The link between osteoporosis and cardiovascular disease

Ghada N. Farhat[a]
Jane A. Cauley[b]

[a] Department of Epidemiology and Division of Cancer Prevention and Population Science, University of Pittsburgh, PA, USA
[b] Department of Epidemiology, University of Pittsburgh, PA, USA

Address for correspondence:
Jane A. Cauley, DrPH
University of Pittsburgh
Graduate School of Public Health
Department of Epidemiology
130 DeSoto St, Crabtree A524
Pittsburgh, PA 15261, USA
E-mail: jcauley@edc.pitt.edu

Summary

Cardiovascular disease (CVD) and osteoporosis are common age-related conditions associated with significant morbidity, mortality, and disability.
Traditionally, these two conditions were considered unrelated and their coexistence was attributed to independent age-related processes. However, an increasing body of biological and epidemiological evidence has provided support for a link between the two conditions that cannot be explained by age alone. Several hypotheses have been proposed to explain the link between osteoporosis and CVD including: 1) shared risk factors, 2) common pathophysiological mechanisms, 3) common genetic factors, or 4) a causal association.
This review highlights the epidemiologic literature on the association of bone density with cardiovascular mortality, cardiovascular morbidity, and subclinical measures of atherosclerosis. It also summarizes the different potential mechanisms involved in the link between osteoporosis and CVD.

KEY WORDS: osteoporosis, bone mineral density, cardiovascular disease, atherosclerosis, vascular calcification.

Osteoporosis and cardiovascular disease

Cardiovascular disease (CVD) and osteoporosis are common age-related conditions. Mounting biological and epidemiological evidence supports a link between the two diseases. Low bone mineral density (BMD) has been related to increased cardiovascular mortality, cardiovascular morbidity, and subclinical measures of atherosclerosis in cross-sectional as well as longitudinal epidemiologic studies.

Biological link

Atherosclerotic calcification and bone mineralization share a number of intriguing common features. It is now recognized that calcification of the arterial tissue is not merely a passive process of calcium phosphate precipitation or adsorption in end-stage atherosclerosis, but instead is a highly organized process that is regulated by mechanisms similar to those involved in bone mineralization (1, 2).
The mineral observed in calcium deposits of atherosclerotic plaques has a very similar chemical composition to hydroxyapatite crystals which form the inorganic bone matrix (3, 4). Calcifiable vesicles were isolated from human atherosclerotic aortas (5), suggesting that these may be involved in mineral deposition, similar to "extracellular matrix vesicles" that are secreted from chondrocytes and osteoblasts and are involved in initial bone mineralization. Calcified plaques were also shown to express several bone matrix proteins such as type I collagen, gla (gamma carboxyglutamate)-containing proteins such as osteocalcin (bone-gla protein) and matrix-gla protein, bone morphogenetic protein (BMP)-2 and -4, osteopontin, osteonectin, and bone sialoprotein (3, 6-8). Osteogenic cells, called calcifying vascular cells (CVCs), were identified in atherosclerotic plaques. These are a subpopulation of vascular smooth muscle cells (VSMC) that are capable of osteoblastic differentiation (3, 9). When stimulated by BMP-2 and BMP-4, these cells begin expressing osteoblast genes including alkaline phosphatase, collagen I, and osteocalcin which are needed for bone formation. Other cells involved in bone metabolism including osteoclast-like cells, chondrocyte-like cells, and hematopoietic bone marrow cells were also seen in plaques (10).

Epidemiologic link

Bone mass and cardiovascular mortality

Low BMD and bone loss appear to be risk factors for cardiovascular mortality in both women (11-14) and men (15, 16) (Table I). The Study of Osteoporotic Fractures (SOF) showed that an increase in BMD loss at the hip in the order of one standard deviation (SD) was associated with a 1.3-fold increase in CHD mortality among white women 65 years of age and older. Similarly, calcaneal bone loss was related to increased risk of death due to atherosclerosis [Relative Risk[1] (RR = 1.2, 95% CI = 1.1-1.4) and CHD (RR = 1.3, 95% CI = 1.0-1.6)] (12). In the same cohort, lower broadband ultrasound attenuation (BUA) and calcaneal BMD were related to higher cardiovascular death (11), and decreased BMD of the proximal radius was related to increased risk of stroke mortality (RR = 1.91, 95% CI 1.25-2.92) (14). In a population of Danish women, low bone mineral content in the forearm at the menopause was associated with an increased cardiovascular death later in life (RR = 2.3 per SD decrease in BMD, 95% CI 1.0-4.9). In the same study, a prevalent vertebral compression fracture was independently associated with cardiovascular death in late postmenopausal women (RR = 2.0, 95%CI 1.4-3.3) (13).
Similar results were observed in men. Results from the NHANES I Epidemiologic Follow-up Study indicated that low phalangeal BMD was a significant predictor of subsequent car-

[1] Relative Risk (RR) was used to refer to both Risk Ratios and Hazard Ratios.

Table I - Summary of epidemiologic studies of BMD and cardiovascular mortality.

