Bone Mineral Density: What Is Its Relationship to Heart Disease?

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Low bone mineral density (BMD) is associated with obstructive coronary artery disease (CAD); this article reviews several recent studies that have demonstrated the association. In one study, for every 1-unit reduction in femoral neck T score, a 0.23 minute decrease in treadmill exercise duration was found after values were adjusted for age and other patient characteristics (95% confidence interval [CI], 0.11–0.35, p<0.001). For every 1-unit reduction in femoral neck T score, there was a 22% increased risk of myocardial ischemia after values were adjusted for age and other patient characteristics (95% CI, 1.06–1.41, p = 0.004). Overall after adjustments, patients with a low BMD who were referred for exercise echocardiographic stress testing had a 43% greater risk of myocardial ischemia than did patients with normal BMD referred for exercise echocardiographic stress testing (95% CI, 1.06–1.94, p = 0.02). Reduced physical activity may contribute to both low BMD and CAD through the development of atherosclerotic vascular disease.

In a second study, stress test-induced myocardial ischemia developed in 95 of 254 patients (37%) with osteoporosis, in 81 of 260 patients (31%) with osteopenia, and in 62 of 251 patients (25%) with normal BMD (p= 0.009) (p= 0.002 comparing osteoporosis with normal BMD; p=0.007 comparing osteoporosis or osteopenia with normal BMD). Patients with osteoporosis or osteopenia had a 1.7 times higher chance of stress test-induced myocardial ischemia than those with normal BMD after controlling the confounding effects of systemic hypertension, diabetes mellitus, body mass index, and age.

Key words: osteoporosis, osteopenia, bone mineral density, coronary artery disease, myocardial ischemia

Introduction

A few recent studies have investigated the relation of low bone mineral density (BMD) and atherosclerotic vascular disease; low BMD and elevated risk for coronary atherosclerosis; and myocardial ischemia occurring during exercise echocardiography among patients with low BMD. Early data suggest that, when treating low BMD, the primary care clinician should give consideration to measures aimed at preventing cardiovascular events.

Bone Mineral Density and Atherosclerotic Vascular Disease

A retrospective case comparison pilot study analyzed the charts of 101 postmenopausal women. Mean age was 76 years, and the women were in a long-term care facility affiliated with New York Medical College and had a dual energy x-ray absorptiometry (DEXA) scan for diagnosing bone mineral density (BMD).[1] These DEXA scans were obtained because the United States Preventive Services Task Force and the National Osteoporosis Foundation recommend measuring BMD at least once in all women older than 65 years.[2,3] Bone mineral density was measured in the hips and spine in all 101 patients by DEXA scan obtained from a computerized radiology database. Low BMD was defined as ≥1.5 standard deviations below the mean of a cohort of young women. Of the 101 patients, 51 (51%) had a low BMD. The mean age and prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia did not differ significantly between the women with low BMD and normal BMD. However, atherosclerotic vascular disease defined as symptomatic coronary artery disease, cerebrovascular disease, or peripheral arterial disease was present in 31 of 51 women (61%) with osteoporosis or osteopenia and in 19 of 38 women (38%) with normal BMD (p<0.025).[1]

A retrospective analysis was performed of 1,000 postmenopausal women, mean age 68 years (range 51–97 years), who were seen consecutively at a general medicine clinic at the University of Iowa School of Medicine between January 2004 and May 2004 to investigate the prevalence of atherosclerotic vascular disease in patients with osteoporosis, osteopenia, and no osteoporosis or osteopenia.[4] A patient was diagnosed as having osteoporosis or osteopenia according to the criteria of the World Health Organization (Table 1).[5,6] Of the 1,000 women, 154 (15%) had osteoporosis, 179 (18%) had osteopenia, and 667 (67%) had no osteoporosis or osteopenia.[4] The mean age, racial characteristics, and prevalence of current cigarette smoking, hypertension, diabetes mellitus, and hypercholesterolemia were not significantly different between the women with osteoporosis, osteopenia, and no osteoporosis or osteopenia. Atherosclerotic vascular disease was defined as the presence of coronary artery disease, ischemic stroke, or peripheral arterial disease. Atherosclerotic vascular disease was present in 92 of 154 women (60%) with osteoporosis, in 63 of 179 women (35%) with osteopenia, and in 148 of 667 women (22%) with no osteoporosis or osteopenia. P values were <0.001

comparing osteoporosis with osteopenia, <0.001 comparing osteoporosis with no osteoporosis or osteopenia, and <0.001 comparing osteopenia with no osteoporosis or osteopenia.[4]

