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The relationship between volumetric thoracic bone mineral density and coronary calcification in men and women – results from the Copenhagen General Population Study

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ABSTRACT

Background: The association between low bone mineral density (BMD) and the presence of coronary artery calcium (CAC) as a marker of atherosclerosis is unclear. The aim of this study was to assess the potential relationship between volumetric thoracic bone mineral density and coronary calcification in a large population of men and women.

Methods: Participants from the Copenhagen General Population Study underwent multidetector computed tomography. Volumetric thoracic BMD and CAC were assessed in the same scan. CAC was measured using calibrated mass score (cMS). cMS was dichotomized as cMS = 0 or cMS > 0. The association between BMD and cMS was analyzed using multiple logistic regression in men, premenopausal and postmenopausal women. The model was adjusted for age, BMI, hypertension, hypercholesterolemia, diabetes, known cardiovascular disease and smoking.

Results: Of 2548 eligible participants, 1163 men and 1385 women, mean age 61 ± 10 were included in the study. Mean BMD was 138 ± 46 mg/cm^3 for men and 151 ± 49 mg/cm^3 women. In 696 men (67%) and 537 women (41%) cMS was found to be above zero. For men, a decrease in BMD of 100 mg/cm^3 was associated to an odds ratio of 1.49 for cMS > 0 (95% confidence interval: 1.04–2.13, $P = 0.03$). In postmenopausal women, a decrease in BMD of 100 mg/cm^3 was associated to an odds ratio of 1.47 for MS > 0 (95% confidence interval: 1.04–2.08, $P = 0.03$). For premenopausal women, no significant association was found between BMD and cMS (odds ratio = 0.74, 95% confidence interval: 0.36–1.52, $P = 0.4$).

Conclusion: Bone mineral density and coronary calcification are 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.

1. Introduction

Osteoporosis and coronary artery disease are both common in the elderly population and contribute to major mortality and morbidity. But whether the diseases are directly related independently of shared risk factors remains unclear. Several studies reported no association [1–6], others reported an association, but mainly in women [7–10].

The microarchitectural changes of bone tissue seen in osteoporosis [11] leads to increased bone fragility, susceptibility to fracture and, ultimately, death. The diagnosis and treatment of osteoporosis relies on the measurement of BMD. BMD is most commonly assessed by Dual energy X-ray absorptiometry (DXA), but can also be assessed by CT [12]. CT has some advantages over DXA: it measures true volumetric BMD independent of body size, provides purely trabecular bone measurements and it is not confounded by aortic calcification and degenerative bone changes [12]. BMD is traditionally measured in the femur

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; CAC, Coronary artery calcification; CGPS, Copenhagen General Population Study; cMS, Calibrated mass score; CT, Computed tomography; DXA, Dual energy X-ray absorptiometry; ROI, Region of interest

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or the lumbar spine, but it has recently been demonstrated that thoracic CT measurements obtained during coronary artery calcification (CAC) scanning yield adequate and precise measures of BMD with high degrees of reproducibility and can be correlated to lumbar measurements [13]. In a clinical setting BMD can be measured in all patients who undergo cardiac CT.

Vascular calcification is the pathological process of mineral deposition in the vascular system [14]. Calcification of the coronary arteries can be quantified by CT. CAC is a marker of coronary heart disease and is reliably associated with the risk of coronary events [15]. CAC is traditionally quantified using the Agatston Score. However, recent studies have shown that the so-called calibrated mass score (cMS) method is more accurate and reproducible than the Agatston Score [16–18]. The cMS measures an actual mineral mass of the calcifications, whereas AS is a weighed score of CAC [19]. cMS has lower detection thresholds than AS, and have been shown to detect small calcifications missed by the AS [18]. This might allow for identification of atherosclerotic plaques at an earlier stage of the disease. Minimal CAC have been suggested to convey an increased risk of future cardiovascular events compared to zero CAC [20].