Author	Design	Study	Population	BMD measurement	Mortality	Result	Comment
Mussolino et al., 2003	Prospective (median follow-up= 18.5 years)	NHANES I Epidemiologic Follow-up Study	White and black, men and women, 45-74 years, n=3501	Phalangeal BMD (RA)	Mortality (total, cardiovascular, non-cardiovascular)	– 1 SD lower BMD in white men was associated with 14% increase in CVD mortality, 16% increase in all-cause mortality, and 21% non-cardiovascular mortality – 1 SD lower BMD in white women was associated with 26% increase in non-cardiovascular mortality – 1 SD lower BMD in blacks was associated with 22% increase in all-cause mortality, and 41% increase in non-cardiovascular mortality	Adjusted for age, smoking, alcohol, diabetes, heart disease, education, BMI, physical activity and blood pressure medications
Mussolino et al., 2003	Prospective	NHANES I	White and black men and women, 45-74 years, n=3402	Phalangeal BMD (RA)	Stroke mortality	No association between BMD and stroke mortality	Adjusted for age, smoking, alcohol consumption, history of diabetes, history of heart disease, education, BMI, physical activity, and blood pressure medications
Bauer et al., 2002	Prospective (average follow-up= 5 years)	SOF	White, postmenopausal women, 70 years and older, n= 5816	– Broadband ultrasound attenuation (BUA) (CUS) – Total hip BMD (DXA) – Calcaneal BMD (SXA)	Total and cause-specific mortality (CVD, cancer)	– 1 SD decease in BUA was associated with 19% increase in CV mortality (95% CI 1.04-1.37) – 1 SD decrease in calcaneal BMD was associated with 17% increase in CV mortality (95% CI 1.01-1.37) – BUA, calcaneal and hip BMD associated with total mortality	Adjusted for age, weight, height, health status, smoking, physical activity, history of diabetes, hypertension, cancer, CVD, and stroke
Trivedi et al., 2001	Prospective (average follow-up= 6.7 years)	The Cambridge General Practice Health Study	White men, 65-76 years, n= 1002	Total hip BMD (DXA)	Mortality (all-cause, cardiovascular)	– 1 SD increase in BMD associated with 28% reduction in CVD mortality and 29% reduction in all-cause mortality	Adjusted for age, BMI, smoking, cholesterol, SBP, past history of MI, stroke, or cancer, physical activity, alcohol, and general health status
Kado et al., 2000	Prospective (average follow-up= 3.2 years)	SOF	White, postmenopausal women, 65 years and older, n= 6046	– Calcaneal bone loss (SPA, for a mean of 5.7 years) – Hip bone loss (DXA, for a mean of 3.5 years)	Mortality (CHD, stroke, atherosclerosis, cancer , all other causes)	– 1 SD increase in hip BMD loss associated with CHD mortality (RH=1.3), total mortality (RH=1.3), and pulmonary disease mortality (RH=1.6) – 1 SD increase in calcaneal bone loss associated with CHD (RH=1.3), atherosclerosis (RH=1.3), and all causes mortality (RH= 1.1)	Adjusted for age, baseline BMD, diabetes, hypertension, incident fractures, smoking, physical activity, health status, weight loss, calcium use
von der Recke et al., 1999	Retrospective cohort	Danish Study	White, early postmenopausal (5,216 years of follow-up) and late postmenopausal (6,292 years of follow-up) women, n= 1,063	–Bone mineral content of the distal forearm (SPA) – Vertebral fractures (radiography)	Mortality (cerebrovascular disease, heart disease, vascular disease, cancer)	– In early postmenopausal women: 1 SD decrease in BMC associated with increase in total mortality (RR= 1.4) and cardiovascular death (RR= 2.3). – In late postmenopausal women: 2 SD decrease in BMC associated with CVD mortality (RR= 3.2, p=.005), cardiovascular mortality (RR= 5.2, p=.002), and MI mortality (RR= 4.2, p=.01); a prevalent vertebral compression fracture associated with CVD death (RR= 2.0).	Adjusted for age, systolic blood pressure, diastolic blood pressure, BMI, cholesterol levels, smoking
Browner et al., 1991	Prospective (average follow-up= 2.8 years)	SOF	White, postmenopausal women, 65 years and older (n= 9704)	Distal radius, proximal radius, and calcaneal BMD (SPA)	Mortality (all-cause, stroke)	– 1 SD decrease in proximal radius BMD was associated with 1.91-fold increase in stroke mortality (95% CI 1.25-2.92). – Calcaneal and proximal radius BMD were significantly associated with all-cause mortality in age-adjusted analysis. Associations became not significant after adjusting for covariates including measures of general health.	Stroke mortality: adjusted for history of previous stroke, hypertension, postmenopausal use of estrogen, thiazide diuretic treatment, diabetes mellitus, and smoking

Table II - Summary of epidemiologic studies of BMD and cardiovascular morbidity.

Author	Design	Study	Population	BMD measurement	CVD endpoint	Result	Comment
Farhat et al., 2007	Prospective (average follow-up of 5.4 years)	Health ABC	2,310 participants, 55% women, 42% black, aged 68-80 years	– Areal BMD (aBMD) measures of the hip – Volumetric BMD (vBMD) measures of the spine (integral, trabecular, cortical)	Incident CHD, cerebrovascular disease, or carotid artery disease	– In women: – In men: Spine vBMD measures were inversely associated with incident CVD in white men HR(integral)= 1.39, 95%CI 1.03-1.87; HR(cortical)= 1.38, 95%CI 1.03-1.84), but not in black men	–
Farhat et al., 2006	Cross-sectional	Health ABC	3,075 participants, 51% women, 42% black	– Areal BMD (aBMD) measures of the hip – Volumetric BMD (vBMD) measures of the spine (integral, trabecular, cortical)	Prevalent CVD (CHD, peripheral arterial disease, cerebrovascular disease, or congestive heart failure)	– In women, for each SD decrease in integral vBMD, cortical vBMD, or trochanter aBMD, the odds of CVD were significantly increased by 28%, 27%, and 22%, respectively. – In men: spine vBMD measures were inversely associated with CVD in men (OR(integral)= 1.34, 95%CI 1.10-1.63; OR(trabecular)= 1.25, 95%CI 1.02-1.53; OR(cortical)=1.36, 95%CI 1.11-1.65)	–
Tanko et al., 2005	Prospective (4-years follow-up)	MORE Study	2,576 postmenopausal women assigned to the placebo arm of the MORE trial, mean age= 66.5 years.	– Osteoporosis (=having a vertebral fracture or a total hip BMD t-score of -2.5 or less) – Low bone density (having a t-score greater than -2.5 but less than -1.0 without vertebral fractures)	Incidence of fatal and non-fatal cardiovascular events (coronary events and cerebrovascular events)	– Women with osteoporosis had a 3.9-fold increased risk for cardiovascular events, compared to those with low bone mass – Presence of at least 1 vertebral fracture, versus no vertebral fracture, was associated with a 3.0-fold increased risk for cardiovascular events	– Did not exclude prior CVD – 53% had osteoporosis, rest had low bone mass – Did not adjust for physical activity
Magnus et al., 2005	Cross-sectional	NHANES III	5,050 African-American, Mexican-American, and Caucasian men and women. Aged 50-79 years	Total hip BMD (DXA)	Myocardial infarction	– Previous MI was associated with low BMD in the total group (OR= 1.28, 95% CI 1.01-1.63) and in men (OR= 1.39, 95% CI= 1.03-1.87). – No association in women	– Associations present only after adjusting for covariates
Marcovitz et al., 2005	Retrospective	Ambulatory adult patients	209 patients, 89% women, 91% white, average age= 67 years	Spine, femur, ultradistal radius, and 1/3 distal radius (DXA)	Angiographically-determined coronary artery disease (≥50% luminal narrowing in a major artery)	– Osteoporosis was an independent predictor of CAD (OR= 5.6, 95%CI 2.6-12.0)	– Most of patients (75%) were diagnosed with osteoporosis/ osteopenia. – 56% had significant CAD. – DEXA and coronary angiogram performed within a 12-month period
Samelson et al., 2004	Prospective (30-year follow-up)	The Framingham Study	White, men and women, 47-80 years, (n= 2,059)	Relative metacarpal cortical area (Radiogrammetry)	Incident CHD	– In women, highest MCA quartile was related to a 73% reduced risk of CHD incidence compared to lowest quartile. – No association in men	Adjusted for age, education, BMI, smoking, alcohol, systolic blood pressure, cholesterol, HDL, and diabetes
Jørgensen et al., 2001	Case-control	Norwegian Study	White men and postmenopausal women, age ≥ 60 years, n= 260	Femoral neck BMD (DXA)	Acute stroke	– 1 SD decrease in BMD was associated with 1.9 fold increase in odds of stroke. – No significant association in men	Adjusted for BMI, alcohol, previous MI, and medication for hypertensive
Mussolino et al., 2003	Prospective	NHANES I	White and black, men and women, 45-74 years, n=3402	Phalangeal BMD (RA)	Stroke incidence	Incidence of stroke was not associated with a decrease in BMD in white men, white women or blacks	Adjusted for age, smoking, alcohol consumption, history of diabetes, history of heart disease, education, BMI, physical activity, and blood pressure medications
Laroche et al., 1994	Cross-sectional		18 men	BMC of legs (DXA)	Symptomatic peripheral arterial disease	BMC of the more severely affected leg was lower significantly lower than BMD of the less affected leg	–
Browner et al., 1993	Prospective (1.98-years follow-up)	SOF	White, postmenopausal women, 65 years and older, n= 4024	Calcaneal BMD (SPA)	Incident stroke	– 1 SD decrease in calcaneal BMD was associated with 1.31 fold increase in stroke	Adjusted for age, follow-up time, diabetes, systolic blood pressure, alcohol, smoking, HRT use, cognitive ability, grip strength, and functional ability

diovascular mortality among white men aged 45 to 74 years (RR = 1.16, 95% CI 1.0-1.30). This association, however, was not present in white women or blacks (15). In another prospective study, low bone density at the hip was found to be a significant predictor of cardiovascular mortality in a cohort of British men aged 65-76 years (16).
Contrary to the above studies, Mussolino et al. did not find a significant association between BMD and stroke mortality in white men, white women, or blacks in NHANES I (17).

