# Cosegregation of cardiovascular diseases and osteoporosis: instrumental diagnosis

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**Summary**

**Both atherosclerosis and osteoporosis are responsible for significant morbidity and mortality, are independent predictors of cardiovascular disease (CVD) events, and may share common regulatory mechanisms as well as histopathology. Abdominal aortic calcification (AAC), an indication of atherosclerosis, is significantly associated with both cardiovascular heart disease and stroke. The increased risk of cardiovascular disease mortality associated with moderate to severe AAC is similar to the increased risk of hip fracture in the presence of a moderate to severe vertebral fracture. A negative association between bone mineral density (BMD) and AAC severity has been also demonstrated.**
**Several non-invasive methods are available to investigate the presence and the severity of osteoporosis. With some of these is possible to measure aortic calcification and bone mass in the same exam. A new method for the evaluation of aorta calcification by dual X-Ray absorptiometry (DXA) has been recently suggested, the Instant Vertebral Assessment (IVA), which offers the possibility to obtain in the same scan an assessment of vertebral fracture and AAC. Therefore, a single IVA exam could assist in stratifying patients into high and low risk groups for two highly prevalent and significant health care problems.**

*KEY WORDS: aortic calcification, bone mineral density, dual X-ray absorptiometry, quantitative computed tomography, instant vertebral assessment.*

## Introduction

Cardiovascular events and osteoporotic fractures are major causes of morbidity and mortality in elderly (1-4).
Cardiovascular disease (CVD) often presents atypically, making clinical recognition difficult; the need for timely referral of high-risk individuals identified by different independent predictors of cardiovascular risk is also urged by the fact that more than two-third of women suddenly die for cardiovascular events without prior sign of the disease (5). Prevalence of these events is expected to rise in upcoming years owing the increasing longevity of population in most of the industrialized countries of the world. Important studies, based on prospective cohort of the Framingham Heart Study and the Rotterdam Study, have demonstrated that men and women with calcific diseases in the abdominal aorta are more likely to develop coronary heart disease (CHD), CVD, and CVD mortality (6) and that aortic calcifications are stronger predictors of incident stroke (7). In a recent paper carried out in 1453 women and 1046 men (mean age 61 years) followed for 35 years, a strong association between aortic calcification and increased of death has been confirmed (8): in fact mortality was 91% in women and 94% in men with aortic calcification compared to 60% in women and 74% in men without aortic calcification, with a linear increase of hazard ratios for mortality according to the severity of aortic calcification score (8). The increased risk of CVD mortality associated with abdominal aortic calcification (AAC) is similar to the increased risk of hip fracture in the presence of a moderate to severe vertebral fracture.
Several studies have also showed that low bone mass and osteoporotic fractures are independent predictors of mortality in men and women (2, 3, 9, 10).
A positive association between osteoporosis and CVD has been reported in prospective study and in retrospective analysis (11, 12). Tanko et al., in more than 2500 women assigned to placebo and followed for 4 years in an osteoporosis treatment trial, showed that postmenopausal osteoporotic women are at an increased risk for cardiovascular events that is proportional to the severity of osteoporosis at the time of the diagnosis: the incidence of cardiovascular events was 3.8% in osteoporotic women, and 0.9% in women with low bone mass with an 3.9-fold increase of risk for acute cardiovascular events in women with osteoporosis (11). In the same study it has been showed that incidence of cardiovascular events is associated with the number and the severity of vertebral fractures (11). Ness et al., in a retrospective analysis of 1000 postmenopausal women, demonstrated an association between low BMD and atherosclerotic vascular disease (12). An unified hypothesis of vascular calcification that combines both active and passive mechanisms of vascular mineralization with aspects of bone resorption and age-related changes has been recently proposed (13).
In the last 25 years, several non-invasive techniques have been developed to quantify bone mineral density in the axial and peripheral skeleton, some of these also offer the possibility to assess and quantify vascular calcification.

