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Review

Osteoporosis and ischemic cardiovascular disease

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ABSTRACT

Osteoporosis and cardiovascular disease were long viewed as independent of each other. However, numerous epidemiological studies, which are discussed in the first part of this review, have provided incontrovertible evidence of a link. Thus, the risk of coronary artery disease and stroke is higher in patients with a history of osteoporotic fracture or low bone mineral density than in non-osteoporotic patients. In the other direction, patients with cardiovascular disease are at higher risk for bone loss and osteoporotic fracture. The link between osteoporosis and cardiovascular disease is due in part to shared conventional risk factors such as estrogen deprivation in women, smoking, low physical activity, and diabetes. In addition, atheroma plaque calcification involves cytokines and growth factors that also play a role in bone turnover, including proinflammatory cytokines (IL-6 and TNFα), osteoprotegerin, sclerostin, matrix GLA protein, and FGF-23. Several recent studies have provided support for these pathophysiological hypotheses. Thus, elevation of osteoprotegerin, sclerostin, or FGF-23 levels may explain and predict the occurrence of both osteoporotic fractures and cardiovascular events. The association between osteoporosis and cardiovascular disease found in most epidemiological and pathophysiological studies suggests a need for evaluating potential benefits from routine bone absorptiometry and osteoporotic fracture detection in patients with cardiovascular disease and from exercise testing and arterial Doppler imaging in patients with osteoporosis.

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1. Introduction

Osteoporosis is an extremely common disease with prevalences of 40% in women and 15% in men in France. Both the management of osteoporosis and the approach to evaluating its risk factors are changing [1–3]. Cardiovascular disease is the leading cause of death in France. Severe osteoporotic fractures are associated with excess mortality, with some deaths being related to decompensation of a cardiovascular disease. The incidence of both osteoporosis and cardiovascular disease is rising due to the aging of the population. These two diseases were long viewed as independent of each other, until epidemiological studies produced incontrovertible evidence of an association. Furthermore, our understanding of pathophysiological factors shared by both diseases has improved.

We systematically reviewed the relevant literature by searching the PubMed and Cochrane databases using the following terms: osteoporosis, osteoporotic fractures, atherosclerosis, vascular calcifications, peripheral arterial disease, coronary arterial disease, ischemic heart disease, myocardial infarction, and stroke.

2. Epidemiology

2.1. Retrospective and cross-sectional studies show correlations between vessel wall alterations and low bone mineral density (BMD)

Coronary calcium burden was measured by electron beam computed tomography (CT) and lumbar spine BMD by dual energy absorptiometry (DXA) in 45 asymptomatic postmenopausal women [4]. The mean coronary calcium score was 42 in the group with normal BMD (T-score > −1), 115 in the group with osteopenia, and 221 in the group with osteoporosis (T-score < −2.5). Another

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cross-sectional study assessed potential associations between carotid artery intimal medial thickness (IMT) measured by Doppler ultrasonography and BMD measured by DXA in 535 women and 335 men [5]. In the subgroups of females and males older than 60 years, BMD correlated negatively with IMT. Similarly, carotid IMT or plaque thickness and BMD were measured in 155 patients within 7 days after an acute ischemic stroke [6]. Mean age was 68 years. Osteoporosis (T-score < −2.5) was significantly and independently associated with IMT/plaque thickness in females ($P = 0.001$) but not in males.

A retrospective study in 209 patients (89% women) looked for an association between osteoporosis (BMD T-score < −2.5) and coronary angiography findings. The risk of coronary artery stenosis > 50% was higher in the group with osteoporosis (OR, 5.6; $P < 0.0001$). BMD was more strongly associated with coronary artery disease than were the conventional cardiovascular risk factors (smoking, hypertension, diabetes, and family history) [7].

In 357 volunteers (176 women and 181 men) undergoing a routine health check, BMD was measured at the lumbar spine and magnetic resonance angiography of the brain was performed to assess the middle cerebral, basilar, carotid, and vertebral arteries [8]. Mean age was 52 years and 171 had low BMD defined as a T-score < −1. In the females, low BMD correlated significantly with atherosclerosis in the posterior, but not the anterior, cerebral arteries (OR, 2.57). No significant association was found in the males.

2.2. Other retrospective studies show an excess risk of cardiovascular disease in patients with osteoporosis

High-resolution quantitative CT was used to measure total, cortical, and trabecular volumetric BMD and bone microarchitecture at the distal radius and distal tibia of 350 patients aged 71.5–80.5 years, including 75 with and 275 without ischemic heart disease. After adjustment for confounders, cortical volumetric BMD at the distal radius was significantly lower ($P < 0.001$) and cortical porosity significantly higher ($P < 0.05$) in the group with ischemic heart disease. When men were analyzed separately, only distal radius cortical volumetric BMD was significantly lower in the group with ischemic heart disease ($P < 0.001$). In females, none of the differences were statistically significant [9].