Bone mass and cardiovascular morbidity

A number of studies have investigated the association between BMD and cardiovascular morbidity (Table II). In a cross-sectional analysis from the Health, Aging, and Body Composition (ABC) Study, we observed that volumetric BMD (vBMD) measures of the spine were significantly and inversely associated with prevalent CVD in men and women, and areal BMD (aBMD) of the trochanter was related to CVD in women (18). In a longitudinal analysis from the same cohort, we found that vBMD measures of the spine were associated with incident CVD in white men, but not in blacks. In women, aBMD measures of the total hip, femoral neck, and trochanter exhibited significant relationships with incident CVD in black women, but not in whites. All of these associations were independent of age and shared risk factors between osteoporosis and CVD, and were not explained by inflammatory cytokines or oxidized LDL (Tables III and IV) (19).
Other studies have reported significant associations between osteoporosis and CVD in women. Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial indicated that os-

Table III - Effect of controlling for IL-6, TNF-α, or oxLDL on the adjusted associations of aBMD measures with incident CVD in black women, the Health, Aging, and Body Composition Study.

BMD	N at risk (events)	Adjusted for risk factors* Hazard Ratio (95% CI)	Adjusted for risk factors + IL-6, TNF-α, or oxLDL** Hazard Ratio (95% CI)
Total Hip aBMD			
IL-6	502 (84)	1.39 (1.09-1.83)[a]	1.39 (1.06-1.82)[a]
TNF-α	486 (77)	1.32 (0.99-1.76)	1.33 (1.00-1.77)
oxLDL	524 (86)	1.32 (1.02-1.72)[a]	1.35 (1.03-1.77)[a]
Femoral Neck aBMD			
IL-6	502 (84)	1.51 (1.14-1.99)[b]	1.49 (1.13-1.96)[b]
TNF-α	486 (77)	1.46 (1.09-1.96)[a]	1.48 (1.10-1.98)[b]
oxLDL	524 (86)	1.42 (1.09-1.86)[b]	1.44 (1.09-1.89)[b]
Trochanter aBMD			
IL-6	502 (84)	1.36 (1.05-1.77)[a]	1.35 (1.05-1.74)[a]
TNF-α	486 (77)	1.32 (1.01-1.73)[a]	1.31 (1.01-1.72)[a]
oxLDL	524 (86)	1.32 (1.02-1.69)[a]	1.34 (1.03-1.72)[a]

* Models in women were adjusted for age, study site, physical activity, Health ABC physical performance score, BMI, cholesterol, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs, calcium supplements, and oral estrogen.
** oxLDL models did not include cholesterol level due to the high correlation between the two measures.
[a] p<0.05
[b] p≤0.01

Table IV - Effect of controlling for IL-6, TNF-α, or oxLDL on the adjusted associations of vBMD measures with incident in white men, the Health, Aging, and Body Composition Study.

BMD	N at risk (events)	Adjusted for risk factors* Hazard Ratio (95% CI)	Adjusted for risk factors + IL-6, TNF-α, or oxLDL** Hazard Ratio (95% CI)
Integral vBMD			
IL-6	280 (62)	1.37 (1.01-1.86)[a]	1.38 (1.02-1.88)[a]
TNF-α	276 (63)	1.40 (1.04-1.89)[a]	1.40 (1.04-1.89)[a]
oxLDL	292 (66)	1.39 (1.04-1.87)[a]	1.41 (1.05-1.89)[a]
Cortical vBMD			
IL-6	280 (62)	1.37 (1.02-1.85)[a]	1.38 (1.02-1.86)[a]
TNF-α	276 (63)	1.39 (1.03-1.86)[a]	1.38 (1.03-1.85)[a]
oxLDL	292 (66)	1.39 (1.04-1.85)[a]	1.41 (1.05-1.88)[a]

* Models in men were adjusted for: age, study site, education, physical activity, Health ABC physical performance score, BMI, HDL, LDL, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs.
** oxLDL models did not include LDL level due to the high correlation between the two measures.
[a] p<0.05

teoporosis was a strong predictor of incident cardiovascular events in postmenopausal women independent of age and other traditional cardiovascular risk factors (adjusted RR = 3.9, 95% CI 2.0-7.7) (20). Osteoporosis was also associated with angiographically-determined coronary artery disease in a retrospective analysis of a population predominantly of women referred for angiography and BMD assessment (21). A report from the 30 year follow-up of the Framingham study found that metacarpal cortical area (MCA) predicts coronary heart disease in women free from CVD at baseline, with a significant trend of decreasing coronary heart disease risk with increasing MCA (RR for highest vs. lowest MCA quartile = 0.73, 95% CI 0.53-1.00, p for trend = 0.03). No association, however, was observed in men in this study (22). In SOF, low calcaneal bone mass was significantly associated with stroke incidence (RR = 1.31 per SD, 95%CI 1.03-1.65) (23). In line with these findings, low femoral neck BMD was associated with an increased odds of stroke in women, but not in men, in a Norwegian population (24).

Similar associations were also reported in men. A History of myocardial infarction was associated with low BMD in a multiethnic population of men in the Third National Health and Nutrition Examination Survey (NHANES III) (25). Additionally, in a study involving 18 men with asymmetrical symptomatic peripheral arterial disease, bone mineral content was shown to be significantly lower in the affected compared to the unaffected leg (26).

In contrast to the above studies, and consistent with their mortality finding, Mussolino et al. found no relationship between BMD and stroke incidence among white men, white women or blacks in NHANES I (17).

Bone mass and subclinical atherosclerosis

An inverse relationship between bone mass and various measures of subclinical disease, especially in women, has been reported by many studies (Table V). Cross-sectionally, vascular calcification, in both the aorta (27-33) and the coronary arteries (34, 35) was found to be negatively correlated with bone density (28-33) and directly related to vertebral and hip fractures, (28, 29) predominantly in white postmenopausal women. We observed an inverse cross-sectional association between trabecular BMD of the spine and aortic calcification in a biracial cohort of healthy middle-aged women from the Study of Women's Health Across the Nation (SWAN). This association was not age-related, was independent of shared risk factors between BMD and calcification, and was not influenced by estradiol. Meanwhile, we noted no associations with coronary artery calcification after adjusting for age (Fig. 1) (27).