## Conventional Radiography (Xr)

Vertebral fractures are the most common of all osteoporotic fractures and are present in a significant percentage (25%) of the population over the age of 50, especially in Caucasian women and men in Europe and the United States (14-18). Vertebral fractures are associated to an increased mortality rate (18) and loss of independence and impaired quality of life (19, 20). Even asymptomatic, vertebral fractures could have clinical consequences for the patient because of the increased, approximately five-fold, risk of future fractures that may be symptomatic (21). For these reasons the prevention of future fractures for patients with vertebral fractures has been considered

the endpoint in clinical trials on osteoporosis therapy (22-26). Because a majority of vertebral fractures often occur in absence of specific trauma and are asymptomatic, they are often difficult to identify clinically. It is in the accurate diagnosis of asymptomatic vertebral fractures that radiologists make perhaps the most significant contribution to osteoporotic patient care. In everyday clinical practice, the qualitative reading of spinal radiographs is still the standard tool to identify vertebral fractures. The assessment by radiologists of conventional radiographs of the thoracic and lumbar spine in lateral and anterior-posterior (AP) projections generally is uncomplicated, allowing the identification of moderate and severe vertebral fractures. However, the osteoporotic vertebral fractures often appears such as mild vertebral deformities, without the visible discontinuity of bone architecture. So the visual radiological approach may cause disagreement about whether a vertebra is fractured (27). In an effort to improve the accuracy of the diagnosis of vertebral fractures was introduced more than a decade ago the semiquantitative assessment (SQ) and the quantitative measurement of vertebral heights (e.g., vertebral morphometry) for the definition of vertebral fractures.

In this approach the conventional radiographs are evaluated by skeletal radiologists or experienced clinicians in order to identify and to classify the vertebral fractures (28). Vertebrae T4-L4 are graded by visual inspection and without direct vertebral measurement as normal (grade 0), mild fracture (grade 1 with approximately 20-25% reduction in anterior, middle, and/or posterior height and 10-20% reduction in area), moderate fracture (grade 2 with approximately 25-40% reduction in any height and 20-40% reduction in area), and severe fracture (grade 3 with approximately 40% or greater reduction in any height and area). Incident fractures are defined as those vertebrae that show a higher deformity grade on the follow-up radiographs. The SQ method is a simple but standardized approach that provides reasonable reproducibility, sensitivity, and specificity, allowing excellent agreement for the diagnosis of prevalent and incident vertebral fractures to be achieved among trained observers (29).

From lumbar Xr it is possible to assess the location, severity and progression of aortic calcification (30). Kauppila et al. developed a reliable indices of the radiopaque calcifications in the abdominal aorta, which include assessment of individual aortic segments and summary scores, derived from the severity scores of the individual aortic segments. This approach provides a fast and low-cost assessment of location and severity of aortic atherosclerosis. The scoring systems are a practical tool to follow the progress of aortic calcification. Furthermore, these measure have been applied to several studied that investigate the correlates and outcomes of aortic calcification (8, 31). Kiel et al. performed lateral lumbar spine and hand radiograph between 1966 and 1970 and repeated between 1992 and 1993, to evaluate aortic calcification, according to the Kauppila method (30), and bone mass (by radiogrammetry), in 364 women and 190 men from the original population-based Framingham Heart Study cohort (31). This longitudinal study showed that women with the greatest magnitude of bone loss demonstrate the most severe progression of abdominal aortic calcification, suggested that the two processes may be related (31). The same quantitative method to grade the severity of vascular calcification has been utilized in a recent paper that examines the relation between severity of vascular calcification in middle-age years and subsequent risk of hip fracture in men and women in the population-based Framingham Study (8). In this study, no evidence that vascular calcification increases subsequent risk hip fracture in men or women was found, suggesting that common radiographic finding of aortic calcification cannot be recommended in the clinical setting for identifying persons at increased risk of hip fracture (8). On the contrary, Naves M. et al. have recently demonstrated an independent positive and statistically significant association between the severity of aortic calcifications and osteoporotic fractures, particularly prevalent vertebral fractures; in this study a positive association between the progression of aortic calcifications and the rate of decline in BMD at lumbar spine has been also showed (32).

