and Sweden (1 study, 5.9%). Nine studies recruited both male and female participants, five studies only recruited postmenopausal women and one study only recruited men. Most of studies measured BMD by dual-energy X-ray absorptiometry (DXA), six studies measured BMD by QCT.

**Quality assessment**

The quality assessment of the included studies is shown in S_Figure 1. Ludmila N. Bakhireva’s recruited middle-class and upper-class individuals, we labeled it as high-risk bias of representativeness of the cases. C. Celik’s study included a small sample (35 women), we marked it as unclear risk bias of representativeness of the cases. Only four studies reported whether CAG readers were blinded to the BMD results, other studies that did not mention it were regarded as unclear risk of bias. Six studies explained why the patients were excluded from the statistical analysis. In summary, most of the studies were mid-grade or high-grade quality.

**Association between BMD and CAC**

Four articles reported the prevalence of CAC in different levels of BMD, and the BMD values were all measured by DXA. The pooled OR for the prevalence of CAC in patients with low BMD versus patients with normal BMD was 2.11 (95% CI: 1.11 – 4.02, $p = 0.02$, $I^2 = 89\%$; random-effects model; Figure 2). The prevalence of CAC in patients with low BMD was higher than that in patients with normal BMD.

**CAC score difference in low BMD and normal BMD**

Five articles reported CAC score in low and normal BMD, and the BMD values were all measured by DXA. The data pooled for comparing CAC score in patients with low BMD and normal BMD were 19.82 (95% CI: 18.73–20.90, $p = 0.000$, $I^2 = 0\%$; Figure 3) in women, 68.10 (95% CI: 60.19–76.02, $p = 0.000$, $I^2 = 0\%$; Figure 2) in postmenopausal women, 24.21 (95% CI: 23.77–43.77, $p = 0.000$, $I^2 = 97\%$; random-effects model) in total. There was no significant difference in men subgroup. CAC score in low BMD patients was much higher than that in normal BMD ones, especially in postmenopausal women.
Six articles\textsuperscript{22-25,32,33} reported the BMD in non-CAC and CAC, and BMD values were derived from QCT (the unit of BMD is mg/cm\(^3\)). The data pooled for comparing BMD difference in patients with Non-CAC and CAC were 16.21 (95% CI: 11.50 - 20.92, \(p=0.000\), \(R^2=97\%\); Figure 4) in women, 17.31 (95% CI: 10.27 - 24.35, \(p=0.000\), \(R^2=0\%\)) in postmenopausal women, 12.49 (95% CI: 6.42–18.56, \(p=0.000\), \(R^2=98.6\%\)).
I2 = 99%) in men, and 14.42 (95% CI: 10.55–18.30, p = 0.000, I2 = 99%; random-effects model) in total, respectively. The BMD of patients with CAC was lower than the BMD of non-CAC people.

### Relationship between BMD and CAC score (Correlation coefficient)

Three articles26,27,29 reported the results of correlation analysis (r value), and the BMD values were all measured by DXA. The pooled correlation coefficient of BMD of lumbar spine and CAC score was -0.07 (p = 0.10, I2 = 63.39%; random-effects model; Figure 5(a)), and the pooled correlation coefficient of BMD of femur and CAC score was -0.11 (p = 0.01, I2 = 67.71%; random-effects model; Figure 5(b)). BMD of femur was inversely correlated with CAC; no correlation was found between lumbar BMD and CAC.

### Multivariate logistic regression analysis of the relationship between low BMD of different locations and CAC

Four articles12,19,20,22 reported the ORs of multiple logistic regression analysis of the relationship between low BMD (lumbar spine or femoral neck) and CAC. The covariates adjusted for analysis include: waist, systolic blood pressure, fasting plasma sugar, triglyceride, HDL-C, cholesterol, BMI, smoking, LDL-C, hs-CRP, and alkaline phosphatase in Lin T 2011’s study; age, fat-free mass, HDL, smoking and use of cholesterol lowering medications in Bakhireva LN’s study; age, total cholesterol: HDL cholesterol ratio, hypertension, smoking history, diabetes status, and hormone therapy (women only) in Hyder JA 2007’s study; age, race, study site, menopause status, alcohol drinking, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level in Farhat GN 2006’s study.

