Bone alterations have been observed in the course of HIV disease, representing a pivotal clinical problem in the management of HIV patients, especially for a possible development of bone fractures. In particular, reduced bone mineral density (BMD) is the most common bone lesion found in HIV-infected individuals. BMD is a parameter that predicts fracture risk, which in turn correlates with a shorter life expectancy. In the elderly, osteoporotic fractures and cardiovascular events are major causes of mortality and morbidity in the general population.(1,2) In HIV-positive subjects, prevalence of these events is expected to rise in the next future (165), owing to the increasing longevity of our patients,(3) so the need for early referral of high-risk subjects identified by different independent predictors of cardiovascular risk is urged.(4) Atherosclerosis and osteoporosis are degenerative diseases common in the elderly population, and their prevalence is increasing. Because they are common, both diseases are frequently observed in the same individual, and many studies have suggested a link between these two conditions. Osteoporosis and related fractures are well-recognised public-health issues, and increased mortality after fracture is accepted. Excess mortality varies after hip fracture, with 12-month rates ranging from 12% to 35%. This variation may relate to differences in age, demography of people studied, study size, and completeness and length of follow-up. Major fractures identify a group at twofold increased risk of mortality. Increased mortality is associated with all major osteoporotic fractures, but there is also an association with other fractures, including pelvic, distal femur, proximal tibia, multiple rib, and proximal humerus. Mortality rates for pelvic, rib, and humeral fractures are higher than those for the non-fracture subjects. Most excess mortality occurs within the first 3–12 months after fracture,(106–109) and increases with age.(109-115) Fracture patients have a higher mortality than does the general population, especially those with hip fractures. Men with major fractures have higher mortality ratios than women. The increased mortality associated with vertebral fractures in men, is comparable with that for men with hip fractures, and greater than that seen in women. Low bone-mineral density is associated with increased mortality, independent of fracture. (116, 117) Many studies suggest that osteoporosis is a risk factor for cardiovascular events, suggesting an independent association between loss of BMD and vascular calcification, (5–9) an index of atherosclerosis and cardiovascular risk. (10,11) These studies investigated the possible relations between calcified plaques, a risk factor for atherosclerosis and cardiovascular disease (36), and the two morphological traits that characterize osteoporosis: low bone density and fragility fractures (35). Patients with vascular calcifications are predisposed to osteoporosis and fragility fractures, and subjects with osteoporosis are at increased risk of mortality unrelated to the occurrence of fractures but due to coronary disease (37, 38). The increased risk associated with osteoporosis is independent of traditional cardiovascular risk factors, is proportional to the severity of osteoporosis, and is not part of a general inclination to morbidities caused by frailty of osteoporotic subjects. Calcium mineral deposition frequently accompanies atherosclerosis, and is associated with myocardial infarction and coronary disease (49-53). Arterial calcification is the result of a processes with many similarities to osteogenesis (51, 54-56). Vascular disease is accompanied by loss of BMD, more

From Bone To Heart

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ABSTRACT

To investigate the relationship between bone mineral density and cardiovascular disease, between aortic calcification, bone mineral density and fractures, and between vitamin D deficiency and risk of cardiovascular disease; describe the mortality rate after all types of osteoporotic fracture, and speculate about the role of osteoclast-like cells in arterial calcification.
severe in the hip and lower extremity more affected by atherosclerosis. (12, 13) Low BMD is associated with increases in the risk of cardiovascular events and related mortality, (14–17) and we need to use BMD and vertebral fracture assessment, and investigate the relationship between severity of osteoporosis and cardiovascular events; to answer if low BMD values and vertebral fractures are associated with an increased risk of cardiovascular events, and if the risk of cardiovascular events is proportional to the severity of osteoporosis. There is a significant age-independent relation between atherosclerosis and osteoporosis, and increases in vascular calcification and bone loss progress in parallel. There is a significant association between the degree of vascular calcification and bone mineral density, and an inverse relation between gains in vascular calcification and bone loss. There is an association between the progression of vascular calcification and bone loss. The yearly percentage gains in vascular calcification account for nearly 50% of the variance in the percentage rate of bone loss. Patients with vascular calcification had more than double the rate of bone loss as subjects without calcified plaques. After the mid-60s the prevalence of cardiovascular disease show an increasing prevalence (18), so these patients are particularly suitable for assessing the use of bone assessment for the prediction of the risk for cardiovascular events. Low bone mass is a stronger predictor of cardiovascular disease than other risk factors, such as cholesterol and smoking (37, 38). Similarly, patients with a progression of vascular calcification are at increased risk for osteoporosis, and subjects who lose bone have an increased rate of mortality due to cardiovascular disease (39). Diagnosis of osteoporosis indicate