The progression of aortic calcification was also linked to volumetric trabecular BMD loss in white postmenopausal women, (28) and to metacarpal bone loss in women in the Framingham study and in a Dutch population-based longitudinal study (31, 36).

Ankle-arm index was positively correlated with BMD in an elderly population of Chinese men and women (37) and in European postmenopausal women (38). In SOF, women with the highest decline in AAI were shown to have the largest magnitude of bone loss (39).

Femoral artery intima-media thickness was negatively related to calcaneal osteo-sono assessment index (OSI) in a population of Japanese men and women (40). In another small group of postmenopausal Japanese women, higher carotid plaque score was significantly associated with lower total BMD (41). Low BMD was also related to echogenic calcified carotid artery plaques in a large population of Norwegian men and postmenopausal women (42). And in a small case-control study in an Italian population of men and postmenopausal women, patients with atherosclerotic involvement of the carotid and/or femoral artery had low bone mass, and significantly lower osteocalcin and bone-specific alkaline phosphatase than controls (43). In another Italian population of postmenopausal women, the prevalence of carotid atherosclerosis was higher among women with low BMD and osteocalcin levels above the median (44).

Additionally, pulse wave velocity (PWV), a marker of early stage atherosclerosis, was inversely associated with calcaneal quantitative OSI in a large Japanese population with a median age of 50 years. This association was stronger in women than men and in pre-menopausal than postmenopausal women (45). A recent report on forearm endothelial function and spine BMD in early postmenopausal Japanese women indicated that osteoporotic women had a lower maximal forearm blood flow response to reactive hyperemia than those with normal BMD or osteopenia (46).

Other studies have failed to observe an association between osteoporosis and subclinical measures of atherosclerosis. In the Framingham Study, vascular calcification was not found to increase long-term hip fracture risk (47). In SOF, no significant association was observed between aortic calcification and bone density at the hip, spine, or calcaneus after adjusting for age; only a weak association with radial BMD was noted (48). These findings were consistent with others reported by Frye et. al. among women in Rochester, Minnesota (49), by Aoyagi et. al. in Japanese-American women (50), and by Anderson et al. in a population of British men and women (51).

Limitations of the existing epidemiologic literature

Most of the previous reports relied on white postmenopausal women and blacks have been excluded from analyses due to their reduced risk for osteoporosis and fractures (11-14, 20-24, 28-30, 32, 34, 36, 39, 44, 48, 49). Given the well-known racial differences in the burdens of CVD and osteoporosis, an investigation into the association between the two diseases in separate ethnic groups is warranted.

Additionally, a number of studies did not exclude people with baseline CVD from analyses (11, 12, 14-17, 20, 23, 24, 28, 30, 31, 36-39, 42, 44, 48, 50). Therefore, those associations might have been confounded by factors such as reduced physical activity ensuing from CVD, which in itself contributes to lower BMD.

In a large number of studies, bone mass was determined using radiographic techniques, single-photon or single X-ray absorptiometry, or dual-photon absorptiometry (13-15, 17, 22, 23, 31, 33, 36, 42, 44, 45, 50, 51). Some studies have employed DXA in bone determination (11, 12, 16, 20, 21, 24-26, 29, 30, 34, 35, 37-41, 43, 46, 48); however, this technique is limited by its 2-dimensional areal assessment of BMD which does not adjust for bone size. This is especially important in studies of different ethnic and gender groups since there are well-established differences in bone size by race and gender (52, 53). DXA is also affected by the presence of extra-osseous calcium such as aortic calcification and degenerative osteoarthritic changes, which get incorporated in the region of interest and lead to a falsely increased bone density at the spine (32). This is an important drawback, particularly in the elderly who have an increased prevalence of such degenerative conditions (54). Quantitative computed tomography (QCT) allows for a three-dimensional volumetric determination of bone density, an adjustment for bone size, and an assessment of purely trabecular bone. Only a few studies have utilized QCT for BMD assessment (18, 19, 27, 28, 32).

Another limitation for the existing epidemiologic studies is that some reports did not sufficiently control for important covariates including physical activity, lipids, blood pressure, and the use of medications such as statins (11, 12, 14, 15, 17, 20, 23, 24, 26, 28, 31-39, 41, 43, 46, 48, 50, 51).

Table V - Summary of epidemiologic studies of BMD and subclinical measures of atherosclerosis.

Author	Design	Study	Population	BMD measurement	Subclinical atherosclerosis measure	Result	Comment
Aortic calcification							
Farhat et al., 2007	Cross-sectional	Study of Women's Health Across the Nation	White and black women, 45-58 years, n = 490	Trabecular volumetric BMD (EBCT)	Aortic calcification (AC) (EBCT)	– Per 1 SD decrease in BMD, the adjusted odds of high AC relative to no AC was significantly increased by 68% (95% CI: 1.06-2.68)	– No associations with moderate AC – Estradiol did not influence this association
Schulz et al., 2004	– Cross-sectional – Retrospective cohort (2.1 years of follow-up on average)	Study at Loma Linda University Medical Center	White postmenopausal women, 50 years and older, n= 1848 for cross-sectional and 228 for longitudinal	– Trabecular volumetric BMD (EBCT) – Vertebral and hip fractures (CT radiographs)	Aortic calcification (AC) (EBCT)	– BMD significantly associated with AC, adjusted for age (AC predicted 26% of the variance in BMD). – The odds ratios for vertebral and hip fractures in those with calcification, compared to those without AC, were 4.8 (95% CI 3.6-6.5) and 2.9 (95% CI 1.8-4.8), respectively. – Yearly rate of change in aortic calcification significantly related to yearly rate of bone change (r^2 = 0.471, p<.001)	– 70% of population had osteoporosis, 30% had at least one vertebral fracture – 76% had AC. – Sample selected from review of medical records
Tanko et al., 2004 (abstract)	Cross-sectional	Prospective Epidemiological Risk Factor Study, Denmark	Postmenopausal women, aged 60-85 years, n=5409	Hip, spine, and radius BMD (DXA)	Aortic calcification (Radiography)	– Age adjusted BMD was inversely related to AC severity at the hip and forearm. – RR of vertebral fractures was increased by 29% in the highest compared with the lowest AC quartile	– Age adjusted – 10% had manifest CVD
Tanko et al., 2003	Cross-sectional	Prospective Epidemiological Risk Factor Study, Denmark	Postmenopausal women, aged 60-85 years, n= 963	Hip, spine, and radius BMD (DXA)	Aortic calcification (Radiography)	– AC contributed significantly and independently to variations in hip BMD. – No association between spine or radius BMD and AC	Adjusting for intermittent claudication did not alter the association between AC and hip BMD
Kiel et al., 2001	Prospective cohort (25 year follow-up)	Framingham Heart Study	White, men and women, 47-80 years, (n= 554)	Relative metacarpal cortical area (Radiogrammetry)	Aortic calcification (Radiography)	– Significant association between percent change in MCA and change in AC in women (for each % decline in MCA, the AC index increased by 7.7%, p= 0.01). – No association in men	Adjusted for recognized risk factors for atherosclerosis
Hak et al., 2000	– Longitudinal (9 years of follow-up) – Cross-sectional	Dutch Study	White premenopausal (n=236) and postmenopausal women (n=720), 45-64 years old	Relative metacarpal cortical area (Radiogrammetry)	Aortic calcification (Radiography)	– Significant association between the extent of aortic calcification and metacarpal bone mass – Metacarpal bone loss was higher in premenopausal women (at baseline) with progression of AC than women with no progression (adjusted change in MCA= -3.5 mm^2 vs. -2.0 mm^2, respectively, p<.01)	In women already postmenopausal at baseline, no association was found between progression of aortic calcification and metacarpal bone loss
Aoyagi et al., 2001	Cross-sectional	Hawaii Osteoporosis Study	Japanese-American women, n= 524	BMD at distal and proximal radius and calcaneus (SPA)	Aortic calcification (Radiography)	– BMD (mean SD for all 3 sites) was not significantly associated with AC after adjusting for age.	– Associations between BMD and AC were significant before adjusting for age – Age, SBP, physical activity, and smoking were independently associated with AC.
Vogt et al., 1997	Cross-sectional	SOF	White postmenopausal women, 65 years and older, n= 2051	– Hip and spine BMD (DXA) – Calcaneal, proximal and distal radius BMD (SPA)	Aortic calcification (Radiography)	– All sites, except spine, were significantly associated with AC in unadjusted analysis. – After adjusting for age and other risk factors, all associations become not significant, except for BMD at the proximal and distal radius	– Adjusted for age, BMI, estrogen use, smoking, exercise, and diabetes. – Significant association with radial BMD was attributed to Type I error