**Quantitative ultrasound of bone (QUS)**

Quantitative ultrasound (QUS) methods have been introduced for the assessment of skeletal status in osteoporosis and, because of the lack of ionising radiation, relative portability of the equipment, ease of use, and low cost, has seen marked success around the world.

Ultrasound is a mechanical wave vibrating at a frequency range from 20.000 waves/s to 100.000 waves/s; when these waves pass through bone, the physical and mechanical properties of the bone alter the shape, the intensity and the speed of the propagation of the wave. Velocity and attenuation are ultrasound variables commonly evaluated. The velocity of ultrasound wave propagation is determined by the transit time and by the width crossed, and it is expressed as m/s. Current commercial systems for studying the bone use two transducers (a transmitter and a receiver), positioned on each side of the tissue to be measured, or a single transducer that transmits and receives the signal. Attenuation (broadband ultrasound attenuation BUA) of the wave is determined by mechanisms of diffraction, scattering and absorption in the bone, marrow and soft tissue. Absorption predominates in cortical bone and scattering in trabecular bone. Attenuation is a measure of the frequency dependence of the attenuation of ultrasound. This dependence is approximately linear and it is expressed on a logarithmic scale over the range 0.1-1 MHz. The increase in attenuation as a function of the frequency is measured by comparing the amplitude spectrum for a reference material with that of the measured sample. The slope of attenuation (BUA) in dB/MHz is given by linear regression of the spectral amplitude difference. Combined parameters, derived from the mathematical combination of SOS and BUA, have been developed by Lunar (Stiffness) and Hologic (Quantitative Ultrasound Index = QUI). The combination of BUA and SOS into a single parameter has been shown to improve precision; furthermore, from the point of view of clinical interpretation, a single parameter, which combines velocity and attenuation, can simplify interpretation.

Different manufacturers have developed several ultrasound devices since the late 1980s, and continuing improvements have been made in recent years. QUS devices can measure velocity and attenuation at different skeletal sites: calcaneus, phalanxes and tibia. Also “multisite” devices can measure US parameters at different skeletal sites such as radius, phalanxes, calcaneus. The calcaneus, composed almost entirely of trabecular bone is the most studied and validated skeletal site for QUS assessment; in fact, the high percentage of trabecular bone, which has a turnover higher than cortical bone, allows early evidence of metabolic changes. Another good site is the distal metaphysis of the first phalanx of the last four fingers. At this level, both cortical and trabecular bone are present; both of which are sensitive to age-related bone resorption and are appropriate for the evaluation of osteoporotic fracture risk. It is currently accepted that QUS parameters are not only influenced by bone density, but also by bone structure and composition (33). Theory suggests that BUA is determined by bone density and bone microarchitecture, while SOS is influenced by the elasticity of bone as well as by bone density. However, the exact mechanisms of ultrasound interaction with bone and the physical properties measured remain undetermined (33). The

relative contribution to bone assessment of both ultrasound and the current gold standard method for bone assessment, dual x-ray absorptiometry (DXA), is still to be determined; nevertheless, QUS has demonstrated that it is able to detect bone fragility as well as DXA (34-38).
QUS at calcaneus [osteo-sono assessment index (OSI)] to assess osteopenia and brachial-ankle pulse wave velocity (baPWV) to assess atherosclerosis have been utilized in a Japanese study aimed to evaluate the relationship between atherosclerosis and bone mass (39). In this study, a significant negative correlation between baPWV and OSI has been showed suggesting that common or related mechanisms control both atherosclerosis and osteoporosis from the early stages (39).