No large-scale studies have examined the association of CAC quantified by cMS and BMD in a population-based study of men and women.

The aim of this study was to determine the possible association between CT-derived volumetric BMD at the thoracic spine and coronary calcification in a large population of apparently healthy men and women.

2. Methods

2.1. Study population

From July 2011 to July 2013, 2548 participants from the Copenhagen General Population study (CGPS) underwent Cardiac CT at Rigshospitalet, Copenhagen. The CGPS is a large ongoing cross-sectional population study where phenotypic data of relevance to a wide range of health-related conditions are obtained by questionnaires, physical examination and blood samples [21]. The Danish National Committee of Biomedical Research Ethics approved the research protocol and all participants gave oral and written consent. Inclusion criteria for CT scan was age $>$ 40 years and a normal kidney function (s-creatinin $<$ 100 µmol/L) Exclusion criteria for this study were: 1) calcium calibration phantom not sufficiently included in the scan field of view 2) inadequate image quality due to heavy noise or motion artefacts 3) extensive vertebral abnormalities or fractures 4) Software failure 5) Self-reported Percutaneous coronary intervention (PCI) or CT-evidence of previous coronary intervention.

2.2. Demographic data

Information about medical history, cardiovascular risk profile, smoking habits, prescribed medication and physical activity was based on a detailed questionnaire completed by all participants. The height and weight of all participants was measured. Blood pressure at rest for each patient was measured at two clinics. Hypertension was defined as self-reported use of antihypertensive medication or a systolic blood pressure of $>$ 140 mm Hg and/or a diastolic blood pressure of $>$ 90 mm Hg at both locations as previously described [22]. Hypercholesterolemia was defined as self-reported use of statins or LDL $>$ 4,9 mM or total cholesterol $>$ 8,0 mM [22]. Diabetes was defined as self-reported use of diabetes medication or blood glucose $>$ 11,1 mM. Smokers were categorized as either active or former smoking. Menopausal status was self-reported. Low physical activity was defined as $<$ 4 h of physical activity per week. Known cardiovascular disease was defined as self-reported myocardial infarction or coronary by-pass.

2.3. CT imaging

CT imaging was performed using a 320 Multidetector Scanner (Aquilion One, Canon Medical Systems, Japan). Cardio-selective oral beta-blockers were given to all subjects with heart rate $>$ 55 bpm and no other contraindications 1 h before scanning. The following scanner settings were used: Gantry rotation time 350 ms, detector collimation 0.5 × 320, tube voltage ranging from 100 to 135 depending on BMI and tube current between 280 and 500 mA. Reconstructions at best phase of the R-R interval using an automated raw data motion analysis tool (PhaseXact, Toshiba) were performed. Scans were reconstructed 0.5/0.5 mm thickness/increment for calibrated mass scoring and BMD assessment.

A contoured calibration pad, 130 cm × 41 cm (INTable, Image Analysis, KY, USA) was placed underneath each subject during the scan. It contained four cylindrical calibration phantom rods 127 cm × 1,6 cm made from calcium hydroxyapatite (CaHa) homogenously distributed in a base material composed of a CT water equivalent compound. Three of the calibration rods had sample concentrations of 0 mg/cm^3, 75 mg/cm^3 and 150 mg/cm^3 respectively. The fourth rod had a fat equivalent density.

2.4. Image analysis

The Agatston score was analyzed on an external post-processing workstation according to the Agatston method[23] using commercially available software (Vitrea 6.3, Vital Images Inc., MN, USA). Calcification within each coronary artery was defined as a distinct voxel with an attenuation threshold ≥130 Hounsfield Units [23]. The lesion score was determined by multiplying the lesion area by the density score for the area. The total calcium score was calculated by summing up all individual scores for the four major coronary arteries.

cMS and BMD were assessed using a dedicated external post-processing workstation and commercially available semi-automated software (Nvivo™, Image Analysis, Kentucky, USA).

