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Bone health and coronary artery calcification: The Rotterdam Study

Natalia Campos-Obando [a, 1], Maryam Kavousi [b, 1], Jeanine E. Roeters van Lennep [a], Fernando Rivadeneira [a, b, c], Albert Hofman [b, c], André G. Uitterlinden [a, b, c], Oscar H. Franco [b, c, 2], M. Carola Zillikens [a, b, c, *, 2]

[a] Department of Internal Medicine, Erasmus MC, 3000 CA Rotterdam, The Netherlands
[b] Department of Epidemiology, Erasmus MC, 3000 CA Rotterdam, The Netherlands
[c] Netherlands Genomics Initiative-Sponsored Netherlands Consortium for Healthy Ageing (NCHA), 2300 RC Leiden, The Netherlands

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ABSTRACT

Objectives: Vascular calcification has been associated inconsistently to low bone mineral density and fractures. The aims of the present study were to investigate the associations between coronary artery calcification (CAC) and BMD change, BMD and fracture risk in elderly subjects of the population-based Rotterdam Study.

Methods: BMD was assessed through dual-energy X-ray absorptiometry and CAC through Electron-Beam Computed Tomography in 582 men and 694 women. We investigated the associations between BMD change (6.4 years follow-up) and CAC at follow-up and between BMD and CAC (measured simultaneously). In sensitivity analyses we stratified analyses for estradiol levels in women. The association between CAC and fracture risk (9 years follow-up) was tested through competing-risks models. Models were sex-stratified and adjusted for age, body mass index, smoking, bisphosphonate use and age at menopause.

Results: There was no association between BMD change and CAC in men. In women, each 1% increase in annual BMD loss was significantly associated with higher follow-up CAC [β = 0.22 (0.06–0.38), p = 0.006; prevalence ratio: 4%]. Stratified analyses showed significant associations between BMD loss and follow-up CAC only in women with lower estradiol levels. We found no association between CAC and fracture risk and no association between BMD and CAC cross-sectionally.

Conclusions: BMD loss was associated with higher follow-up CAC in women, which might be related to low estrogen levels. No association between CAC and BMD or fracture risk was found. Further studies are required to elucidate the mechanisms that might underlie the association between BMD change and coronary calcification in women.

1. Introduction

Osteoporosis and cardiovascular disease (CVD) are common age-related diseases that have an increased co-existence independent of shared risk factors such as increased age, menopause, physical inactivity, alcohol intake and vitamin D deficiency [1]. Common pathophysiological mechanisms have been proposed such as inflammatory cytokines, oxidized lipids, increased homocysteine levels and decreased estrogen levels [1].

Vascular calcification is defined as the abnormal deposition of calcium in the vascular system [2]. Formerly considered a passive consequence of atherosclerosis, it is nowadays recognized as a highly active process associated with an increased risk of cardiovascular events independently of other traditional risk factors [3]. The resemblance that ectopic calcification shares with the normal calcification process of bone is remarkable and several studies [4,5] have verified the observation made by Virchow in 1863 that cardiovascular calcification is “an ossification, not a mere calcification” [6].

The increased co-existence of vascular calcification with osteoporosis [7] is called the *calcification paradox*. It has motivated several investigators to evaluate whether bone mineral density (BMD) and vascular calcification (VC) in several vascular beds are

* Corresponding author. PO Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail address: m.c.zillikens@erasmusmc.nl (M.C. Zillikens).
[1] These authors contribute equally to this work.
[2] These authors jointly directed this work.

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associated beyond the aging process and independent of potential confounders [8–14]. Among studies with a cross-sectional design, an inverse relation between aortic or coronary artery calcification (CAC) and BMD has been reported by some [8,9] but not others [10,11]. In contrast, longitudinal studies have consistently shown that increased BMD loss is associated with increased aortic vascular calcification assessed through different imaging modalities, such as X-rays and radiogrammetry [12,13] as well as through computed tomography [14], this relation has not been explained by aging and other shared risk factors and has been found mainly in women. Longitudinal studies evaluating the association between bone turnover and CAC have been performed mainly in subjects with chronic kidney disease, and results have been inconsistent; while some studies have shown that low bone turnover is associated with increased risk of CAC [15] others have not replicated such findings [16].

Studies addressing the association between vascular calcification and fracture risk have focused mainly on aortic calcification, and the results have been conflicting. While some of them have reported an increased fracture risk with increased vascular calcification [14,17], other studies have not found such results [11,18].

Since previous studies found an association in women between BMD loss and aortic vascular calcification we aimed to investigate whether in the prospective population based Rotterdam study changes in BMD are associated with vascular calcification measured in the coronary arteries (CAC) in either sex and whether CAC is associated with incidental fractures and BMD. We also studied whether findings can be explained by hormonal status or bone turnover.

