Therapeutic perspectives

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Summary

Osteoporosis and atherosclerosis are linked by biological association. This encourages the search for therapeutic strategies having both cardiovascular and skeletal beneficial effects. Among drugs that may concordantly enhance bone density and reduce the progression of atherosclerosis we can include bisphosphonates (BP), statins, β-blockers, and possibly anti-RANKL antibodies. Available data come from experimental animals and human studies. All these treatments however lack controlled clinical studies designed to demonstrate dual-action effects.

KEY WORDS: osteoporosis, atherosclerosis, bisphosphonates, β-blockers, dual-action therapies.

Introduction

Among the degenerative conditions occurring with aging, osteoporosis and atherosclerosis are critical healthy problems. The role these chronic diseases play in the decline in quality of life and as a major cause of morbidity and mortality can not be overlooked. From a clinical point of view, both osteoporosis and atherosclerosis are silent illnesses, that may remain asymptomatic until a fragility fracture or a thrombotic obstruction occurs. Although osteoporosis and cardiovascular diseases have been considered independent processes, increasing evidence suggests the existence of a biological linkage between bone and vascular system. The association between bone mass loss and carotid atherosclerosis, coronary artery disease, arterial disease of lower limbs, and aortic calcification has been demonstrated in several studies (1-5). Some of them show that the progression of the arterial plaque parallels bone loss, however the nature of the possible link remains uncertain. Several hypotheses have been suggested to explain this association, which include age-related mechanisms, diabetes mellitus, estrogen deficiency, hypovitaminosis D and K, cigarette smoking, and renal failure (6). Inflammatory cytokines and oxidized LDL have been suggested as crucial determinants of both calcification in the vascular intima and reduction in osteoblast activity (7). The existence of an age-independent causal relationship between vascular calcifications and osteoporosis may have great importance in suggesting therapeutic approaches that may benefit patients with both conditions (8).
This review will focus on the evidence supporting the possibility that some therapies based on biological linkage may act as dual-purpose therapies, reducing the risks of bone loss and of the progression of atherosclerosis.

Bisphosphonates

The bisphosphonates (BP) are approved therapies for the prevention or treatment of osteoporosis and related fractures. They are currently considered the drugs of choice because of their demonstrated efficacy and safety in reducing vertebral as well as non vertebral fracture risk (9). Bisphosphonates are stable analogues of inorganic pyrophosphate, in which the oxygen bridge of the P-O-P bond has been replaced by a carbon binding with two additional side chains. The more potent BP have nitrogen atoms in their side chains. They appear to inhibit selectively farnesylpyrophosphate, an enzyme downstream of HMG-coenzyme A in the mevalonate pathway of cholesterol biosynthesis. BP then inhibit the prenylation of small GPT-binding proteins, and reduce the synthesis of isoprenoid lipids. BP not containing amino groups (clodronate and etidronate) do not interfere with the synthesis of lipids, but are metabolized to a cytotoxic analogue of ATP, which induces the death also of cells of osteoclast lineage (10). Several studies reported that both amino and non-amino BP inhibit the development of experimental atherosclerosis, an effect that appears independent of the lowering of cholesterol level in the circulation. Animal studies have shown that etidronate decreases the amount of lipid-containing plaques in medium-sized arteries and limits the proliferation of lipid-laden foam cells in the aorta (11, 12). Intravenous clodronate was able to reduce significantly the area of lipid-stained atheromatous lesions in the aorta of rabbits fed with high-cholesterol diet (13). Alendronate and ibandronate (both nitrogen-containing BP) inhibit calcification of arteries and heart valves in rats treated with warfarin (14). Human studies seem conflicting. Koshiyama et al. (15) reported a decrease in carotid intima-media thickness (CIMT) (an early marker of atherosclerosis) in osteopenic type 2 diabetic patients treated for one year with cyclic etidronate, whereas Delibasi et al. (16) observed no significant change in CIMT in postmenopausal women with osteoporosis after one year of treatment with alendronate 70 mg/week. A retrospective study on the assessment of mortality in the patient population from the Risedronate Phase III Clinical Trial Progamm (17) revealed a trend toward lower cardiovascular mortality in the ITT group compared with placebo, largely dependent on a significant reduction in mortality due to stroke in the risedronate-treated patients.
The biological mechanisms of such effects are not clear. Adami et al. (18) reported that in osteoporotic women neridronate (an aminobisphosphonate structurally very similar to pamidronate) produced a significant decrease in serum LDL-cholesterol and ApoB with a concomitant increase in serum HDL-cholesterol and ApoA-I, with non significant changes in mean total cholesterol and triglycerides. If this effect of neridronate on the lipid profile

holds for BPs as a class, clinical implications may be relevant and favourable. A further possible mechanism by which BP may be protective with respect to cardiovascular morbidity and mortality could be related to a direct effect on arterial wall. BP are taken up by bone tissue, however they accumulate also in the arterial walls, regardless of the presence of calcified atheromatous lesions (19). Macrophages and some other endocytotic cells are able to internalize BP (20), which may then interact with enzymes in these cells and influence the inflammatory re-sponse leading to atherosclerosis and further vascular events. Further studies are needed to evaluate the clinical relevance of such findings. The possibility to deliver a high concentration of BP to tissues by encapsulating them in liposomes (8) makes this compounds more available for phagocytosis by macrophages, and may increase their potential for therapeutic use in patients.