Calibrated mass score is a calcium scoring method that measures an absolute mass of mineral in the arteries. It is quantified based on the known mineral concentration within the simultaneously scanned calibration phantoms. An automated hybrid calibration method is incorporated in the NVivo software, which uses both the calibration phantoms and calibrations from the patient's tissues, blood and muscle/fat to calculate the mass of mineral in milligrams [24]. From within a segmented volumetric ROI containing the whole heart the software automatically identified and quantified calcified plaques based on the calibration rods. The method has previously been described in details elsewhere [18]. cMS is expressed in mg of calcium hydroxyapatite equivalence. Intra- and interobserver variability in cMS measurements were performed in vivo on 100 participants in the previous study by Knudsen et al. [18]

Volumetric thoracic BMD was measured as previously described [7,13] and is described in brief in the following section. The operator, who measured BMD, was blinded to coronary calcium scoring and demographical data. BMD was measured in three consecutive thoracic spine vertebrae with the top vertebra at the level of left main coronary artery [13]. The vertebral levels were not the same in all participants. The majority was measured from T7–T9, but some participants were measured from either T6–T8 or T8–T10. The center of the ROI was located at the center of the vertebral body with a 2–3 mm distance to the spinal cortical bone. The operator examined each ROI and changed its placement using manual free tracing to exclude cortical bone and vertebral abnormalities such as bone islands and diffuse density variations [7,13]. All participants with senile kyphosis were excluded from the study except in patients in whom at least two vertebrae could be identified without compression fracture or extensive osteophytes. The mean BMD was calculated for the three consecutive vertebrae [13]. Both interobserver and intraobserver data were obtained in vivo in

patient. For interobserver data BMD was measured by two different readers in 50 randomly selected participants included in this study. The two readers only measured BMD once in each participant. For intraobserver data BMD was measured two times by the same reader in 50 randomly selected participants.

2.5. Statistical analysis

Demographic data were stratified by gender. Normally distributed continuous variables were expressed as means with standard deviation (SD). Non-normally distributed continuous variables were expressed as medians with interquartile range (IQR). Categorical variables were expressed as amounts and percentages. Student's *t*-tests and Chi-squared tests were performed to compare gender differences for normally distributed numeric variables and categorical variables respectively. The non-parametric Mann–Whitney *U* test was used to compare non-normally distributed numeric variables.

Intra- and interobserver variability were evaluated with Bland-Altman agreement analysis and Coefficient of Variance.

In an exploratory data analysis univariate linear regression was used to assess the association of various cofactors with BMD in men, premenopausal and postmenopausal women.

Logistic regression was used to assess the association between BMD and cMS. The mass score was dichotomized as cMS = 0 and cMS > 0. The model was adjusted for age, BMI, hypertension, hyperlipidemia, diabetes, smoking and known cardiovascular disease. Adjusted odds ratios of cMS > 0 at a given BMD compared to 100 mg/cm^3 higher BMD were calculated for men, premenopausal and postmenopausal women. The same logistic model was used to examine the association between BMD and Agatston score.

Statistical significance was defined as a P value < 0.05. All statistical analyses were performed using SAS statistical software (SAS9.3, SAS Inc., Cary, North Carolina USA) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

Of the 2548 participants who underwent CT examination 90 (4%) were excluded due to calibration phantoms insufficiently included in the scan, 29 (1%) due to inadequate image quality and noise, 20 (< 1%) due to extensive vertebral abnormalities, 12 (< 1%) due to software failure and 31 due to previous coronary revascularization (1%). The final study group consisted of 1044 men (44%) and 1322 women (56%). 39 of the participants had missing data on hypertension, hypercholesterolemia, smoking, diabetes, known CVD, physical activity and menopause status. Demographic data of the population are summarized in Table 1.