2. Materials and methods

2.1. Study population

The Rotterdam Study is a prospective cohort study of elderly men and women designed to investigate the incidence and determinants of chronic disabling diseases. Rationale and design have been described elsewhere [19]. The Rotterdam Study I cohort (RS-I) was initiated in 1990 and consisted of 7983 participants. All subjects were >55 years at recruitment and reside in Ommoord, a district in Rotterdam and they have been assessed at baseline and through four follow-up visits. BMD was measured in all follow-up evaluations of the participants, and CAC scores were measured at RS-I-3 visit (third evaluation of the RS-I cohort). In total, 1276 subjects had available information on CAC levels, previous BMD measurements and incident fracture data (Fig. 1). The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus MC.

2.2. DXA scanning

BMD was assessed using dual-energy X-ray absorptiometry (DXA). Trained radiographic technicians performed BMD measurements for participants at the first visit (1990–1993) and the third visit (1997–1999) with a GE Lunar DPX-L densitometer. For the longitudinal analysis of BMD change and its association with follow-up CAC, absolute annual percent BMD change at the femoral neck was calculated with the formula [100*($BMD_{RS\text{-}I\text{-}1} - BMD_{RS\text{-}I\text{-}3}$)/($BMD_{RS\text{-}I\text{-}1}$)*time length between measurements] [20], with a positive value reflecting BMD loss. Results are expressed per 1% increase in annual femoral neck BMD loss. Femoral neck BMD (from henceforth referred to simply as BMD) was chosen, as it is not affected by degenerative changes seen with age as lumbar spine BMD and has been proposed for defining osteoporosis in

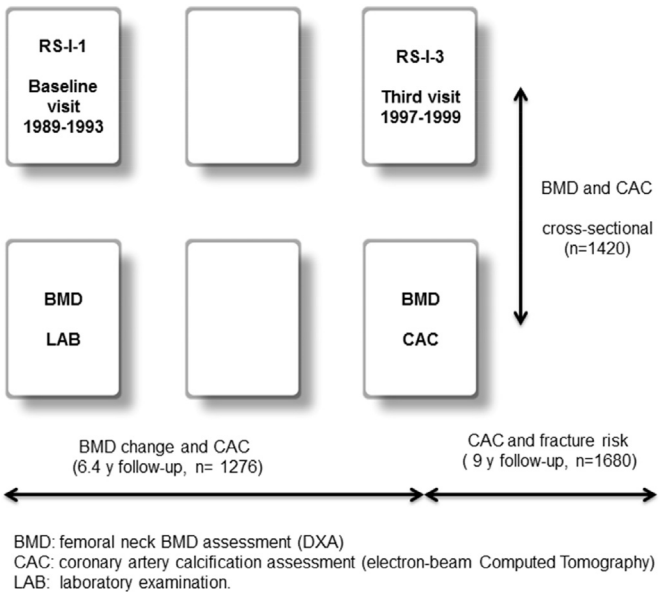

Fig. 1. Flowchart for time line, design and sample size for the analyses.

epidemiologic studies [21]. For the cross-sectional analyses of BMD and CAC, BMD is expressed in sex-specific standard deviations (SD).

2.3. Coronary artery calcification assessment

At the third visit of the Rotterdam Study all participants who completed the third phase of the Rotterdam Study were invited to participate in the Rotterdam Coronary Calcification Study [22]. Epicardial coronary arteries calcification was detected by electron-beam Computed Tomography (EBT; C-150 Imatron Scanner, GE Healthcase, South San Francisco, CA). Before the subjects were scanned, they performed adequate breath-holding exercises. From the level of the root of the aorta through the heart, 38 images were obtained with a 100-ms scan time and a 3-mm slice thickness. During one breath hold, images were acquired at 80% of the cardiac cycle by using echocardiographic triggering. Quantification of coronary calcification was performed with AccuImage software (AccuImage Diagnostics Corporation, South San Francisco, CA) displaying all pixels with a density >130 Hounsfield Units (HU). The presence of calcification was defined as a *minimum* of 2 adjacent pixels (area = 0.65 mm^2) with a density >130 HU. Calcium scores were calculated by multiplying the area in mm^2 of individual calcified lesions with a factor based on the peak density of the lesion. The total calcification score for the entire epicardial coronary vascular system comprised the sum of the scores for all individual lesions.

2.4. Fracture assessment

Fracture events were obtained from computerized records of general practitioners (GPs) in the research area (covering 80% of the cohort); additionally research physicians regularly followed participant information in the GP's records outside the research area. All reported events were verified by two trained research physicians, who independently reviewed and coded the information. Finally, all coded events were reviewed by a medical expert for final classification according to the International Classification of Diseases, tenth revision (ICD-10) [23]. Participants were followed from the date of the CAC scan until January 1, 2007, or until a first fracture or death occurred.