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Role of Lipids in Osteoporotic Bone Loss

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Introduction

Age-related osteoporotic bone loss remains one of the significant causes of morbidity and mortality in the aging population, resulting in increase fracture incidence at the hip, spine, and other sites. It is estimated that 30 million people are at risk for osteoporosis in the United States, and that approximately 100 million people are similarly at risk worldwide.(1) Osteoporosis causes nearly 1 million fractures in the United States each year.(2)

Osteoporotic bone loss is characterized by a marked decrease in osteoblast number and bone forming activity, in the face of an unaltered or slightly increased osteoclastic bone resorption.(3) In parallel, there is an increase in bone marrow adipocyte content.(4,5) The factors and mechanisms underlying these age-related pathogenic changes are not clearly understood. Recently, several studies have focused on the role of lipids in osteoporosis. The decrease in bone mineral density (BMD) associated with osteoporosis has been closely related to high lipid levels,(6-9) as well as other disorders that may be a consequence of high lipids, including cardiovascular calcification(10-12) and atherosclerosis.(6,7) Several in vitro studies have implicated the role of lipid and lipoprotein oxidation in inhibiting or altering the normal differentiation pathway of osteoblastic progenitor cells.(13,14) In vivo studies have also shown that mice on an atherogenic high-fat diet have reduced bone mineral density.(15) These results suggest that an effective therapeutic approach to reducing the risk of osteoporosis would be to reduce lipid consumption, and/or perhaps to utilize antioxidants as a means of suppressing lipid oxidation, in addition to lipid-lowering agents.

Lipid Oxidation, a High-fat Diet, and Antioxidant

Lipids have been shown to accumulate in bones of mice and around bone vessels in patients with osteoporosis.(16) In each cylindrical unit of bone, the osteon, a central vessel is lined with endothelial cells and a subendothelial matrix. Osteoblast progenitor cells are located immediately outside the matrix. Since the progenitors are located immediately adjacent to the subendothelial matrix of bone vasculature, lipid accumulation in the subendothelial matrix would be expected to alter the differentiation of the bone-forming osteoblastic progenitor cells.(17) In vitro studies, using bone- and marrow-derived preosteoblastic cells, have found that treatment with minimally oxidized low-density lipoprotein (MM-LDL) and other bioactive oxidized lipids inhibit various markers of osteoblastic differentiation, including alkaline phosphatase, collagen I, osteocalcin, and finally accumulation of hydroxyapatite minerals.(13,14) Meanwhile, oxidized lipid treatment has been shown to promote adipogenic differentiation in such preosteoblastic cells.(14) Similarly, preosteoblasts harvested from the bone marrow of mice that were fed a high-fat, high-cholesterol diet, have been shown to have significantly less osteoblastic differentiation,(14) suggesting that excess lipid consumption may lead to lipid accumulation and subsequent oxidation within bone vasculature, wherein osteoblastic differentiation may be altered.

In addition to their inhibitory role in osteoblastic differentiation, it is believed that because oxidized lipids induce endothelial expression of monocyte chemotactic factors, as well as other potent inducers of osteoclastic differentiation, oxidized lipids may also

promote bone resorption. That is, through recruitment and differentiation of osteoclast precursor cells,(17) oxidized lipids may contribute to increased bone breakdown. Consistent with these findings are the results of two in vivo studies that have shown that mice(15) and chickens(18) fed on a high-fat, high-cholesterol diet have reduced bone mineral density. Perhaps even more significant are data reporting that the reduction in bone mineral density can be rescued with antioxidants,(18) suggesting a possible therapeutic mechanism of action; that is, through suppression of lipid oxidation levels.