These data showed that atherosclerotic vascular disease was more prevalent in women with osteoporosis or osteopenia than in women with no osteoporosis or osteopenia. These data also showed that women with osteoporosis had a higher prevalence of atherosclerotic vascular disease than women with osteopenia. The next section addresses the association between coronary artery disease and osteoporosis and osteopenia.

Bone Mineral Density and Coronary Artery Disease

Several recent studies have investigated the connection between low BMD and coronary artery disease. In one observational study 5,050 women and men aged 50–79 years, self-reported myocardial infarction was insignificantly increased by 22% (95% confidence interval [CI], 0.80–1.86) in women with a low BMD and was significantly increased ($p = 0.03$) by 39% in men with a low BMD (95% CI, 1.03–1.87).[7] In 45 postmenopausal women who had DEXA scans and coronary artery calcium scores, the coronary artery calcium scores were 42 for women with normal BMD, 182 for women with osteopenia, and 222 for women with osteoporosis, suggesting that women with low BMD are at higher risk for coronary atherosclerosis.[8]

Using the Framingham coronary heart disease risk prediction algorithm in 1,804 women aged 50–74 years, women with a 10–19% coronary heart disease risk within 10 years were 45% more likely to have low BMD than women with a less than 10% chance of developing coronary heart disease within 10 years (95% CI, 1.03–2.06).[9] Women with a 20% or higher coronary heart disease risk within 10 years were 73% more likely to have low BMD than women with a less than 10% chance of developing coronary heart disease within 10 years (95% CI, 1.12–2.66).[9] Similar increases in low BMD risk were not observed in men.[9]

Table 1: World Health Organization's Criteria for Osteopenia and Osteoporosis

Category	Fracture Risk	Action
Normal		
BMD <1 SD below young adult reference range	Below average	Be watchful for "clinical triggers"
Osteopenia		
BMD 1–2.5 SD below young adult reference range	Above average	Consider prevention in peri/postmenopausal in women. Be watchful for clinical triggers. Possibly repeat investigations in 2–3 years.
Osteoporosis		
BMD > 2.5 SD below young adult reference mean	High	Exclude secondary causes. Therapeutic intervention indicated in most patients.
Severe Osteoporosis		
BMD > 2.5 SD below young adult reference mean, plus 1 or more fragility fractures	Established osteoporosis	Exclude secondary causes. Therapeutic intervention indicated in most patients.

SD = standard deviation

Source: World Health Organization Study Group on Assessment of Fracture Risk and Its Application to Screening and Postmenopausal Osteoporosis. Report of a WHO Study Group. Technical Report Series (No. 84), 1994.

Marcovitz *et al.* showed in 209 patients (89% women and 11% men), mean age 67 years, that obstructive coronary artery disease with ≥ 50% narrowing of at least one major coronary artery was present in 122 of 157 patients (78%) with low BMD and in 26 of 52 patients (50%) with normal BMD (p <0.001).10 In this study, multivessel coronary artery disease was present in 86 of 157 patients (55%) with low BMD and in 13 of 52 patients (25%) with normal BMD ($p = 0.0002$). The DEXA scans and coronary angiograms were performed within the same 12-month period.