The pooled OR (age-adjusted) was 1.00 (95% CI: 0.92 - 1.10, p = 0.95, I2 = 23%; fix-effects model; Figure 6), the pooled ORs of subgroup were 0.98 (95% CI: 0.86–1.13, p = 0.35, I2 = 9%) in lumbar spine (DXA), 1.25 (95% CI: 1.01–1.55, p = 0.58, I2 = 0%) in lumbar spine (QCT) and 0.93 (95% CI: 0.81 - 1.07, p = 0.31, I2 = 17%) in femoral neck. The pooled OR (multivariable-adjusted) was 0.95 (95% CI: 0.86–1.05, p = 0.33, I2 = 38%; fix-effects model; Figure 7). The pooled ORs of subgroup were 0.96 (95% CI: 0.83–1.12, p = 0.48, I2 = 0%) for low lumbar spine (DXA), 1.30 (95% CI: 0.95 - 1.79, p = 0.11, I2 = 0%) for lumbar spine (QCT) and 0.86 (95% CI: 0.74–1.01, p = 0.07, I2 = 61%) for low femoral neck. The pooled data showed that no relation was found between low BMD and CAC by age or multivariable adjustment.

### Sources of heterogeneity

The meta-analyses of CAC comparison of low BMD vs normal BMD and BMD difference of non-CAC vs CAC showed obvious heterogeneity
Sub-group analyses by sex and postmenopause revealed that the heterogeneity appeared in men sub-group ($I^2 = 75\%$) from the meta-analysis of CAC comparison of low BMD vs normal BMD, and in women ($I^2 = 97\%$) and men ($I^2 = 99\%$) sub-groups from the meta-analysis of BMD difference of non-CAC vs CAC, respectively. While, the results from the studies of postmenopausal women were homogeneous ($I^2 = 0\%$). For the pooled data of multivariate logistic regression analysis (age-adjusted), the heterogeneity of sub-groups divided by DXA or QCT decreased (Figure 6), which meant the assessment method for BMD was also the source of heterogeneity.

**Publication bias**

Four meta-analyses including more than 5 studies conducted publication bias exploration (S_Figure 2). The funnel plots of CAC comparison between low BMD and normal BMD and logistic regression analysis of the relationship between low BMD and CAC (age-adjusted) were asymmetric, showing that these two meta-analyses may exist publication bias. The funnel plots of BMD difference in non-CAC and CAC and logistic regression analysis of the relationship between low BMD and CAC (multivariable-adjusted) did not display any publication bias.

**Discussion**

Without confounders adjustment, our study results indicated that the prevalence of CAC in patients with low BMD was higher than that in patients with normal BMD, and CAC score in low BMD patients was much higher than that in normal BMD ones. Pooled multiple regression analysis results showed that no relation was found between low BMD at femoral neck or lumbar spine and CAC after adjusting age only or other risk factors, which means that osteoporosis and CAC may be two independent processes with aging. We formerly performed the meta-analysis to explore the association of coronary artery calcification with low BMD and CAC (age-adjusted) were asymmetric.
disease (CAD) with BMD, and concluded that low BMD was not found to be associated with prevalence of CAD.\textsuperscript{34} CAC as one of the manifestations of CAD, is proposed to be related to the metabolic disorder of calcium. The increased coexistence of bone loss and vascular calcification is called the ‘calcification paradox’, which suggested that the risk of CAC be higher in people with low BMD.\textsuperscript{35} Moreover, another confounding for the different results of trials on this issue may be calcium supplementation for osteoporosis/osteopenia.\textsuperscript{36} There are some evidences that calcium/vitamin D supplementation augments coronary calcification. a large cohort study involving 2742 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) without cardiovascular disease found that calcium supplement use was associated with a 22\% increase in risk of incident CAC (RR, 1.22; 95\% CI, 1.07–1.39).\textsuperscript{37} An intra-vascular ultrasound study also found that oral calcium supplementation may increase calcium deposition in the coronary vasculature independent of changes in atheroma volume.\textsuperscript{38} However, the Women’s Health Initiative Calcium/vitamin D Supplementation Study (WHI CaD) reported that calcium carbonate and vitamin D supplementation had no adverse effect on any cardiovascular endpoints or on coronary artery calcification.\textsuperscript{39} Also, the Framingham study does not support the hypothesis that high calcium intake increases coronary artery calcification.\textsuperscript{40} Disparities results in trials of calcium metabolism, coronary calcification and reposition of calcium in different doses should be investigated in the future.