Table V - *(continued)*

Author	Design	Study	Population	BMD measurement	Subclinical atherosclerosis measure	Rsesult	Comment
Banks et al., 1994	Cross-sectional	Therapeutic RCT for prevention of postmenopausal bone loss	White early postmenopausal women, age 49-64 years, n for AC analysis= 170	– Hip and spine BMD (DPA) – Spine BMD (QCT)	Aortic calcification (defined using combination of radiography and CT)	– Women with aortic calcification had lower QCT spine BMD and DPA hip BMD compared to those without calcification	– Purpose of study was to look at degenerative change and extra-osseous calcification in general, not AC specifically. – Higher DPA spine BMD was found in women with spinal degenerative calcification – Adjusted for age, time since menopause, weight and height
Frye et al., 1992	Cross-sectional	Study in Rochester, Minnesota	White women 50 years and older, n= 200	– Vertebral fracture – BMD	Aortic calcification (Radiography)	– In age-adjusted analysis, AC was positively correlated with BMD at lumbar spine only – The association between AC and vertebral fractures and BMD at other sites were not significant after adjusting for age	–
Boukhris et al., 1972	Cross-sectional	Study in George Washington University	White and Black women (n=290) and White and Black men (n=299)	Osteoporosis of the lumbar spine (normal, moderate, severe) (Radiography)	Aortic calcification (Radiography)	Positive correlation between osteoporosis and AC in all race and gender groups	Adjusted for age only
Anderson et al., 1964	Cross-sectional		Men and women attending bone clinic, n= 823	– Spine osteoporosis (defined using relative vertebral density) and metacarpal osteoporosis (defined using cortico/ medullary ratio) (Radiography)	Aortic calcification (Radiography)	– Significant associations between prevalence of osteoporosis and AC in both genders – Associations were eliminated after stratifying by age, except for AC and hand osteoporosis in men 70-79 years old	–
Coronary calcification							
Farhat et al., 2007	Cross-sectional	Study of Women's Health Across the Nation	White and black women, 45-58 years, n= 490	Trabecular volumetric BMD (EBCT)	Coronary calcification (CAC) (EBCT)	– Per 1 SD decrease in BMD, the odds of high CAC relative to no CAC was increased by 35% (95% CI: 1.08 - 1.70) – Association disappeared after adjusting for age	–
Ramsey-Goldman et al., 2001	Cross-sectional	Pilot study	13 women with Systemic Lupus Erythematosus, mean age= 45 years, 40% menopausal, 95% white	Lumbar spine and total hip BMD (DXA)	Coronary artery calcification (EBCT)	– Correlation between CAC and spine BMD= -0.57 (p=0.04) – Correlation between CAC and hip BMD= -0.55 (p=0.05)	Unadjusted results
Barengolts et al., 1998	Cross-sectional	–	Postmenopausal women, n=45	Lumbar spine and hip BMD (DXA)	Coronary calcification (CAC) (EBCT)	– CAC was significantly higher in the osteoporotic women compared with the control group – Negative correlation between CAC and hip BMD (r=-0.34, p=.002)	Unadjusted results

Table V - *(continued)*

Author	Design	Study	Population	BMD measurement	Subclinical atherosclerosis measure	Result	Comment
Ankle-arm index							
Wong et al., 2005	Cross-sectional	Mr. and Ms Os (Hong Kong)	3[illegible]8 Chinese men and women 65 years and older	Lumbar spine and total hip BMD (DXA)	Ankle-arm index (<0.9)	– A 1 SD increase in AAI was associated with an increase in hip BMD of 0.5%. – No significant association between AAI and spine BMD	– Associations were not significant when stratified by gender. – Did not exclude CVD but adjusted for it
van der Klift et al., 2002	Cross-sectional	Rotterdam Study	Men and women, age 55 years and older, n=5268	Femoral neck and spine BMD (DXA)	Ankle-arm index (<0.9)	– Low femoral neck BMD was associated with PAD in women (OR= 1.35, 95%CI 1.02-1.79) – No association between spine BMD and PAD in men or women	– Did not exclude those with history of CVD. But results did not change after excluding subjects with prevalent MI, intermittent claudication, or current use of diuretics – Adjusted for age, BMI, SBP, smoking, cholesterol, walking, age at menopause, estrogen use
Vogt et al., 1997	Cross-sectional and longitudinal (6 years of follow-up)	SOF	White, postmenopausal women, 65 years and older, n= 1292	– Hip and spine BMD (DXA) – Calcaneal and radius BMD (SPA)	Ankle-arm index	– AAI was positively correlated with BMD at the total hip, calcaneus and the distal and proximal radius in age-adjusted analysis (a decrease in AAI of 2 SD was associated with a 3.7% decrease in hip BMD (95%CI 1.7-5.8; age-adjusted) – Significant age-adjusted positive correlation between annual change in hip BMD and annual change in AAI – Rate of bone loss in the hip and calcaneus was higher in women whose annual AAI decrease was more than 1 SD above the mean, compared to those whose change was within 1 SD around the mean (association remained after adjustments)	– The age-adjusted associations between AAI and BMD measures disappeared after adjusting for smoking and BMI – AAI >1.5 was excluded from analysis. Intima-Media Thickness and Carotid Plaque
Intima-media thickness and carotid plaque							
Yamada et al., 2005	Cross-sectional	Healthy Japanese population	106 males and 154 females, mean age= 51.4 years	– Spine BMD (DXA) – Calcaneal OSI (QUS)	Carotid and femoral artery IMT	– Femoral artery IMT was significantly associated with calcaneus OSI – No associations with spine BMD	Adjusted for gender, age, BMI, SBP, smoking, LDL, physical functioning
Jørgensen et al., 2004	Cross-sectional, Population-based	Trømso Study, Norway	Men (n=2,543) and postmenopausal women (n=2,726), aged 55-74 years	Distal and ultradistal forearm BMD (SPA)	– Carotid atherosclerotic plaque score (B-mode ultrasonography) – Plaque echogenicity	– Prevalence of echogenic plaques was lower in highest BMD quartile compared to lowest (OR=0.51, 95%CI 0.31-0.83) – No association between BMD and echolucent plaques	– Pooled results for men and women – Results for ultradistal forearm were similar to distal and were not reported – Did not exclude those with history of CVD
Pennisi et al., 2004	Case-control	Italian Study	36 white men and postmenopausal women with peripheral atherosclerosis, 30 age and gender-matched controls	– Lumbar spine, total body, and total hip BMD (DXA) – BUA (QUS) – Bone turnover markers	– Common carotid and femoral artery IMT (B-mode ultrasound imaging) – Plaque score – Plaque echogenicity	– High occurrence of osteoporosis in cases – Osteocalcin and bone-specific alkaline phosphatase were lower in cases than controls	–