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl-coenzime A (HMG-CoA) reductase, the limiting step in the cholesterol synthesis pathway. Statins are largely prescribed worldwide because of their demonstrated effect to decrease cardiovascular morbidity and mortality. As a consequence of the inhibition of HMG-CoA reductase, statins decrease the production of mevalonate, geranyl pyrophosphate, and farnesyl pyrophosphate, then reducing prenylation of small GTP-binding proteins (21). Statins share these effects with nitrogen-containing BP, and could inhibit inflammation intracellularly interfering with Ras superfamily protein function (22). Like BP, statins can inhibit osteoclast formation and activity (23), giving powerful evidence for therapeutic linkage of atherosclerosis and osteoporosis. Besides the inhibition of bone resorption, statins also stimulate osteoblasts differentiation by enhancing expression of bone morphogenetic protein 2 in cultured osteoblasts, neonatal murine calvaria and the cortical bone of mice (24). This finding was confirmed in experimental and clinical studies (25,26), suggesting that statins may act as anabolic agents in the bone tissue.
Although several case-control studies have found a beneficial effect of statins on fractures, no placebo-controlled clinical trial has been performed to evaluate the effect of statins on fracture risk. Many studies have evaluated the effects of statins on bone mineral density (BMD), a less stringent criterion than the search for an effect on fracture risk, but still a valuable step in the evaluation of anti-osteoporotic drugs. A recent meta-analysis by Uzzan et al. (27) on the effects of statins on bone mineral density, studied the impact of statins on BMD at various sites and compared the effects of lipophilic and more hydrophilic statins. This meta-analysis analyzed sixteen studies, which included mostly postmenopausal osteoporotic women under statins. The effect size reached a statistically significant value for total hip and femoral neck BMD, but not for lumbar spine BMD. The meta-analysis also showed that lipophilic statins (simvastatin and lovastatin) had an effect on total hip and femoral neck BMD significantly greater than more hydrophilic statins (pravastatin, atorvastatin, and fluvastatin). Favourable actions of statins on bone may be part of their pleiotropic effects, which include upregulation of eNOS (the isoform most widely expressed in bone) (28), inhibition of plasminogen activator inhibitor-1 (29), activation of protein kinase Akt, a further inducer of eNOS (30), an over-expression of Kloto mRNA (a peptide hormone involved in the pathogenesis of osteoporosis and vascular disease in mice) (31, 32), and an enhanced production of OPG by osteoblast (33). A study by Wang et al. (34) showed that simvastatin can promote fracture healing in ovariectomized rats when injected in close proximity of the fracture, a procedure that prevents statins from being stored in the liver and that results in much higher concentration at the fracture site. Statins and bisphosphonates have similar mechanisms of action, in that both of them inhibit cholesterol synthesis and cause isoprenoid depletion, which in turn inhibits the signalling pathway for IL-6 mediated inflammation. Statins and bisphosphonates inhibit bone resorption, however only statins might directly stimulate bone formation. One could hypothesize that combination treatment with statins and BP should be the most effective strategy for prevention and therapy of atherosclerosis, CVD, and osteoporosis. To date, only a study attempting to investigate prospectively whether statins have an additive effect to BP in producing an increase in lumbar spine and total hip BMD has been performed (35). This study reported that statins have modest additive effects to bisphosphonates in increasing spine BMD, but produced no additive effect at femoral level.
Although statins would represent a theoretically ideal candidate as antiosteoporotic drug, large prospective randomized placebo-controlled trials are required before acknowledging them in osteoporosis the same reassuring role they play in cardiovascular disease.