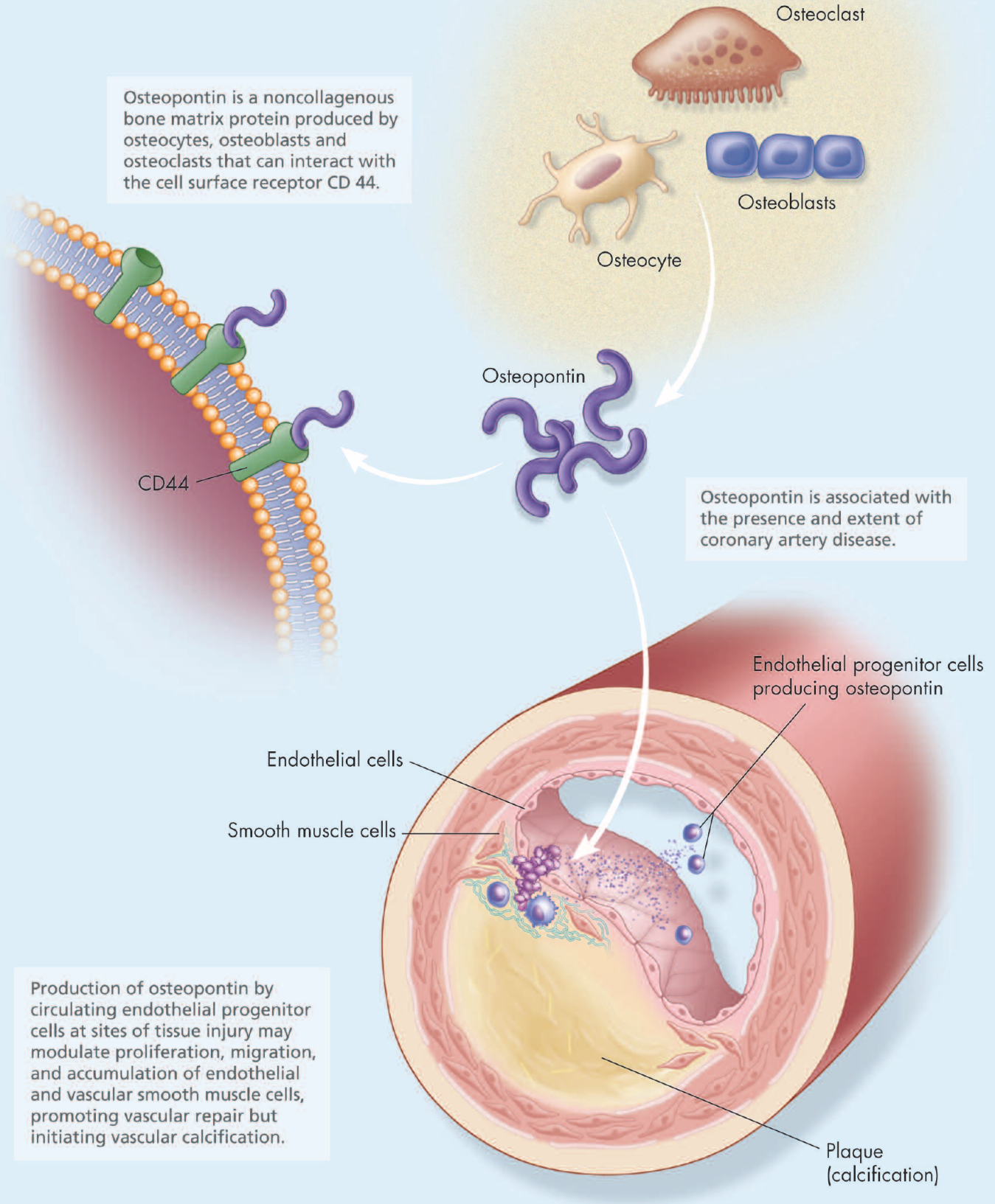
Multivariate step-down logistic regression analysis showed that significant independent predictors of obstructive coronary artery disease were osteoporosis (odds ratio [OR] = 5.58; 95% CI 2.59–12.0, $p<0.0001$), hypertension (OR = 3.92; 95% CI, 1.81–8.45, $p = 0.0005$), family history of premature coronary artery disease (OR = 2.99; 95% CI, 1.39–6.46, $p = 0.0052$), and fasting glucose level greater than 110 mg/dl (odds ratio = 3.28; 95% CI, 1.64–6.58, $p = 0.0008$).[10] Osteoporosis and osteopenia were also associated with any degree of vessel narrowing, $p =0.0001$).[10]