**Computed tomography**

Quantitative computed tomography (QCT) is a three-dimensional technique that measures BMD volumetrically and that permits separate characterization of bone geometry and bone density as elements of fracture risk. This volumetric measurement removes the confounding influences of bone size and shape and provides an integral measure of cortical and trabecular bone (40). In recent years, sophisticated imaging techniques that combine non-invasive evaluation with high resolution [electron-beam computed tomography (EBCT), multi-detector computed tomography (CT) and ultrafast spiral CT] now detailed assessment of coronary artery disease and arterial calcification *in vivo* (13).
From the same CT axial scans used to obtain bone measurements it is possible quantify the extent of calcification in the aortic wall at the lowest thoracic vertebra (T12) and the first four lumbar vertebrae (L1-L4), using specially designed software (41).
With these methods Schulz et al. investigated the relation between aortic calcification and the number of osteoporotic fractures in 2348 healthy postmenopausal women (41). To determine whether increases in vascular calcification and bone loss progress in parallel, baseline values were compared with measurements obtained 9 months to 8 yr later in a subgroup of 228 women. Aortic calcifications were inversely related to bone density and directly related to fractures. Compared with women without calcification, the odds ratios for vertebral and hip fractures in those with calcification were estimated to be 4.8 (95% confidence interval, 3.6-6.5) and 2.9 (95% confidence interval, 1.8-4.8), respectively. The subgroup analysis of 228 women longitudinally studied showed that the percentage of yearly increase in aortic calcification accounted for 47% of the variance in the percentage rate of bone loss. Moreover, a strong graded association was observed between the progression of vascular calcification and bone loss for each quartile. Women in the highest quartile for gains in aortic calcification had four times greater yearly bone loss (5.3 vs.1.3% yearly) than women of similar age in the lowest quartile (41). Therefore in this study it has been demonstrated that aortic calcifications are a strong predictor for low bone density and fragility fractures (41). A negative relationship between BMD and aortic calcification both assessed by CT, has been recently confirmed in a biracial cohort of 490 middle-aged women in the Study of Women's Health Across the Nation (SWAN study) (42).

**Dual X-ray Absorptiometry (DXA)**

Dual energy X-ray absorptiometry (DXA) measurements of spine and hip bone mineral density (BMD) have an important role as a clinical tool for the evaluation of individuals at risk of osteoporosis, and in helping clinicians give advice to patients about the appropriate use of antifracture treatment. Compared with alternative bone densitometry techniques such QCT and QUS, DXA has a number of significant advantages that include a consensus that BMD results can be interpreted using the World Health Organization (WHO) T-score definition of osteoporosis, a proven ability to predict fracture risk, and proven effectiveness at targeting antifracture treatments (43).
DXA at lumbar spine and femoral neck was utilized in order to investigate the independent association between BMD and the severity of atherosclerosis in a large population of postmenopausal women (N=1456, age range 60-85) using aortic calcification as a marker of cardiovascular disease, in an observational study published in 2003 (44). Aortic calcification was graded on lateral radiographs according to Kauppila (30). In this study the severity score of AAC showed statistically significant negative correlation with BMD at hip, suggesting that severe osteoporosis at hip may indicate advanced atherosclerosis and thereby an increased risk for not only hip fractures but also for coronary heart disease (44). In a prospective epidemiological study successively published from the same group (45), a significant association at baseline between advanced AAC and lower BMD has been demonstrated; considering the annual rate of changes in AAC versus annual rate of changes in hip BMD, women with the most progressive AAC revealed the highest annual rate of bone loss at the hip (45). It has been also demonstrated that the AAC severity was independent predictor of hip fracture after adjustment for age (45, 46).
The visual semiquantitative method for identification of vertebral fractures has been applied to images of the spine acquired by fan-beam DXA devices, and called "instant vertebral assessment" (IVA ) by Hologic and "vertebral fracture assessment" (VFA) by GE/Lunar. The scanner arm of some models of densitometers can be rotated 90°, so that lateral scans can be obtained with the patient in the supine position without repositioning (Figure 1). The main attraction of IVA is that the effective dose-equivalent to the patient is considerably lower than for conventional radiography (47). IVA has been compared with SQ evaluation of spinal radiographs demonstrating good agreement (96.3%, k=0.79) in classifying vertebrae as normal or deformed in the 1978 of 2093 vertebrae deemed analyzable on both the DXA scans and conventional radiographs (48). IVA/VFA showed good sensitivity (91.9%) in the identification of moderate/severe SQ deformities and an excellent negative