Table V - *(continued)*

Author	Design	Study	Population	BMD measurement	Subclinical atherosclerosis measure	Result	Comment
Montalcini et al., 2004	Cross-sectional	Italian Study	White postmenopausal women, aged 45-75 years, n= 157	Calcaneal BMD (QUS)	– Carotid intima-media thickness – Carotid plaque.	The prevalence of carotid atherosclerosis was increased in women with low BMD and osteocalcin levels above the median compared to women with low BMD and osteocalcin levels below the median (61% vs 29%, p<.05)	Women with low BMD did not have higher prevalence of atherosclerosis
Ramsey-Goldman et al., 2001	Cross-sectional	Pilot study	85 women with Systemic Lupus Erythematosus, mean age= 45 years, 40% menopausal, 95% white.	Lumbar spine and total hip BMD (DXA)	Carotid plaque index and IMT (B-mode ultrasonography)	– Women in the middle and lowest tertiles of hip BMD had higher carotid plaque index than those in the highest tertile of BMD – No association with IMT was observed	Unadjusted results
Uyama et al., 1997	Cross-sectional	Japanese Study	Postmenopausal women, 67-85 years, n=30	Lumbar spine and total BMD (DXA)	Carotid atherosclerotic plaque score (B-mode ultrasonography)	– Total BMD negatively correlated with plaque score in unadjusted (r=0.55, p<.0002) and adjusted analysis (r=0.54, p<.01). – No association with spine BMD	Total cholesterol was also correlated with plaque score in adjusted analysis
Pulse wave velocity							
Hirose et al., 2003	Cross-sectional	Japanese study	Men and women, 21-81 years, n= 7865	Calcaneal OSI (QUS)	Brachial-ankle pulse wave velocity	– OSI negatively correlated with PWV in both genders	All subjects had normal ankle-arm index
Endothelial function							
Sanada et al., 2004	Cross-sectional	Japanese study	Postmenopausal women, average age 53.8 years, without a history of smoking or diabetes, n= 110	Lumbar spine BMD (DXA)	Endothelial function: forearm blood flow (FBF) at baseline, during reactive hyperemia, and after the administration of sublingual nitroglycerine	Women with osteoporosis had a lower maximal FBF response to reactive hyperemia than those with normal BMD or osteopenia	ANCOVA adjusted for age, BMI, time since menopause, and basal FBF

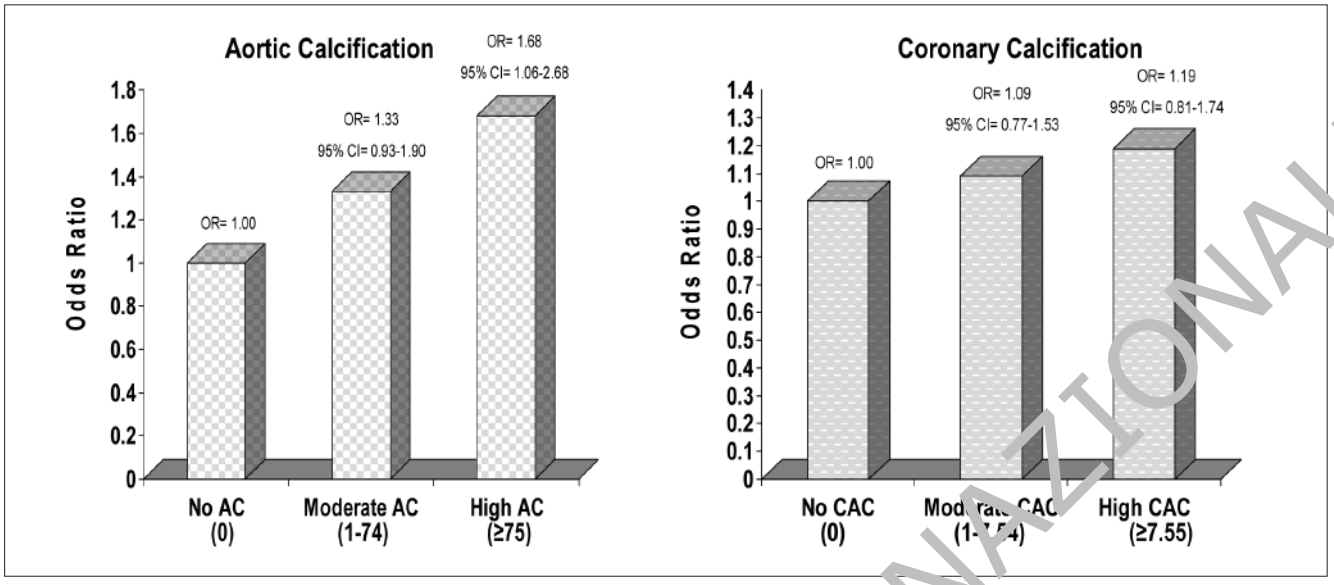

Figure 1 - Adjusted odds ratios for moderate and high aortic and coronary calcification* (relative to no calcification) per 1SD decrease in vBMD**
* Aortic calcification model: adjusted for age, race, study site, menopause status, educational level, smoking status, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level. Coronary artery calcification model: adjusted for age, race, study site, menopause status, alcohol drinking, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level.
** vBMD SD= 37.2 mg/cc

Potential mechanisms for the link between osteoporosis and cardiovascular disease

The nature of the putative link between osteoporosis and cardiovascular disease remains unclear. Traditionally, these two conditions were considered unrelated and their progression was attributed to independent age-related processes (48-50). However, recent evidence from many studies points to a link between osteoporosis and CVD that cannot be explained by age alone. While this evidence has been consistent in older populations, further support for the role of factors other than age is derived from observations in younger populations. For instance, osteoporotic fractures and cardiovascular outcomes have been shown to coexist in young women with systemic lupus erythematosus (SLE), an autoimmune systemic inflammatory disease that predominantly affects young premenopausal women. The increased risk for both conditions in this young group suggests that factors beyond age are at play in the pathogenesis of osteoporosis and CVD (35). Several hypotheses have been proposed to explain the link between the two conditions.