β-blockers

The discovery of the role of leptin in the regulation of bone mass has given new enphasys on the role of the sympathetic nervous system in the regulation of bone turnover. Studies in animals have shown that propranolol antagonizes the negative effect on bone induced by intracerebral injection of leptin (36). β-blockers also increased bone formation in ovariectomized rats (36). It has been reported that β-blockers exert their action on bone through a stimulation of bone formation and a reduction of bone resorption (37), the latter as a result of an inhibition of the stimulating action of sympathetic nervous system on the beta-adrenergic receptors on osteoblast, which leads to an overproduction of RANKL. Since β-blockers are widely used in human disease, and particularly in cardiovascular disease, a possible effect on bone mass would be of interest with respect to the treatment of osteoporosis. Two recent epidemiological studies have shown that the β-blocker use was associated with a 20-30% decrease in fracture risk (38,39). These data were not confirmed in the study by Reid et al. (40), who reported an inconsistent association between β-blocker use and BMD. This inconsistency may be due to the fact that the effect of sympathetic nervous system on bone depends on several factors like mechanical loading, muscle mass, and a balance among different hormonal effects. More recent papers also provide conflicting results. Bonnet et al. (37) reported that patients taking β-blockers had higher spine (+3%) and femoral neck (+4%) BMD, and a 49% reduction in fracture prevalence than controls. Interestingly, β-blocker users had a significant increase in femoral neck cortical width. Bone parameters differences are however attenuate if weight is taken into account. Meisinger et al. (41) studied the association between use of β-blockers and incidence of fractures in a large population over a mean follow up period of 10.7 years. They found that the use of β-blockers was associated with a lower risk of any fracture (odd's ratio 0.57). Perez-Castrillon et al. (42) prospectically studied a small sample of 40 patients hospitalized for an acute myocardial infarction; 30 of them were treated with cardioselective β-blockers. After one year of follow up, no beneficial effect of treatment on BMD or biochemical parameters of bone metabolism was observed. Although of great interest, available data do not allow to conclude that β-blockers are expected to exert beneficial effects on bone of such a relevance to recommend the use for osteoporotic treatment. *Ad hoc* studies using a less heterogeneous population are needed to detect a clear effect of β-blockers on bone mass.

Table I - Therapies which may exert dual-action effects on both cardiovascular and skeletal system.

Therapies	Actions on cardiovascular system	Actions on bone
Bisphosphonates	– Inhibit arterial and heart valves calcification. – Lower LDL-cholesterol	– Inhibit osteoclast activity – Increase bone density – Reduce fracture risk
Statins	– Lower cholesterol – Antiatherogenic	– Stimulate osteoblast differentation. – Increase bone density – Reduce fracture risk?
β-blockers	– Control blood pressure – Reduce cardiovascular mortality	– Increase bone density – Reduce fracture risk?
Anti-RANKL antibodies	– Uncertain	– Decrease osteoclast activity – Increase bone density

Drugs interfering with the OPG/RANKL/RANK system

The role of the RANK/RANKL/Osteoprotegerin pathway has been well documented in animal and clinical studies (43-46). This system is perhaps the best candidate to play a central role in the bone-arterial wall biological linkage. Breafly, RANKL (Receptor Activator of Nuclear Factor B Ligand) binds to and activates its receptor RANK, a protein receptor on the surface of osteoclast precursor, and induces differentiation, activation and survival of osteoclasts, thus increasing bone resorption. Osteoprotegerin (OPG) is a glycoprotein produced by osteoblast, which acts as a natural inhibitor of RANKL, preventing RANKL from binding to its osteoclast receptor, and, as a consequence of this, preventing bone resorption and bone loss. OPG knockout mice have severe osteoporosis and present multiple osteoporotic fractures, and, surprisingly, also develop severe medial arterial calcifications. The mechanism by which OPG regulates calcification in arteries is not fully understood. Min et al. (47) reported that OPG injected into adult mice lacking OPG reversed the osteoporotic phenotype but did not reduce arterial calcification, while the vascular abnormalities were completely rescued using an OPG transgene approach. Clinical data appear conflicting. Kiechl et al. (48) showed a positive association between high serum OPG levels and serious atherosclerotic vascular disease and mortality. Surprisingly, postmenopausal osteoporotic women have serum OPG levels higher than age-matched controls (49). Since also patients with coronary artery disease have OPG serum levels higher than healthy subjects (50), the role of OPG in humans appears more complex than in animals. A human monoclonal antibody for human RANKL is under investigation in osteoporotic women (51, 52). If the animal model holds for human, a reduction in cardiovascular morbidity and mortality should be expected in treated patients. Data on this point are however not still available.

Conclusions

Available data would suggest that some drugs approved for the treatment of osteoporosis, and some other drugs known to reduce the risk of mortality in cardiovascular disease, may have dual action in that they could improve bone density, reduce fracture risk and at the same time limit progression of atherosclerosis (Table I). This appears particularly useful in polymedicated patients, where the use of a treatment having both cardiovascular and skeletal beneficial effects would be very useful. The existence of a biological linkage between osteo-porosis and atherosclerosis, and particularly atherosclerosis with calcifications, encourages to designs controlled studies to better clarify the outcome of such therapies.

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