3.2. Characteristics of bone mineral density

The mean BMD was 138 mg/cm^3 (SD = 46) for men and 151 mg/cm^3 (SD = 49) for women (Table 2). Intraobserver and interobserver showed good correlation (Intraobserver: Mean difference = −0.54, limits of agreement = [−7.7–6.6], coefficient of variance = 2.3%; Interobserver: Mean difference = 1.17, limits of agreement [−5.4–8.8] coefficient of variance = 2.4%). In univariate linear regression analysis BMD was negatively correlated with increasing age, hypertension, hypercholesterolemia, smoking and low physical activity (all P < 0.02). BMD was positively correlated with BMI (P < 0.0001). BMD was not associated with diabetes (P = 0.52) or known cardiovascular disease (P = 0.19).

Median of cMS in mg is only reported for participants with cMS > 0.

Table 1
Characteristics of the population stratified by gender.

Variable	Men	Women	P
N (%)	1044 (44)	1322 (56)	–
Age, y, mean (SD)	61 (11)	60 (10)	0.01
BMI kg/m^2, mean (SD)	26.6 (3.2)	25.4 (4.1)	< 0.0001
Hypertension, N (%)	623 (61)	637 (49)	< 0.0001
Hypercholesterolemia, N (%)	227 (22)	235 (18)	0.02
Statins, N (%)	176 (17)	173 (13)	0.02
Smokers, N (%)	614 (60)	716 (55)	0.01
Diabetes, N (%)	38 (4)	24 (2)	0.006
Known CVD, N (%)	31 (3)	17 (1)	0.004
Low physical activity, N (%)	421 (41)	590 (45)	0.04
Menopause, N (%)	–	979 (76)	–
HRT, N (%)	–	157 (16)	

Abbreviations: N, number; y, years; SD, Standard deviation; BMI, Body mass index; Known CVD, Known cardiovascular disease; HRT, Hormone replacement therapy.

Table 2
Bone mineral density and calibrated mass score values in men and women.

	Men	Women	P
BMD mg/cm^3, Mean (SD)	138 (46)	151 (49)	< 0.0001
cMS > 0, N (%)	696 (67)	537 (41)	–
cMS, mg, Median (IQR)	24.8 (6–96.3)	12.6 (2.6–42.5)	< 0.0001

Abbreviations: BMD, Bone mineral density; SD, Standard deviation; N, Number; cMS, Calibrated mass score; IQR, Interquartile range.

3.3. Characteristics of calibrated mass score

The median cMS in men was 24.8 mg of hydroxyapatite equivalence (IQR 6–96.3) and 12.6 mg in women (IQR 2.6–42.5) (Table 2). 696 men (67%) and 537 women (41%) had a cMS above zero. Univariate logistic regression analysis showed that age, BMI, hypertension, hypercholesterolemia, diabetes, smoking status and known cardiovascular disease were all associated with cMS (Table 3).

3.4. Association between bone mineral density and calibrated mass score

BMD was associated to cMS in men and postmenopausal women in multivariable logistic regression analysis after adjustment for confounding factors including age, BMI, hypertension, hypercholesterolemia, diabetes, smoking status and known cardiovascular disease (Table 4, Fig. 1). These cofactors were examined for interaction, and this existed between smoking and gender- and -menopause status as hypertension and gender- and-menopause status.

For men, a decrease in BMD of 100 mg/cm^3 was associated with an odds ratio of 1.49 for cMS > 0 (95% confidence interval: 1.04–2.13, P = 0.03). In postmenopausal women, a decrease in BMD of 100 mg/

Table 3
Unadjusted odds ratios for the univariate association between risk factors and cMS > 0.

Variable	OR	95% CI	P
Age	1.12	1.10–1.13	< 0.0001
BMI	1.05	1.03–1.07	< 0.0001
Hypertension yes vs. no	3.10	2.61–3.67	< 0.0001
Hypercholesterolemia yes vs. no	3.27	2.61–4.10	< 0.0001
Smoking yes vs. no	1.62	1.37–1.91	< 0.0001
Diabetes yes vs. no	2.96	1.65–5.32	0.0003
Known CVD yes vs. no	4.08	1.97–8.46	0.0002
Low physical activity yes vs. no	1.03	0.87–1.21	0.76

Abbreviations: cMS, calibrated mass score; OR, Odds ratio; 95%CI, 95% confidence interval; BMI, Body mass index; Known CVD, Known cardiovascular disease.

