Role of Lipids in Osteoporosis

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Abstract—Cardiovascular disease and osteoporosis together account for most of the morbidity and mortality in our aging population despite significant improvements in treatment. Recently, converging lines of evidence suggest that these 2 diseases share an etiologic factor—that hyperlipidemia contributes not only to atherosclerotic plaque formation, but also to osteoporosis, following a similar biologic mechanism involving lipid oxidation. In vitro studies indicate that lipid products of oxidation promote osteoblastic differentiation of vascular cells and inhibit such differentiation in bone cells. Ex vivo, in vivo, and clinical studies further suggest that lipid-lowering agents reduce both atherosclerotic calcification and osteoporosis. Whether lipid-lowering agents reduce osteoporosis directly or indirectly through lipid reduction remains controversial. (Arterioscler Thromb Vasc Biol. 2000;20:2346-2348.)

Key Words: atherosclerosis ■ osteoporosis ■ calcification

Growing evidence links vascular and bone disease. Osteoporosis is associated with both atherosclerosis and vascular calcification.1-9 Although this association is often dismissed as a consequence of aging, the relationship remains significant after age adjustment in some1,9 but not all10 studies. Osteoporotic postmenopausal women are at significantly greater risk for cardiovascular disease than age-matched controls.11 Patients with lower bone density and osteoporosis also have higher lipid levels, more severe coronary atherosclerosis, and have a greater risk of stroke death.2,3,12-15 The common finding of simultaneous vascular calcification and osteoporosis in individual patients suggests that local tissue factors govern regulation of biomineralization.

Bone and vascular tissue share several features at the molecular and cellular levels. Bone and marrow both contain endothelial cells, preosteoblasts, and monocyte-derived osteoclasts, all of which have counterparts in the artery wall. Both bone and atherosclerotic arteries contain osteopontin, bone morphogenetic protein, matrix Gla protein, collagen I, osteonectin, osteocalcin, nitric oxide, and matrix vesicles. Atherosclerosis and osteoporosis both involve recruitment and differentiation of monocytic cells that differentiate into macrophage-foam cells in artery and osteoclasts in bone. Each cylindrical unit of bone, the osteon, contains a central vessel lined with endothelial cells and a subendothelial matrix. Osteoblast progenitor cells are located immediately outside this matrix.

The artery wall contains cells capable of differentiation into osteoblasts, following the same stages of differentiation as occur in bone-derived osteoblasts, and ultimately producing bone mineral.16 The same oxidized lipids that induce atherosclerosis also induce mineralization and differentiation of the osteoblastic cells in the artery wall.16 Consistent with this finding, hyperlipidemia is associated with vascular calcification in mice.17 However, in bone and bone osteoblasts, osteoblastic differentiation is inhibited by oxidized lipids and hyperlipidemia.16,18

Lipids have been shown to accumulate in bones of mice and around bone vessels in patients with osteoporosis.19,20 Because the immature osteoblasts are located immediately adjacent to the subendothelial matrix of bone vessels, lipid accumulation in subendothelial matrix would be expected to inhibit differentiation of the bone-forming cells. In addition, because oxidized lipids induce endothelial expression of monocyte chemotactic factors and M-CSF, a potent inducer of osteoclastic differentiation, oxidized lipids would be expected to promote bone resorption by recruitment and differentiation of osteoclast precursor cells. Consistent with this possibility, high-fat diet inhibits bone growth in chickens and the effect is reversed by antioxidants.21

Clinical studies also support a role for lipids in both vascular calcification and osteoporosis. Lipid-lowering agents reduce coronary vascular calcification in patients, where the degree of improvement follows in direct relation to the degree of lipid lowering.22 Lipid-lowering agents also enhance bone mineralization in rodents23 and patients24 and may reduce osteoporotic fractures in patients.25-27 These effects on bone were originally attributed to a direct effect of the specific class of lipid-lowering agents used, HMG-CoA reductase inhibitors (statins).

It is possible that statins may directly protect bone. However, it is extremely difficult to dissect out the effects of statins versus effects of lipid lowering. In whole organisms,
including rodents, statins strongly induce lipid clearance, thus lowering lipid levels. Therefore, from these clinical studies, it is not possible to distinguish whether the improvement in bone density and reduction in fracture risk are due to lipid lowering or to a direct effect of statins.