1. Shared risk factors

One hypothesis puts forth that the coexistence of osteoporosis and CVD is due to their shared etiological factors (such as smoking, physical activity, alcohol intake, menopause, hypertension, etc), which may simultaneously promote or inhibit atherosclerosis and bone demineralization, and could partly explain the association between the two diseases (16, 30, 55, 56). However, in many epidemiologic studies, the association between osteoporosis and CVD remained even after the adjustment of some of these risk factors.

2. Common pathophysiological mechanisms

Common pathophysiological mechanisms involving inflammatory cytokines, (43) endogenous sex hormones (16, 45), oxidized lipids (57), vitamin K deficiency (58), and vitamin D (59) were implicated in the progression of the two conditions.

Inflammatory markers and cytokines

Inflammation is known to play a central role in all stages of atherogenesis from fatty streak formation to plaque rupture (60), and there is evidence for its involvement in bone loss. Animal models suggest that osteopenia can be induced in rats by triggering a generalized inflammation through the subcutaneous administration of nonspecific irritants (such as magnesium silicate and cellulose) (61). This induced osteopenia was mainly due to inhibition of bone formation (62). Chronic inflammatory diseases such as rheumatoid arthritis, lupus, and Crohn's disease are associated with a significant risk for secondary osteoporosis and fractures. The pathogenesis of osteoporosis in these settings is attributed to systemic inflammatory processes among other factors such as glucocorticoid therapy (63).
Inflammation is a complex process that is mediated by many cytokines including IL-1, TNF-α, and IL-6. Aging is associated with increased levels of circulating inflammatory cytokines such as IL-6 and TNF-α (64). IL-6 was shown to stimulate osteoclasts, thereby increasing the rates of bone remodeling and bone loss (65). This cytokine was also observed to act as a marker of subclinical CVD in elderly people (66) and to predict CVD mortality in relatively healthy people aged 65 years and older (67). TNF-α was also shown to stimulate bone resorption and inhibit bone formation (68). Results from the Health ABC study indicated that TNF-α and IL-6 were significantly associated with prevalent clinical and subclinical disease (69), as well as incident cardiovascular events (70). In the same cohort, elevated levels of these inflammatory cytokines were related to increased risk of fracture (71).
Other cytokines may be involved. The OPG/RANK/RANKL triad, a novel signaling pathway recognized as a key regulator of bone resorption, was also shown to play a role in vascular calcification. OPG deficient mice were found to develop early-onset osteoporosis and calcification of the aorta and renal arteries (72). In another animal study, OPG was shown to be a po-

tent inhibitor of warfarin- and vitamin D-induced arterial calcification at doses known to inhibit bone resorption (73). In epidemiologic studies, low OPG levels were related to higher prevalence of osteoporosis and vertebral fractures (74). Increased osteoprotegerin levels were also associated with higher prevalence of CAD, suggesting that elevated OPG may reflect a compensatory mechanism to prevent further vascular damage (75).

Endogenous sex hormones

Estrogen deficiency has been identified as the major determinant of age-related bone loss in women and men (76, 77). Despite recent evidence from randomized, placebo-controlled trials on the adverse effects or lack of effects of postmenopausal hormone therapy on CVD outcomes (78, 79), endogenous estrogen may have protective effects on the cardiovascular system in women. Estradiol prevents endothelial dysfunction by increasing the proliferation of endothelial cells, regulating the production of endothelium-derived factors such as nitric oxide, and decreasing the expression of leukocyte adhesion molecules. It inhibits the proliferation and migration of smooth muscle cells. It is also known to improve the lipid profile (80). Estrogen receptor alpha (ESR1) was shown to have an effect on CVD susceptibility in both women and men (81). Estrogen may be involved in the pathogenesis of atherogenesis and bone loss, either directly (80, 82), or through modulation of other factors including cytokines (83) and oxidized lipids (80). The direct effect of estrogen is manifested by the expression of estrogen receptors on osteoblasts, osteoclasts (84), and vascular endothelial and smooth muscle cells (80).
Androgens also seem to have an effect on bone and vascular health. A positive correlation between testosterone levels and bone density has been observed in men and women (85, 86). Androgens were also related to cardiovascular risk factors in men (87) and perimenopausal women (88) and to aortic atherosclerosis in men (89).

Lipid metabolism and oxidized lipids

Oxidized lipids have been suggested as a potential mechanism for the paradoxical occurrence of bone loss with vascular calcification. The role of oxidized lipids in atherogenesis is well established (60, 90). *In vitro*, Parhami et al. have observed that lipid oxidation products, including, minimally oxidized LDL, ox-PAPC (oxidized 1 palmitoyl-2-arachidonyl-sn-glycero-3-phosphocholine), and the isoprostane iso-PGE2, have opposite effects on the differentiation of calcifying vascular cells (CVCs) and bone cells. Oxidized lipids were found to stimulate osteoblast differentiation in CVCs as manifested by their induction of alkaline-phosphatase, a marker of osteoblastic differentiation (91), and their promotion of the formation of extensive areas of calcification in CVCs. In contrast, the same lipids were observed to inhibit osteoblast differentiation in bone by depressing the induction of alkaline phosphatase activity and reducing mineralization in pre-osteoblastic bone cells. This lead to the suggestion that the accumulation of oxidized lipids in the subendothelial space of arteries promotes arterial calcification, and its accumulation in the subendothelial space of osteons may inhibit bone mineralization (57).
A growing body of evidence suggests a negative effect of an atherogenic lipid profile on bone formation. In a cohort of postmenopausal women, plasma levels of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were negatively and positively related to BMD, respectively (92). In animal studies, an atherogenic high-fat diet was found to reduce bone formation in mice (93). The adverse effects of dyslipidemia are mediated by the resultant increase in lipid oxidation products. Increased levels of circulating lipids result in the diffusion of lipoproteins across the vascular endothelium and their accumulation inside the arterial wall and in highly vascular tissues such as the bone microenvironment. Once outside the plasma, these lipid products are subjected to oxidative modification, thus becoming biologically active molecules capable of affecting a variety of cellular processes that ultimately result in atherogenesis and bone loss (93).
In line with the lipid hypothesis, a potent class of lipid lowering drugs, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as statins), is suggested to have an effect on bone health (94, 95). Statins inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-determining step of cholesterol biosynthesis, the reductive de-acylation of HMG-CoA to mevalonate. In large clinical trials, statins have demonstrated the ability to markedly reduce total cholesterol, LDL-C, and triglycerides, to increases HDL-C, and to reduce the incidence of cardiovascular events and mortality (96, 97). Recent evidence suggests that statin use is related to higher BMD (98) and reduced fracture risk (96, 97). *In vitro* and in animal studies, statins were found to stimulate bone formation and enhance osteoblast differentiation, by increasing the expression and production of BMP-2 by human osteoblasts (99). Like other members of the BMP family, BMP-2, is known to enhance osteoblast differentiation (100).
Another class of drugs, bisphosphonates, which inhibit bone resorption and are widely used for the treatment of osteoporosis, may have cardiovascular effects. Like statins, nitrogen-containing bisphosphonates also act on the cholesterol biosynthesis pathway, however; they target enzymes more distal in the mevalonic acid pathway than HMG Co-A reductase (95). These drugs were found to have unexpected effects on lipids in postmenopausal women with osteoporosis. Chronic intravenous therapy with neridronate was shown to decrease LDL-C and apolipoprotein B and to increase HDL-C (101).