Table 4
Association between BMD and cMS > 0 or Agatston score > 0.

	OR	95% CI	P
cMS > 0.			
Men	1.49	1.04–2.13	0.03
Postmenopausal Women	1.47	1.04–2.08	0.03
Premenopausal Women	0.74	0.36–1.52	0.40
Agatston score > 0.			
Men	1.29	0.92–1.82	0.14
Postmenopausal Women	1.55	1.09–2.24	0.02
Premenopausal Women	0.60	0.27–1.33	0.20

Adjusted odds ratio for the association between BMD pr. 100 mg/cm3 and cMS > 0 or Agatston score > 0.
Adjusted for age, BMI, known cardiovascular disease, diabetes, hypertension, hyperlipidemia, and smoking.
Abbreviations: BMD, Bone mineral density; cMS, Calibrated mass score; OR, Odds ratio; 95%CI, 95% confidence interval.

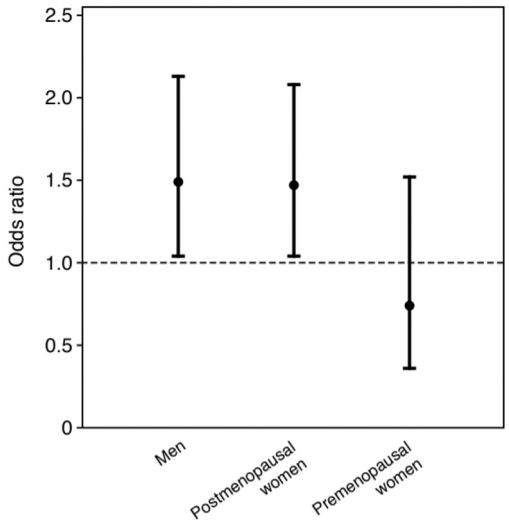

Fig. 1. Adjusted odds ratio for the association between BMD pr. 100 mg/cm^3 and cMS > 0.
Adjusted for age, BMI, known cardiovascular disease, diabetes, hypertension, hyperlipidemia, and smoking.
Men: P = 0.03; Postmenopausal women: P = 0.03; Premenopausal women P = 0.40.

cm^3 was associated with an odds ratio of 1.47 for cMS > 0 (95% confidence interval: 1.04–2.08, P = 0.03). In premenopausal women, no significant association was found between BMD and cMS (odds ratio = 0.74, 95% confidence interval 0.36–1.52, *P* = 0.4).

BMD was associated to Agatston score after adjustment for confounding factors (Table 4) in postmenopausal women (OR = 1.55 95% confidence interval 1.09–2.24, *P* = 0.02), but not in men (OR = 1.29, 95% confidence interval 0.92–1.82, *P* = 0.14) or premenopausal women (OR = 0.6, 95% confidence interval 0.27–1.33, *P* = 0.2).

4. Discussion

In this large-scale population-based study we found an inverse relation between BMD and coronary calcification measured by cMS in men and postmenopausal women. To our knowledge, this is the first study to find an association between BMD and CAC in both women and men in the general population.

Studies of the association of BMD with CAC are inconsistent. Many studies have found little or no association between BMD and CAC [1–6], but several studies did find an association [7–10].

The studies differ with respect to imaging modalities and characteristics of subjects. Some use DXA to assess BMD [3–6,9,10] and some use CT [1,2,7,8,10]. Most studies analyze the association between BMD and CAC in both men and women [2–10], but one study only include female participants [1]. All the studies mentioned used Agatston score to assess CAC.