an increase in risk for cardiovascular disease, even when adjusted for age, prior cardiovascular disease, hypertension, hyperlipidemia, diabetes, smoking. (5–9, 14–17) suggesting that the increased risk cannot be explained by common risk factors. Therefore, the diagnosis of osteoporosis may draw attention to vascular disease, regardless of demographic and lifestyle characteristics of the subject. The increase in risk for cardiovascular events associated with prior fracture suggests that the association with increased hospitalization and mortality (19) may be at least in part attributable to coronary and stroke events. The presence of at least one vertebral fracture is associated with an increased risk of cardiovascular events regardless of total hip BMD, and increasing number and severity of vertebral fracture are associated with a further increase in cardiovascular risk. Estimates of the relative risk for vertebral and hip fractures are about 5- and 3-fold more common, respectively, in subjects with vascular calcification. The percentage of patients with fractures and the number of fractures are significantly greater in subjects with vascular calcification than those without. Women with vertebral fractures have increased mortality, (119) but clinically diagnosed vertebral fractures may represent only a third of all vertebral deformities. The vertebral fractures are generally only those coming to clinical attention. Since routine radiography is not performed, symptomless, prevalent, or incident vertebral fractures, which may represent up to two-thirds of all morphometric vertebral deformities, may have been undetected. In vertebral fractures the increase in mortality is a real phenomenon. Survival seems to be worse in men than in women. (107–111, 113, 114, 118, 120) The mechanism by which osteoporosis and cardiovascular disease may be linked is not fully understood, (20–22) although age, diabetes, dyslipidemia, and hypertension are all established risk factors for cardiovascular disease that also have been associated with decreased BMD or increased fracture risk. (20) Vascular and skeletal biology may share some common pathophysiological mechanisms, suggested by similarities between vascular calcification and bone formation. (21) Arterial tissue is calcified in an organized, regulated process by mechanisms similar to those involved in the mineralization of bone. The mineral deposit in the arterial wall, hydroxyapatite, is the same mineral found in bone, and it is structurally arranged with trabeculae and lacunae in the calcific deposit (40). Osteogenesis may occur in some cells of the arterial wall (41). Cells with both osteoblastic and osteoclastic potential have been described in vascular tissues, and bone-related proteins have been identified in calcified arterial lesions (41–43). There is a divergence of differentiation of MPCs away from the macrophage lineage and toward an osteoclast lineage under the influence of RANKL and macrophage colony-stimulating factor (M-CSF) (76, 77). MPCs are present in plaque during all stages of atherogenesis (95, 96), MPCs and OCLCs are hematopoietic cells in origin, closely related to one another (71, 78, 97), and there are circulating marrow stromal-derived cells in atherosclerotic neointima (98, 99). Monocyte (59, 60) and osteoclast (100) precursors are both recruited by endothelial cells from circulating blood. Circulating mononuclear and extraskeletal fibroblastic cells can be induced to differentiate into osteoclasts (101–103), and monocytes into OCLCs, that show bone resorption activity (104). A common myeloid lineage gives rise to both mononuclear-macrophage lineage and osteoclast lineage (70, 71, 74, 75). Osteoclasts are members of the monocyte/macrophage lineage originating from multiple cellular fusions of their precursors that proliferate and differentiate towards mature osteoclasts by means of (M-CSF) and RANKL (78–81). All cells of the vessel wall express M-CSF (82–84), and vascular endothelial cells express RANKL and OPG (49). RANKL is expressed in small blood vessels of the skin (86), OPG is expressed in arteries (76, 77, 87), and OPG, RANK, and RANKL transcripts, normally expressed by osteoblastic stromal cells and osteoclast precursors (88, 89), are found in cells associated with calcified arterial lesions of OPG-deficient mice. Circulating osteoclast precursors, MPCs, and B cells express c-fms (90), the cell surface receptor for M-CSF (91, 92), and RANK, the cell-surface receptor for RANKL (93). M-CSF- and RANKL-dependent cell signaling may affect processes related to cell survival and function such as mineral resorption in arteries (75, 94). The involvement of sex steroids is supported by studies that show association between these two diseases: (7, 8, and 15) prolonged exposure of adipose tissue to estradiol might be involved in the pathogenesis of insulin resistance and low-grade inflammation. (23–25) Statins have been shown to trigger bone formation. (46) Statins are associated with increased bone mineral density and a reduced fracture risk. (47, 48). Increased circulating levels of hs-CRP and homocysteine are associated with decreased BMD in periph-