The beneficial effects of estrogen on the coronary bed have been reported in women, because estrogen plays a role in vascular calcification inhibition.\textsuperscript{41} Campos-Obando et al.\textsuperscript{41} finding suggest that endogenous estradiol deficiency might underlie both pathological processes and thus be a shared risk factor for BMD loss and CAC. Previous studies had found that the prevalence of CAC in men was significantly higher than that in women, and the prevalence of CAC increased with age. Then, postmenopausal women with decreasing estrogen are at risk of CAC and low

| Study or Subgroup (DXA) | log(Odds Ratio) | SE  | Weight | Odds Ratio [IV, Fixed, 95\% CI] | Year |
|------------------------|---------------|-----|--------|-----------------------------|-----|
| Lumbar spine (DXA)     |               |     |        |                             |     |
| Bakhleira LN 2005 (men) | -0.2744       | 0.158 | 11.6\% | 0.76 [0.56, 1.03]           | 2005|
| Bakhleira LN 2005 (men) | 0.0583        | 0.15 | 12.6\% | 1.06 [0.79, 1.42]           | 2005|
| Lin T 2011 (postmenopausal women) | -0.5447 | 0.9506 | 0.3\% | 0.58 [0.08, 3.74]           | 2011|
| Lin T 2011 (postmenopausal women) | 0.077 | 0.275 | 3.7\% | 1.08 [0.63, 1.85]           | 2011|
| Lin T 2011 (men) | 0.0596 | 0.1226 | 16.8\% | 1.03 [0.81, 1.31]           | 2011|
| Subtotal (95\% CI)     |               |     |        | 47.0\% [0.96, 1.12]         |     |
| Heterogeneity: Chi² = 3.48, df = 4 (P = 0.48); I² = 0% |     |     |        |                             |     |
| Test for overall effect: Z = 0.49 (P = 0.62) |     |     |        |                             |     |

| Study or Subgroup (QCT) | log(Odds Ratio) | SE  | Weight | Odds Ratio [IV, Fixed, 95\% CI] | Year |
|------------------------|---------------|-----|--------|-----------------------------|-----|
| Femoral neck (DXA)     |               |     |        |                             |     |
| Bakhleira LN 2005 (men) | -0.3711       | 0.1542 | 11.9\% | 0.69 [0.51, 0.93]           | 2005|
| Bakhleira LN 2005 (men) | 0.0206        | 0.1619 | 10.8\% | 1.03 [0.75, 1.41]           | 2005|
| Lin T 2011 (postmenopausal women) | -2.5939 | 0.9928 | 0.3\% | 0.01 [0.01, 0.04]           | 2011|
| Lin T 2011 (postmenopausal women) | 0.010 | 0.3009 | 3.1\% | 1.01 [0.86, 1.22]           | 2011|
| Lin T 2011 (men) | -0.0834 | 0.1322 | 16.2\% | 0.92 [0.71, 1.19]           | 2011|
| Subtotal (95\% CI)     |               |     |        | 42.2\% [0.86, 1.01]         |     |
| Heterogeneity: Chi² = 10.21, df = 4 (P = 0.04); I² = 61% |     |     |        |                             |     |
| Test for overall effect: Z = 1.79 (P = 0.07) |     |     |        |                             |     |

Figure 7. Forest plot of Logistic regression analysis of the relationship between low bone mineral density in different locations and coronary artery calcification (multivariable-adjusted).
BMD. Many epidemiological surveys supported the hypothesis,\textsuperscript{10,11,31,42} and some studies suggested that estrogen was involved in bone metabolism and had a certain effect on CAC.\textsuperscript{32,43} Our pooled data also revealed the same results on the gender difference in CAC, but whether the age of men and women is comparable was still unknown.