This is the first study of the association between bone loss and vascular calcification to assess coronary calcification by calibrated mass score. cMS has been demonstrated to be more sensitive than the Agatston Score [18,24]. We propose that the use of the more sensitive cMS could possibly explain why were able to find an association between BMD and CAC in both men and postmenopausal women in a general, unselected population even though many other studies only found an association in women [7–10]. When we used Agatston score to assess CAC we only found an association between BMD and CAC in postmenopausal women and not in men. This supports the hypothesis that the use of cMS could explain our positive result.

Several mechanisms may account for a possible pathophysiological link between osteoporosis and atherosclerosis. Evidence indicates that dyslipidemia plays a role in both atherosclerosis and osteoporosis [25,26]. In both diseases dyslipidemia leads to increased amounts of lipid oxidation products and accumulation of oxidized lipids beneath the vascular intima or perivascular areas in bone [25]. Oxidized lipids have opposite effects on calcification in vascular and bone tissue – they enhance vascular calcification by stimulating the differentiation of calcifying vascular cells and decrease bone mineralization through inhibition of osteoblast differentiation [26]. Inflammation is also involved in the progression of atherosclerosis and bone loss [25]. The inflammatory cytokines TNF-alfa and IL-6 have been shown to be associated with cardiovascular disease and to induce bone resorption and inhibit bone mineralization [26]. Shared metabolic and regulatory factors might also explain the association of osteoporosis and arterial calcification. Furthermore, in knock-out animal models deletion of certain genes involved in bone metabolism leads to both bone and vascular abnormalities [27].

We found a significant association between BMD and CAC in postmenopausal women, but not in premenopausal women. This suggests a potential role of estrogen deficiency in the progression of both osteoporosis and atherosclerosis. Estrogen deficiency is known to be the major cause of bone loss in postmenopausal women [28]. Estrogen regulates osteoclast activity and thereby acts to conserve bone mass by inhibiting bone resorption [28]. It has been proposed that endogenous estrogen may inhibit vascular calcification[26] and a negative association between estrogen and coronary calcification has been observed [29]. Although many mechanisms are assumed to affect both osteoporosis and atherosclerosis, an exact pathophysiological link between the two diseases has not yet been proved.

Men and postmenopausal women with osteoporosis might benefit from an assessment of cardiovascular risk. It is possible that treatment of osteoporosis simultaneously affects cardiovascular calcification and vice versa. This hypothesis is supported by the effects of bisphosphonates and HMG-CoA reductase inhibitors. Bisphosphonates are pharmacological agents widely used in the treatment of osteoporosis. Investigations in animals suggest that bisphosphonates inhibit atherogenesis [25]. HMG-CoA reductase inhibitors also known as statins have been shown to stimulate bone formation in vitro and reduce fracture risk in epidemiological studies [30]. Overall this concept needs further investigation.

4.1. Limitations

This study lacks data describing use of bisphosphonates and serum levels of estradiol, vitamin D and K, PTH and the inflammatory markers TNF-alfa and IL-6. In addition, the cross-sectional design of this study does not allow an evaluation of the causal association between BMD and CAC. In premenopausal women, no inverse relation was found between BMD and cMS, but it should be noted that very few

premenopausal women had a cMS > 0, therefore this result should be interpreted with caution.

Strengths of this study include the large sample size and the use of CT to quantify BMD, which allows adjustment for bone size, exclusion of vertebrae with bony islands or osteophytes and secures measurements of purely trabecular bone [12]. Furthermore, we adjusted for important confounders known to be risk factors for osteoporosis and cardiovascular disease. We used cMS to assess CAC, which detects calcification with higher sensitivity than the Agatston Score.

5. Conclusion

In a population of apparently healthy men and women we found an inverse relation between thoracic bone mineral density and coronary calcification measured by calibrated mass score in men and postmenopausal women after adjustment for multiple shared risk factors. Our results support the hypothesis that a direct relation between bone loss and development of atherosclerosis exist irrespective of gender.

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