A direct effect was inferred from ex vivo studies showing histologic growth following direct injection into bone organ culture and in vitro studies showing BMP-2 induction by lovastatin in a bone cell line culture. However, in whole organisms, statins are nearly completely cleared by the first pass through the liver. In addition, it is not clear how inhibitors of cholesterol biosynthesis influence BMP-2 expression. A key activator of BMP-2, hedgehog, actually requires covalent binding to cholesterol for its activity. Thus, in blocking the cholesterol biosynthetic pathway, statins would be expected to reduce BMP-2 expression.

The 3 observational studies that show reduced fractures in patients taking HMG-CoA reductase inhibitors reported less effect or no effect of other classes of lipid-lowering agents. The reduced effect is consistent with an indirect effect that depends on the degree of lipid lowering, because non-statin lipid-lowering agents are well-known to lower lipids less effectively than statins. The apparent absence of effect of non-statin agents reported by Chan et al is actually entirely attributable to the small number of fracture patients using non-statins (n=6). Based on chi-square simulation analysis, this study had a power of less than 30% for detecting an effect of non-statin drugs equal to that of statins (halving fractures), ie, it had a 70% chance of failing to achieve statistical significance in the association between non-statins and fractures, even if the non-statins had actually reduced fractures 2-fold, simply because of the small sample size. Thus, as above, none of these clinical studies is able to distinguish whether fracture reduction is attributable to lipid lowering or to a direct effect of statins.

Earlier animal studies showed that lipid lowering by non-statins alleviated steroid-induced osteoporosis to the same degree as statins. It is notable that bisphosphonates, leading agents for osteoporosis, also reduce LDL and increase HDL levels in humans. They also reduce atherosclerosis in rabbits, raising the question of whether some of their effects on bone may be through lipid lowering. Another widely-used treatment for osteoporosis, hormone replacement therapy, also lowers lipid levels. These data support the concept that lipids contribute to both vascular calcification and osteoporosis.

The concept that a single factor could promote mineralization in one tissue while inhibiting it in another has biologic precedent. In chronic infection, inflammation, or foreign body reaction, a common response of soft tissue is mineralization (eg, vertebral osteophytes, liver parasites, surgical sponges), whereas bone tissue responds with demineralization (eg, osteomyelitis, lytic periodontitis). If oxidized lipids in artery and bone mimic refractory infection or foreign material, then vascular calcification and osteoporosis would be an expected consequence.

In summary, recent research suggests that cardiovascular disease and bone loss are functionally interwoven. Osteoporosis and osteoporosis correlate positively with atherosclerosis, vascular calcification, and cardiovascular events, with some evidence for age-independence. Lipid oxidation products that promote atherogenesis also inhibit osteoblast differentiation, but they also promote mineral formation by vascular cells. Lipid-lowering agents reduce atherosclerosis, vascular calcification, and osteoporotic fractures. The reduction in vascular calcification is directly related to the degree of lipid lowering. It is not known whether the reduction in fractures is related to the degree of lipid lowering and whether the effect is limited to 1 class of lipid-lowering agents, the HMG-CoA reductase inhibitors. Future studies are needed to determine whether degree and duration of hyperlipidemia correlate with osteopenia in humans; whether experimental hyperlipidemia affects bone density in animals; and whether the degree of lipid lowering determines the degree of reduction in osteoporosis. Randomized trials with adequate power are needed to compare bone density and fracture in individuals randomized to statin versus other lipid-lowering agents and paired to match equal degrees of lipid lowering.

A critical priority is to determine whether treatments for osteoporosis aggravate or benefit vascular calcification and vice versa. The fundamental mechanisms by which lipids modulate differentiation of mineralizing cells and biomineralization must be evaluated, and known mechanisms by which lipids regulate atherogenesis offer a valuable starting point. Existing and exciting new animal models offer promise in identifying genetic regulatory factors. Other research priorities at the interface between bone and vascular biology have been named by a recent NIH Working Group. Ultimately, this research should lead to new and efficient strategies for simultaneous biologic reversal of both vascular calcification and osteoporosis.

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References


38. NIH Working Group. “New Evidence Connecting Cardiovascular Disease and Osteoporosis” September 14–15, 1999, Bethesda, Maryland; sponsored by Drs Claude Lenfant, Director of the National Heart Lung and Blood Institute, and Stephen I. Katz, Director of the National Institute of Arthritis and Musculoskeletal Disease. A summary of this meeting is available at www.nhlbi.nih.gov/meetings/workshops/bnhrtsm.htm.
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