eral skeletal sites, and have both been proposed as independent predictors of cardiovascular events. (26) Hyperhomocysteinemia is also a strong independent predictor of osteoporotic fractures. (27) Regulators of bone turnover have all been identified in calcified atherosclerotic plaques, (22) and increased expression in these proteins has been associated with vascular disease. (28) Proinflammatory cytokines exert proatherogenic effects on the vascular wall (29) and may promote osteoclastogenesis and bone resorption. (30) The artery wall contains cells that retain the capacity to differentiate into osteoblast-like cells (57-67). These cells are referred to as calcifying vascular cells (CVCs) and, under selective stimuli, have the potential to form mineralized nodules and express bone morphogenetic protein (BMP) -2, osteocalcin, osteopontin, osteonectin, alkaline phosphatase, and collagen type I (54, 55, 68, 69). CVCs respond to TGF-beta1, 25-hydroxycholesterol, and BMP-2 by accelerating nodule formation and expression of osteoblast-related genes (66-69). The primary determinant of mineral deposition in arteries is inhibition of mineral resorption by OLCs rather than mineral deposition of osteoblast-like cells. (70-73) Reduced mineral resorption might be secondary to decreased maturation, survival, and/or function of OLCs within developing calcified vascular lesion. Oxidized lipids accelerate atherogenesis and activation of calcifying vascular cells while inhibiting osteoblastic differentiation in bone. (31) The lack of NO synthase (NOS) in mice is associated with accelerated atherosclerosis (32) and decreased osteoblast function leading to low BMD. (33) Genetically engineered animals, susceptible to the development of calcified atherosclerotic lesions, have low values for bone density, whereas those resistant to the development of atherosclerotic lesions have higher bone density values (44, 45). Low levels of 25-hydroxyvitamin D (25-OH D) are present in as many as one third to one half of middle-aged to elderly adults. (121-124) Low levels of vitamin D may adversely affect the cardiovascular system. (125) Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, (126,127) endothelium, (128) and cardiomyocytes. (121) 1,25-dihydroxyvitamin D (1,25-OH D) suppresses renin gene expression, (129,130) regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes, (131) and inhibits cytokine release from lymphocytes. (132) The absence of vitamin D receptor activation leads to upregulation of the renin-angiotensin system, with the development of hypertension and left ventricular hypertrophy. (130,133,134) 1,25-OH D participates in the regulation of renin-angiotensin axis by suppressing renin gene expression. (130,134) Vascular effects of vitamin D include modulation of smooth muscle cell proliferation, (151) inflammation, (132) and thrombosis. (151) Vitamin D deficiency triggers secondary hyperparathyroidism, parathyroid hormone (PTH) promotes myocyte hyper-trophy (154), vascular remodelling (155,156), and has a proinflammatory effect, stimulating the release of cytokines by vascular smooth muscle cells. (127,157) Vitamin D deficiency promotes the development of hypertension, (130, 158) which provides another mechanism linking vitamin D deficiency, hypertension, and cardiovascular risk. Many studies have reported cross-sectional associations between lower vitamin D levels and plasma renin activity, (135) blood pressure, (136,137) coronary artery calcification, (138,139) and cardiovascular disease. (140-142) Other studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator, a phenomenon attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight. (143-146) Vitamin D deficiency is associated with increased cardiovascular risk, above and beyond established cardiovascular risk factors. The higher risk is particularly evident among individuals with hypertension, in whom 25-OH D levels <15 ng/mL are associated with a 2-fold risk of cardiovascular events. Increased cardiovascular risk is present at 25-OH D levels (<15 ng/mL) compatible with at least moderate vitamin D deficiency. Relatively high levels of 25-OH D (>30 ng/mL) are required to maintain normal PTH levels, but optimal levels for cardiovascular protection may differ from those for bone metabolism or normal PTH physiology. (147, 159) In many studies, lower 25-OH D levels have been observed in individuals with acute myocardial infarction, (140) stroke, (141) heart failure, (142) and cardiovascular disease. (148) In 2 studies, 25-OH D was assayed on presentation to the hospital with the cardiovascular event, (140, 141) which suggests that the low 25-OH D levels predated the cardiovascular event. Another study showed an association between vitamin D deficiency and increased cardiovascular mortality in haemodialysis patients. (149) Vascular smooth muscle cells and endothelial cells express receptors for vitamin D and have the ability to convert circulating 25-OH D to 1,25-OH D. (127,150) Transgenic rats constitutively expressing vitamin D-24-hydroxylase develop substantial atherosclerosis. (153) Vitamin D supplementation has promoted reductions in blood pressure, (160, 161) left ventricular hypertrophy, (162) and inflammatory cytokines. (163) Vitamin D did appear to reduce cardiovascular risk in obese individuals, and also in those with vascular risk factors. (164) In conclusions, there is an association between osteoporosis and cardiovascular events independent of age and cardiovascular risk factors; there are links between bone metabolism and atherosclerosis, and subjects with osteoporosis should also be considered for cardiovascular intervention to prevent adverse outcomes. Because approximately 50% of all abdominal CT studies in women 50–60 yr of age depict vascular calcification (34), this finding provides an imaging marker for the identification of who have accelerated bone loss and are at greatest risk for osteoporosis. Clinical management of patients with osteoporosis should include not only prevention of fractures but also prevention of cardiovascular disease. We need effective prevention and treatment strategies that may simultaneously modify the risk for these two common conditions. Moderate to severe vitamin D deficiency is a risk factor for developing cardiovascular disease. These findings may have broad public health implications, given the high prevalence of vitamin D deficiency, the contribution of lifestyle and geography to vitamin D status, and the ease, safety, and low cost of treating vitamin D deficiency. Treatment of vitamin D deficiency, via supplementation or lifestyle measures, could reduce cardiovascular risk. Correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease. (165-170)
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