In a cross-sectional study, BMD was measured and brain CT performed in 646 individuals aged 50 to 75 years [10]. In both males and females, the presence of silent brain infarction correlated significantly with osteopenia (OR, 1.8; $P = 0.01$) and osteoporosis (OR, 2.2; $P < 0.001$).

A retrospective review of data from 101 postmenopausal women living in a nursing home showed that a history of myocardial infarction, stroke, or peripheral arterial disease was found in 51% of women with osteopenia or osteoporosis compared to only 38% of those with normal BMD values ($P = 0.05$) [11]. Similarly, in another retrospective study of postmenopausal women ($n = 1000$), the prevalence of cardiovascular disease was 69% in the group with osteoporosis (hip T-score < −2.5) and only 22% in the group with normal BMD ($P < 0.001$) [12]. A cross-sectional study of 5050 males and females found a significant association between a history of myocardial infarction and low BMD after adjustment for risk factors (OR, 1.28, $P < 0.05$) [13]. In the sex-specific analyses, the association was present in males but not in females.

In a case-control study of 32 men, peripheral arterial disease ($n = 17$) was significantly associated with osteoporosis, independently from diabetes and smoking history [14]. A cross-sectional design was used to study 2235 patients aged 65 years or more who underwent routine BMD measurement and tests for coronary artery disease [15]. Osteoporosis (hip T-score < −2.5) correlated significantly with coronary artery disease (OR, 1.6; $P < 0.05$). An examination of data from a nationwide Korean database showed that the 10-year risk of coronary artery disease (Framingham risk score) was significantly associated with BMD. In males, after adjustments for covariates, the Framingham risk score was significantly associated with BMD at the femoral neck (OR, −2.1; $P = 0.001$) or lumbar spine (OR, −1.54; $P < 0.01$). No significant associations were found in females [16].

2.3. Prospective studies evaluating whether low bone mass predicts cardiovascular events or whether cardiovascular disease predicts osteoporotic fractures confirm the retrospective data

In China, in 1724 postmenopausal women followed-up for 5 years, the presence of aortic calcifications assessed using semi-quantitative radiography at baseline was associated with a higher incidence of vertebral fractures (12.2% vs. 4.5% in women without aortic calcifications, ($P = 0.01$) [17]. The prospective MINOS cohort study included 744 men older than 50 years [18]. During the 7.5-year follow-up, myocardial infarction occurred in 40 patients and stroke in 43. After adjustment for risk factors, the men whose BMD was in the lowest quartile or whose bone resorption markers were in the highest quartile had a 2-fold higher risk of cardiovascular events. Furthermore, after adjustment, BMD was significantly lower in the patients with stroke. Another prospective cohort study evaluated 6872 men and women for 5.7 years, during which time 196 experienced myocardial infarction [19]. Myocardial infarction was significantly associated with low hip BMD (females: OR, 1.33; 95% CI, 1.08–1.66; males: OR, 1.74; 95% CI, 1.34 –2.28).

In a prospective study of 9704 women aged 65 years or older, low bone mineral density at the proximal radius was associated with a higher risk of fatal stroke over the 2.8-year mean follow-up (RR, 1.74; 95%CI, 1.12–2.70) [20]. In China, of 5136 postmenopausal women aged 50 years or older, 148 experienced a stroke during the 5-year follow-up [21]. After adjustments, femoral neck BMD T-score < −2.5 predicted the occurrence of stroke (OR, 2.24; 95% confidence interval [95%CI], 1.47–3.58). Among investigations of peripheral arterial disease, a prospective study of 1332 healthy individuals involved measurements of the ankle-brachial index and BMD [22]. Osteoporosis (hip T-score < −2.5) was significantly higher in the women with a low ankle-brachial index indicating peripheral arterial disease ($P < 0.05$). This association was not found in the men. Peripheral arterial disease was not associated with the occurrence of fractures. Another study involved measurements of the ankle-brachial index and of BMD at the hip and distal radius in 5781 men aged 65 years or older [23]. A low ankle-brachial index was associated with a significantly larger BMD decline at the hip (−0.66%/year vs. −0.34%/year in participants whose ankle-brachial index was normal, $P = 0.001$).

3. Pathophysiological links between osteoporosis and cardiovascular disease

Atherosclerosis is a form of arteriosclerosis, alongside mediacalcosis and arteriolosclerosis (Box 1, Fig. 1). In atherosclerosis, lipids accumulate in the vessel walls under the influence of biochemical, inflammatory, and autoimmune processes [24]. Over 90% of lipid-laden plaques eventually undergo calcification. Numerous studies have demonstrated a direct association between the extent of plaque calcification and cardiovascular mortality [25]. The pathogenic mechanisms that explain why osteoporosis and atherosclerosis tend to affect the same patients deserve scrutiny.

3.1. Clinical and genetic risk factors shared by osteoporosis and atherosclerosis

Estrogen deprivation after the menopause is the main cause of osteoporosis in women (Box 1). Loss of the protective effect of

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