Vitamin K deficiency

Vitamin K deficiency was suggested as a common denominator for atherosclerotic calcification and low bone mass (58). Low vitamin K intake was related to low bone density (102) and increased risk of osteoporotic fracture (103). Intake of menaquinone (vitamin K-2) was inversely associated with all-cause mortality, CHD mortality, and severe atherosclerosis in the Rotterdam study (104). Impaired vitamin K status was also linked to increased atherosclerotic calcification in postmenopausal women (105). Additionally, Jie and colleagues have observed an inverse association between markers of vitamin K status and bone mass in atherosclerotic women; whereas, no such association was found in the non-atherosclerotic group. It is speculated that the effect of vitamin K on bone demineralization and vascular calcification is mediated by a vitamin K-dependent class of proteins, gla-containing proteins, which include matrix gla protein (MGP) and osteocalcin. Gla-containing proteins are thought to be involved in calcium metabolism and in the process of calcification in bone and vascular tissues due to the calcium-binding properties of their gla residues (58). These residues are acquired post-translationally by the action of vitamin K that functions as a coenzyme for glutamate carboxylase, an enzyme that mediates the conversion of glutamate to γ-carboxyglutamate (Gla). The exact physiological role of these proteins is still not clear. However, it is hypothesized that the undercarboxylation of MGP, a mineralization inhibitor, is a risk factor for vascular

calcification, and that the undercarboxylation of osteocalcin, a marker of osteoblastic activity, disrupts the normal bone remodeling process mediated by osteocalcin and results in bone loss (58).

Vitamin D metabolism

Imbalances in the calciferol endocrine system may also be involved. The role of vitamin D deficiency in the pathogenesis of osteoporosis is well-established (106). Reduced levels of vitamin D were also associated with increased incident cardiovascular disease in the Framingham Offspring Study (107).
On the other hand, excess vitamin D was shown to induce atherosclerosis and osteoporosis in humans and laboratory animals, and the use of vitamin D as a food supplement in some countries coincided with an increase in the incidence of both conditions (59). Vitamin D receptor (VDR) polymorphisms are also suggested to simultaneously contribute to the risk of both osteoporosis and CVD (108).

Hyperparathyroidism

Parathyroid hormone (PTH) is one of the main regulators of calcium homeostasis. It stimulates the release of calcium and phosphate from bones. Aging is associated with increased levels of PTH as a result of vitamin D deficiency and decreased calcium intake and absorption. Elevated PTH levels contribute to the age-related bone loss and bone fragility (109, 110). Secondary hyperparathyroidism was also linked to increased risk for fractures, cardiovascular outcomes, and vascular calcification in end-stage renal disease (110, 111).

Homocysteine

Homocysteine is a variant of the amino acid cysteine and is formed during the metabolism of methionine. Its degradation requires folic acid and vitamin B12 as cofactors. Elevated levels of homocysteine could result from genetic or nutritional factors and may lead to osteoporosis and atherosclerosis. Homocystinuria, a genetic disorder of cystathionine β-synthase deficiency, results in early onset osteoporosis and cardiovascular events. There is considerable evidence that elevated plasma homocysteine levels are associated with an increased risk of vascular disease. Homocysteine was reported to enhance the proliferation of vascular smooth muscle cells, inhibit the regeneration of endothelial cells, and increase lipid oxidation (112). High homocysteine levels were also associated with osteoporotic fractures (113) and reduced BMD (114). Homocysteine was observed to impair bone mineralization (115) and inhibit collagen cross-linking (116).

Other factors

Other factors implicated in the pathogenesis of atherosclerosis and bone loss include nitric oxide, endothelin-1, angiotensin converting enzyme activity, ascorbic acid, potassium, hyperphosphatemia, oxidative stress, and the preferential differentiation of bone marrow stromal cells into smooth muscle cells over osteoblasts.

3. Common genetic factors

The *osteoprotegerin*, *matrix-gla protein*, and *apolipoprotein E* (ApoE) genes have been invoked in both atherogenesis and bone loss. Mice lacking the osteoprotegerin gene were found to develop early-onset osteoporosis and calcification of the aorta and renal arteries (72). Similarly, mice lacking the gene for matrix gla protein exhibited vascular calcification as well as osteopenia and fractures (117). ApoE genotype was associated with atherosclerosis in the Framingham Study and in patients with end stage renal disease (118, 119). The *ApoE4* gene was also associated with reduced BMD and increased fracture risk (120, 121).

4. Causal association

Other hypotheses point to a causal association between the two conditions whereby one of them may lead to the other.
The reduced blood flow hypothesis assumes that atherosclerosis, by reducing blood flow to the lower extremities, could affect intraosseous blood circulation. This in turn alters bone metabolism in the hip and results in osteoporosis. This hypothesis is supported by a study which showed that in cases of asymmetrical peripheral arterial disease, hip bone mineral content was lower in the affected leg compared to the unaffected one (26, 122). Consistent with this finding, low ankle-arm index was associated with low BMD at the femoral neck, but not at the spine in the Rotterdam Study (38). Additionally, BMD at the hip, but not at the spine or radius, showed an inverse relation with aortic calcification - a condition thought to affect blood flow to the distal regions or reflect atherosclerosis in arteries directly responsible for blood supply to the hip (30). In line with this theory, one histological study of 100 cadavers, reported the existence of atherosclerotic changes in intraosseous arteries and arterioles of the femur (123).
Physical activity was also suggested to lie on the causal pathway between atherosclerosis and bone loss. CVD might limit physical activity and accordingly contribute to bone loss (23).
It is also hypothesized that as a result of the progressive bone loss leading to osteoporosis, calcium and phosphate salts get redirected from the bone matrix to the arterial wall (33, 34, 48, 124, 125).

Future research

Additional longitudinal studies are needed to confirm the association between osteoporosis and CVD. Furthermore, racial differences in this association deserve further investigation.
Examination of the relation between bone loss and the progression of vascular calcification is certainly warranted. A subclinical assessment of CVD may allow for osteoporosis risk stratification and the early identification of subjects at high risk for developing the condition, and vice versa.
Another key avenue for future research is the elucidation of the common mechanisms underlying the link between osteoporosis and CVD. An understanding of these mechanisms will set the stage for the potential use of common preventive and therapeutic interventions targeted at both conditions.

Conclusion

CVD and osteoporosis are major causes of morbidity, mortality, and disability. Both diseases increase with aging. Traditionally, these two conditions were considered unrelated and their coexistence was attributed to independent age-related processes. Recently, an increasing body of biological and epidemiological evidence has provided support for a link between the two conditions beyond age and shared risk factors. It is suggested that common molecular, cellular, and biochemical processes are implicated in their pathogenesis.
New paradigms for treatment and prevention of both CVD and osteoporosis may emerge from investigating the link between the two conditions and elucidating the mechanisms involved in

their progression. An understanding of the biological linkages may set the stage for dual-purpose preventive and therapeutic interventions aimed at reducing bone loss and the progression of atherosclerosis.

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