Coronary angiography was performed because of chest pain in 198 patients (76% women and 24% men), mean age 66 years, who had DEXA scans of the spine and left hip because of suspected osteoporosis or osteopenia within 6 months of coronary angiography.[11] Osteoporosis was diagnosed if the T score was < –2.5 standard deviations below peak bone mass.[12] Osteopenia was diagnosed if the T score was –1.0 to –2.5 standard deviations below peak bone mass.[12] Normal BMD was diagnosed if the T score was > –1.0 standard deviations below peak bone mass.[12] Obstructive coronary artery disease was diagnosed if there was >50% diameter narrowing of at least one major coronary artery.

Of 198 patients, 53 (27%) had osteo-

Figure 1:

Osteopontin as a Potential Mechanism for the Association Between Osteoporosis and Coronary Artery Disease



porosis, 79 (40%) had osteopenia, and 66 (33%) had normal BMD. The prevalence of gender, mean age, prior myocardial infarction, current smoking, systemic hypertension, diabetes mellitus, hypercholesterolemia, and body mass index ≥ 30 kg/m^2 were not significantly different between patients with osteoporosis, osteopenia, and normal BMD. Obstructive coronary artery disease with >50% narrowing of at least one major coronary artery was present in 40 of 53 patients (76%) with osteoporosis, in 54 of 79 patients (68%) with osteopenia, and in 31 of 66 patients (47%) with normal BMD ($p < 0.005$ comparing osteoporosis with normal BMD and $p < 0.01$ comparing osteopenia with normal BMD).[11]

The prevalence of obstructive coronary artery disease was significantly higher in women with osteoporosis (74%) or osteopenia (66%) than in women with normal BMD (45%).[11] The prevalence of obstructive coronary artery disease was 80% in men with osteoporosis, 75% in men with osteopenia, and 53% in men with normal BMD.[11] These differences were not significantly different because of the small number of men included in the study.

These data confirmed the association of obstructive coronary artery disease with osteoporosis and osteopenia reported by Marcovitz *et al.*[10] A retrospective analysis of 47 men, mean age 65 years, who had DEXA scans and coronary angiography showed that low BMD was an independent predictor of obstructive coronary artery disease with an odds ratio of 5.4 (95% CI, 1.66–17.49).[13] The mechanism of this association remains to be investigated.

Possible Mechanisms

Osteopontin is a noncollagenous bone matrix protein produced by osteocytes, osteoblasts, and osteoclasts that can interact with the cell surface receptor CD 44 (Figure 1).[14,15] Osteopontin is associated with the presence and extent of coronary artery disease.[16] In 178 patients, mean age 65 years, undergoing coronary angiography, plasma osteopontin levels were significantly associated with coronary artery disease (OR = 1.21; 95% CI, 1.05–1.39 for a 100 ng/ml increase) independent of other risk factors.[16] Coronary artery calcification was present in 86 of 178 patients (48%). Plasma osteopontin levels were higher in patients with coronary artery calcification than in patients without coronary artery calcification ($p<0.01$) and correlated with the number of calcified segments ($p<0.001$) but were not independently associated with coronary artery calcification.[16]

Production of osteopontin by circulating endothelial progenitor cells at sites of tissue injury may modulate proliferation, migration, and accumulation of endothelial and vascular smooth muscle cells, promoting vascular repair but initiating vascular calcification.[15,17,18] The same proinflammatory factors involved in the pathogenesis of osteoporosis may lead to expression of an osteogenic phenotype by endothelial lineage cells, providing a potential mechanism for the association between osteoporosis and coronary artery disease.[15]

