Epidemiology of osteoporosis

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Summary

Osteoporosis is defined as a reduction in bone mass and disruption of bone architecture, resulting in reduced bone strength and increase of bone fractures and it is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites. The lifetime risk for any fragility fractures in Caucasian women at age 50 years approaches 40% and 13% in men. During childhood and adolescence there is a rapid linear and appositional skeletal growth with a peak bone mass attained during the third decade of life. During adult life the mechanical integrity of the skeleton is maintained by the process of bone remodeling, in which old bone is removed by osteoclasts and subsequently replaced by new bone, formed by osteoblasts. In recent years, we have come to appreciate that the close association between bone and vasculature plays a pivotal role in the regulation of bone remodeling and fracture repair. Vitamin D, OPG/RANK/RANK-L system, Matrix Gla-proteins (Mgp) and Fetuin-A/calcium phosphate mineral phase complex play an important role in the regulation of bone homeostasis and vascular calcifications. A greater understanding of the biological linkages may lead to new dual-purpose therapies that may ultimately prevent the adverse outcomes of osteoporosis and atherosclerosis.

KEY WORDS: osteoporosis, atherosclerosis, vitamin D, OPG/RANK/RANK-L system, Matrix Gla-proteins (Mgp), fetuin-A/calcium phosphate mineral phase complex.

Osteoporosis is defined as a reduction in bone mass and disruption of bone architecture, resulting in reduced bone strength and increase of bone fractures. Fragility fractures are the hallmark of osteoporosis and are particularly common in the spine, hip and forearm but may also affect other sites (1). Osteoporotic fractures are one of the most common causes of disability and a major contributor to medical care costs in many regions of the world. One out of every two women and one in four men over 50 will have an osteoporosis-related fracture in their lifetime. Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites (2). The lifetime risk for any fragility fractures in Caucasian women at age 50 years approaches 40% and 13% in men (3). Hip fractures have an overall mortality of 15-30% (4), the majority of excess deaths occurring within the first six months after the fracture. They are associated with considerable morbidity, necessity hospital admission for an average of 20-30 days (5). In addition, the risk of future vertebral fractures increased with the number of prevalent fractures, independently of age and BMD (6). The identification of risk factors for fracture has been widely used in case finding strategies. The diagnosis of osteoporosis centers on the assessment of bone mineral density at the hip using DXA. However, other sites and validated techniques can be used for fracture prediction. Several clinical risk factors contribute to fracture risk, in part independently of BMD. These include age, prior fragility fracture, premature menopause, a family history of hip fracture and the use of oral corticosteroids (7). Hip fracture is associated with a higher mortality rate in men than in women. However, mean age of men and women with hip fracture differs markedly. Thus, some of the differences in the clinical pattern and outcome between genders could be related to different ages. Although the reduction in life expectancy was similar in both genders, the proportion of the years of life lost was higher in men, suggesting a worse impact of hip fracture on survival in men, even after consideration of the higher mortality rate in the general male population (8). During childhood and adolescence there is a rapid linear and appositional skeletal growth with a peak bone mass attained during the third decade of life. The regulation of peak bone mass is not well understood but a number of factors have been identified and the most important are genetic influences, physical activity and nutritional factors.

During adult life the mechanical integrity of the skeleton is maintained by the process of bone remodeling, in which old bone is removed by osteoclasts and subsequently replaced by new bone, formed by osteoblasts. During the menopause there is an increase in bone turnover and a decrease in bone formation within individual remodeling units, leading to rapid bone loss (9). Estrogen play a pivotal role in the skeleton acting in order to conserve bone mass. Estrogen suppress bone resorption and maintains a balanced rates of bone formation and bone resorption (10). Estrogen deficiency affects remodeling in several ways. First, it increases the activation frequency ("birth rate") of Basic Multicellular Units (BMUs), which leads to higher bone turnover. Second, it induces a remodeling imbalance by prolonging the resorption phase [osteoclast apoptosis is reduced] (11) and shortening the formation phase [osteoblast apoptosis is increased] (10). Also, increased osteoclast recruitment extends the progression of the BMU. As a consequence of these changes, the volume of the resorption cavity is increased beyond the capacity of the osteoblasts to refill it (12). As with Estrogens (E), the major action of Testosterone (T) at the tissue level is to reduce bone resorption (13). However, much of this action is indirect via aromatization of T to E (14). As with E, T also increases the lifespan of both osteoblasts (10) and osteoclasts (12, 15) by affecting apoptosis.