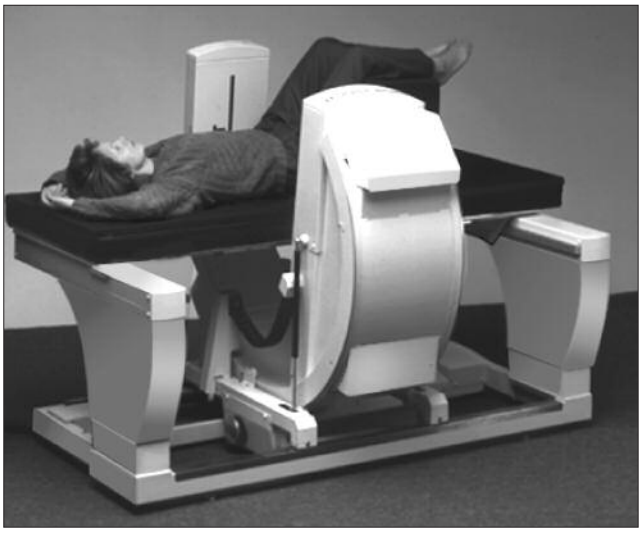

Figure 1 - Detection of Abdominal Aortic Calcification (AAC) with Instant Vertebral Assessment (IVA).

predictive value (98%) to distinguish subjects with very low risk of vertebral fractures from those with possible fractures. The availability of a rapid, low-dose, method for assessment of vertebral fractures, using advanced fan-beam DXA devices, provides a practical means for integrated assessment of BMD and vertebral fracture status. This approach allows the identification of most osteoporotic vertebral fractures, even asymptomatic, in patients with low BMD improving selection of candidates for therapeutic intervention.

A new method for the evaluation of aorta calcification by DXA has been recently suggested: during an IVA scan sufficient soft tissue anterior to the lumbar spine can be included to allow for the detection of calcified plaques in the abdominal aorta (Figure 2). There is good agreement between IVA and lateral radiographs for the detection of AAC (49), similar to the agreement between the two modalities for vertebral fracture detection (48). A quick and simple method was developed for the quantification of AAC (49) and is called AAC-8. The AAC-8 scale estimates the total length of calcification of the anterior and posterior wall of the aorta, assigning a score between 0-4 (Table I). The sum of the two scores for the anterior and posterior walls gives the AAC-8 score; an AAC-8 score greater than two is considered moderate to severe AAC on this scale (49).

IVA's new indication for the detection of AAC may have as much clinical significance as its previous indication for the detection of vertebral fractures.

It has been demonstrated that most patients at high risk for osteoporotic fracture are at high risk for cardiovascular disease (11); therefore, a single IVA exam could assist in stratifying patients into high and low risk groups for two highly prevalent and significant health care problems.

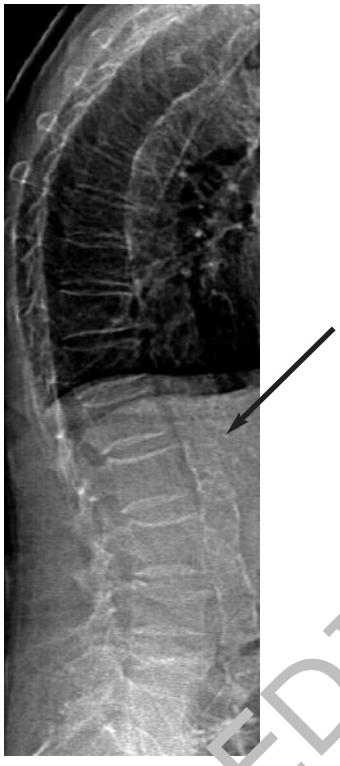

Figure 2 - Hologic fan-beam DXA device.

Table I - AAC-8 scale (49).

| Description | Score |
|---|---|
| No calcification seen | 0 |
| Aggregate length of calcification is < to the height of one vertebra | 1 |
| Aggregate length of calcification is > one, but < to the height of two vertebra | 2 |
| Aggregate length of calcification is > two, but < to the height of three vertebra | 3 |
| Aggregate length of calcification is > to the height of three vertebra | 4 |

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