Epidemiological Studies and Lipid-lowering Therapy

Recent epidemiological and experimental data suggest that increased lipid and lipid oxidation levels may play a significant pathogenic role in age-related osteoporosis. A number of studies have suggested an inverse relationship between dietary cholesterol intake and bone mass in humans and animals. In a population study of 241 osteoporotic and 98 age-matched normal Czech women, Broulik et al. found that the osteoporotic women had significantly greater serum cholesterol levels.(9) Similarly, a study by Semmler et al. showed elevated cholesterol levels in both men and women with osteoporosis.(19) Lin et al. also found a significant inverse relationship between cholesterol intake and spine bone mineral density in 56 Caucasian women, aged 18-31.(20) In addition, several studies have shown that the statin family of lipid-lowering agents, which act by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the cellular cholesterol biosynthetic pathway, have potent anabolic effects on osteoblastic bone formation in animals and in humans. Mundy et al. found that feeding rats with Simvastatin caused a 35% increase in trabecular bone volume.(21) Similarly, such lipid-lowering agents have been shown to enhance bone mineralization in patients(22) and may also reduce osteoporotic fractures in patients.(23-25)

While these anabolic effects on bone were originally attributed specifically to statins, it seems that they can also be seen with other lipid-lowering agents. Indeed, several animal studies have shown that lipid lowering by non-statins alleviates steroid-induced osteoporosis to the same degree as statins.(26) Likewise, it is interesting to note that bisphosphanates, the leading therapeutic agents for osteoporosis, also reduce LDL levels and increase HDL levels in humans.(27) In fact, another widely used treatment for osteoporosis, hormone replacement therapy, also lowers lipid levels. While it has not been proven whether the anabolic action of these agents on bone is through their lipid-lowering activity, the data shown support the concept that lipids contribute to the process of osteoporotic bone loss.

Discussion

In summary, recent research suggests that there is a strong positive correlation between osteoporosis and hyperlipidemia. The mechanism by which lipids may cause osteoporosis is currently being investigated. It is believed that hyperlipidemia, through for example, increased consumption of fats and cholesterol and/or alterations in the endogenous cholesterol biosynthetic pathway, may lead to the accumulation and abnormal deposition of lipids within the vasculature, specifically (in this case) bone vasculature. Abnormal deposition of lipids may occur within the subendothelial matrix, wherein subsequent lipid

oxidation may take place. Here, nearby osteoblastic progenitor cells are likely to respond to lipid oxidation in the same manner that the bone- and marrow-derived preosteoblasts did to MM-LDL.(14,15) That is, the osteoblast progenitors are likely to decrease markers necessary for osteoblastic differentiation, and perhaps upregulate those that lead to adipogenic differentiation.

Lipid-lowering agents, such as statins, have been shown to reduce fracture incidences and enhance bone mineralization in patients. These agents act by inhibiting the endogenous cholesterol biosynthetic pathway, and are directed mainly at the liver. By inhibiting the pathway within the liver, statins upregulate LDL receptors on hepatic cells, which subsequently bind to and decrease systemic lipid levels. Whether the anabolic action of statins on bone is due to the degree of lipid lowering, or simply limited to some other characteristic of the drug, is not yet known. It is notable, however, that bisphosphanates and hormone replacement therapy, the most commonly used therapeutic approaches for treating osteoporosis, also reduce circulating lipid levels.

Finally, in looking at the role of lipids and lipid oxidation in osteoporosis, a relationship between bone and vascular disease becomes evident. Osteoporosis has been associated with both atherosclerosis and vascular calcification(6,7,10-12) for quite some time. Although this association is often dismissed as a consequence of aging, the relationship remains significant, even after age adjustment, in most cases. Osteoporotic postmenopausal women are at greater risk for cardiovascular disease than age-matched controls.(28) Patients with lower bone mineral density not only have high lipid levels, but more severe coronary atherosclerosis, and greater risk of stroke.(6,9) Moreover, the similarity between bone and vascular tissue, at the molecular and cellular levels, is remarkable. Both bone and marrow contain endothelial cells, preosteoblasts, and monocyte-derived osteoclasts, which all have counterparts in the artery wall.(17) The process of cardiovascular calcification and/or atherosclerosis has long been associated with increased lipid levels. In fact, lipid-lowering agents, such as statins, were originally and are currently being used to treat patients with hyperlipidemia, to reduce the risk of cardiovascular disease. Thus, it should not be surprising to find that two disease processes, which share so much in common, may arise from a similar root; namely, abnormal accumulation, deposition, and subsequent oxidation of lipids. More importantly, these findings are encouraging, for they strongly suggest that the use of antioxidants, in addition to regular exercise and a healthy diet, may play a crucial role in preventing osteoporotic bone loss.

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