Choi et al.\textsuperscript{.27} study showed that lower BMD of the femur area and lumbar spine could be a marker for subclinical atherosclerosis in females. Hyder et al.\textsuperscript{20} demonstrated a significant negative correlation between BMD in lumbar spine and aortic calcification. Bakhireva et al.\textsuperscript{.19} univariate and multivariate logistic regression analyses showed that there was a significant inverse correlation between hip BMD and CAC. On the contrary, Lin et al.\textsuperscript{12} found no significant correlation between CAC and low BMD at lumbar spine, femur neck, and proximal femur after adjusted for age and other risk factors. Our meta-analysis also showed that there was no significant difference in the correlation between CAC and BMD after adjust the confounding factors.

Although our combined results showed that there was no statistical difference in the effect of low BMD in lumbar spine or femoral neck and CAC, the BMD at other locations such as thoracic vertebrae or hip may be different, for example, three studies have shown that there was an inverse relationship between BMD of thoracic vertebrae (T - 7 to T - 10) and CAC.\textsuperscript{10,25,32} Unfortunately, we were unable to include them for the meta-analysis because the heterogenous data are unavailable to pool. If the difference is definite, we assume that because the thoracic bones are close to the coronary arteries, the relationship may be stronger than other sites. The location difference is an interesting finding, and need to be explored in the future. In addition, the sub-group analysis in the present study found assessment method for BMD was one of the sources of heterogeneity. The future study may compare accuracy of BMD assessment methods such as DXA and QCT.

Three studies reported the correlation coefficients of relationship between BMD of different sites and CAC score. Our combined results showed that there was a significant inverse correlation between BMD of femur and CAC score. Therefore, bone loss in the femur is more associated with the severity of CAC. A significant negative correlation was also found between carotid intima media thickness and the T score of lumbar spine ($r = -0.35$; $p < 0.001$) and femoral neck ($r = -0.23$, $p < 0.001$), as well as Z score of the lumbar spine in postmenopausal women.\textsuperscript{44} But these studies could not exclude the influence of age and other key confounding factors, so the association of the severity of CAC and BMD is still necessary to explore. More large-scale studies with high-quality design are still needed to understand the relationship of these two processes by excluding confounders.

**Limitations**

Several limitations of our meta-analysis are as follows. First, some of the studies does not directly provide the available data we need. Although we try our best to transformed them to appropriate data for meta-analysis, for example, used the sample’s mean and standard deviation combining method of Altman DG et al.,\textsuperscript{15} some of the data that couldn’t be transformed have been dropped. The drop of these data may cause biases and misleading. Second, each meta-analysis could only include a small number of original studies because of data diversity. Then, it influenced the evidence to support the conclusion, for example, only four studies performed multivariate analysis. Third, the quality of the studies included may cause biases. More than half of the studies didn’t explain how missing data. Some meta-analyses also revealed publication bias. Besides, there is no studies from Africa, affecting the sample representativeness in terms of ethnicity and region. Fourth, all of the included studies are cross-sectional design, and it cannot determine whether there are any causes underlying this association.

**Conclusions**

Low BMD is associated with higher prevalence and severity of CAC, especially in postmenopausal women. But no relation is found after adjusting age and other confounding variables. Low BMD and CAC may be two independent processes with aging. More large-scale studies with high-quality design are still needed to increase the understanding of these two processes.

**Author contributions**

Peiyu Zhang: Data curation; Formal analysis; Methodology; Software; Writing – review & editing.
Liu Yang: Conceptualization; Methodology; Software; Writing – review & editing.
Qingwen Xu: Methodology; Supervision; Writing – review & editing.
Yidi Zeng: Writing – review & editing.
Yipin Yu: Supervision; Validation; Writing – review & editing.
Qinghua Peng: Funding acquisition; Supervision; Validation.
Hao Liang: Conceptualization; Formal analysis; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Conflict of interest statement
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ORCID iD
Hao Liang https://orcid.org/0000-0002-9045-9717

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