Exercise Stress Testing

Exercise capacity measured by exercise stress testing is a predictor of coronary mortality independent of traditional risk factors for coronary artery disease.[19–25] Showing an association between BMD and exercise capacity could help explain the association between BMD and coronary artery disease.[26] From *et al.* hypothesized that exercise stress testing would demonstrate that patients with low BMD would have poor exercise capacity.[26] Therefore, From *et al.* studied a cohort of patients who had undergone both exercise echocardiography and DEXA scans to determine whether patients with low BMD had lower exercise capacities and were more likely to have exercise-induced ischemic changes during exercise echocardiography than patients with normal BMD.[26]

Of 1,142 patients, mean age 64 years, included in the study, 1,001 (88%) were women and 141 (12%) were men.[26] The mean time between the DEXA scans and exercise echocardiography was 15 months in the low BMD group and 13 months in the normal BMD group ($p = 0.03$). Of the 1,142 patients, 126 (11%) had osteoporosis, 517 (45%) had osteopenia, and 499 (44%) had normal BMD. The mean age was 67 years in patients with low BMD versus 60 years in patients with normal BMD ($p<0.001$). Reasons for stopping the exercise echocardiographic stress test were fatigue in 761 patients (67%), dyspnea in 273 patients (24%), hypertension in 66 patients (6%), leg distress in 46 patients (4%), angina pectoris in 15 patients (1%), completion of protocol in 18 patients (2%), and decrease in blood pressure in 10 patients (1%).

The treadmill exercise duration was 7.3 minutes in patients with a low BMD versus 8.1 minutes in patients with a normal BMD ($p<0.001$).[26] Myocardial ischemia occurred during exercise echocardiography in 21% of patients with low BMD versus 14.7% of patients with normal BMD ($p=0.007$). Patients with normal BMD had lower wall motion score indexes during exercise echocardiography than patients with low BMD ($p<0.001$ by Wilcoxon rank sum test).[26]

For every 1-unit reduction in femoral neck T score, a 0.23 minute decrease in treadmill exercise duration was found after values were adjusted for age and other patient characteristics (95% CI, 0.11–0.35, $p<0.001$).[26] For every 1-unit reduction in femoral neck T score, there was a 22% increased risk of myocardial ischemia after values were adjusted for age and other patient characteristics (95% CI, 1.06–1.41, $p = 0.004$).[26] Overall after adjustments, patients with a low BMD who were referred for exercise echocardiographic stress testing had a 43% greater risk of myocardial ischemia than did patients with normal BMD referred for exercise echocardiographic stress testing (95% CI, 1.06–1.94, $p = 0.02$).[26]

This study was the first study to show that low BMD is associated with exercise-induced myocardial ischemia and with reduced exercise capacity.[26] From *et al.* stated that the association between low BMD and reduced exercise capacity suggests that reduced physical activity may in part explain the relation-

Key Points

Older adults with low bone mineral density have a higher prevalence of atherosclerotic vascular disease than older adults with normal bone mineral density.

Older adults with low bone mineral density have a higher prevalence of obstructive coronary artery disease diagnosed by coronary angiography than those with normal bone mineral density.

Low bone mineral density is associated with exercise-induced myocardial ischemia.

Low bone mineral density is associated with reduced exercise capacity.

Treatment of osteoporosis or osteopenia should include consideration of measures to prevent cardiovascular events.

ship between low BMD and myocardial ischemia.[26] These findings support the studies that have linked increased mortality and higher bone turnover to reduced physical activity.[27,28] From *et al.* suggested that reduced physical activity contributes to both low BMD and coronary artery disease through the development of atherosclerotic vascular disease.[26] Reduced exercise capacity and reduced physical activity are well established predictors of coronary artery disease and mortality.[19–25]

These findings are strengthened by research findings demonstrating that various proteins known to regulate bone formation and bone resorption, including osteoprotegerin, matrix Gla protein, bone morphogenetic protein, and osteopontin are present in calcified atherosclerotic lesions.[26,29] In animal models, genetically engineered mouse models lacking osteoprotegerin,[30] matrix Gla protein,[31] or endothelial nitric oxide synthase[32] have vascular calcifications and low BMD.[26]

In another study, DEXA scans of the spine and left hip were performed prior to stress testing for myocardial ischemia in 629 women (82%) and 136 men (18%), mean age 63 years, with chest pain typical of ischemia and no prior history of coronary artery disease.[33] No patients with BMD measurements were excluded from the study. Of the 765 patients, 342 (45%) had an adenosine sestamibi or dipyridamole stress test, 336 (44%) had a treadmill sestamibi stress test, 80 (10%) had a treadmill stress test, and 7 (1%) had an exercise stress echocardiogram. A treadmill stress test was considered positive if ST-segment depression developed at least 1.0 mm below the resting level, with the ST segment extending horizontally for at least 80 msec after the J point or with downsloping of the ST-segment. In the presence of resting ST-segment depression, an increase of at least 2.0 mm below the resting level was required.[34,35] Stress tests were analyzed for the presence of myocardial ischemia without knowledge of patients' underlying osteoporosis, osteopenia, or normal BMD.

Osteoporosis was diagnosed if the T score was < –2.5 standard deviations below peak bone mass.[12] Osteopenia was diagnosed if the T score was –1.0 to –2.5 standard deviations below peak bone mass.[12] Normal BMD was diagnosed if the T score was > –1.0 standard deviations below peak bone mass.12

Of the 765 patients, 254 (33%) had osteoporosis, 260 (34%) had osteopenia, and 251 (33%) had normal BMD. The mean age and prevalence of gender, systemic hypertension, hypercholesterolemia, diabetes mellitus, current smoking, body mass index ≥30 kg/m^2, and estimated glomerular filtration rate <60 ml/min/1.73 m^2 did not significantly differ between patients with osteoporosis, osteopenia, and normal BMD.

Stress test-induced myocardial ischemia developed in 95 of 254 patients (37%) with osteoporosis, in 81 of 260 patients (31%) with osteopenia, and in 62 of 251 patients (25%) with normal BMD (p= 0.009) (p= 0.002 comparing osteoporosis with normal BMD; p= 0.007 comparing osteoporosis or osteopenia with normal BMD).[33] The increased prevalence of myocardial ischemia in patients with low BMD was observed for both exercise and pharmacological stress testing.

Stepwise logistic regression analysis to identify significant independent risk factors for stress test-induced myocardial ischemia were systemic hypertension (OR = 1.7; 95% CI, 1.2 –2.4, p <0.0001), diabetes mellitus (OR = 2.3; 95% CI, 1.6–3.4, p = 0.001), body mass index ?30 kg/m^2 (OR = 1.6; 95% CI, 1.1–2.4, p =0.007), and age (OR = 1.02 per year increase in age; 95% CI, 1.01–1.04, p = 0.005), and low BMD. Patients with osteoporosis or osteopenia had a 1.7 times higher chance of stress test-induced myocardial ischemia than those with normal BMD after controlling the confounding effects of systemic hypertension, diabetes mellitus, body mass index, and age.[33] These data confirm the association between low BMD and stress test-induced myocardial ischemia reported by From *et al.*[26]

Tanko *et al.* found in 2,576 women, mean age 67 years, in the placebo group of the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized study that the risk of cardiovascular events increased incrementally with the number

Clinical Pearl

Persons with osteoporosis or osteopenia with chest pain, especially those with coronary risk factors, should be considered for stress testing.

Persons with osteoporosis or osteopenia should also be treated with intensive risk factor modification.

and increasing severity of baseline vertebral fractures (both p <0.001).[36] After adjustment for potential confounders, women with osteoporosis had a 3.9 increased risk (95% CI, 2.0–7.7, p <0.001) for cardiovascular events compared with women with low bone mass.[36] These investigators recommended that treatment of postmenopausal osteoporosis should include consideration of measures to prevent cardiovascular events.

Conclusion

In conclusion, on the basis of the available findings, patients with osteoporosis or osteopenia with chest pain, especially those with coronary risk factors, should be considered for stress testing. Patients with osteoporosis or osteopenia should also be treated with intensive risk factor modification. Further studies are indicated to investigate the mechanism by which low BMD is associated with coronary artery disease and stress test-induced myocardial ischemia.

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