Although Bio-Estradiol (BioE) and Bio-Testosterone (Bio T) decrease with aging in both sexes (16), the mechanism of the decrease differs: in women, it is caused by menopausal ovarian

failure, whereas, in men, it is caused by the progressive age-related increase in serum SHBG. Although the testis does not fail suddenly, as the ovary does, stimulation studies with clomiphene citrate have established that aging men have a decreased testicular secretory reserve capacity. Because T decreases the hepatic production of SHBG, decreased secretion of T with aging will increase levels of serum SHBG. In addition, decreases in circulating levels of Bio E in aging men will negatively feed back on the hypothalamus to reduce GH pulsatile secretion further. This then will decrease the production of IGF-I and IGF-binding protein 3 (17) that will increase SHBG synthesis still further (18). The increased serum SHBG binds tightly to serum T, rendering a progressively larger fraction unavailable to tissues. Although the decrease in BioT increases gonadotrophin secretion, the aging testis is unable to respond by increasing serum levels of BioT and E to within the young adult range. Thus, a vicious cycle is initiated that leads to progressive age-related decreases in the Bio levels of both sex steroids in men (12).

In recent years, we have come to appreciate that the close association between bone and vasculature plays a pivotal role in the regulation of bone remodeling and fracture repair. In 2001, Hauge et al. (19) characterized a specialized vascular structure, the bone remodeling compartment (BRC). Cytokines including osteoprotegerin (OPG) and RANK-L make the BRC the structure of choice for coupling between resorption and formation (19, 20). The demonstration of specialized vascular spaces in bone adds a new dimension to our understanding of bone biology in general and bone remodeling in particular (20). Vascular calcification and bone loss are common age-related processes that are influenced by both genetic and non genetic factors. The SOF (Study of Osteoporotic Fractures) study did find that an increased heart rate was associated with risk of a hip fracture (21). On the other hand HERS (Heart and Estroprogestinic Replacement Study) enrolled women who already had documented Coronary Artery Disease. These women did not have markedly decreased bone density. Patients with more serious heart failure, however, have osteoporosis (22). In addition a specific association between the severity of osteoporosis and the risk of cardiovascular events have been studied in healthy postmenopausal women and a biological link between bone metabolism and arteriosclerosis has been found, suggesting that postmenopausal women with osteoporosis should also be considered for cardiovascular intervention to prevent adverse outcome (23). Associations between calcifications of the aorta and osteoporosis have been since the '50s.

Factors influencing bone metabolism and vascular system

Vitamin D

Vitamin D play an important role in the regulation cardiovascular system. Calcitriol is able to induce vascular calcification in bovine vascular smooth muscle cells (BVSMCs) increasing the production of alkaline phosphatase and inhibit PTHrP secretion (24). In addition, vitamin D is an important regulator of the renin-angiotensin system (RAS). Numerous studies have shown that the serum level of 1,25-dihydroxyvitamin D3 is inversely associated with blood pressure in normotensive and hypertensive subjects and more interestingly inverse relationship has also been reported between circulating 1,25-dihydroxyvitamin D3 and plasma renin activity in patients with essential hypertension (25, 26). In addition, 1,25-dihydroxyvitamin D3 and calcium insufficiency may negatively influence glycemia, whereas combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism (27).

OPG/ RANKL/ RANK system

Receptor activator of nuclear factor-kB ligand (RANK-L), its membrane-bound receptor RANK and its soluble decoy receptor OPG are members of the tumor necrosis factor (TNF) receptor superfamily. These factors have been identified as candidate mediators for paracrine signaling in bone metabolism but also involved in modulation of the immune response (28). The pleiotropic effects of the OPG/RANKL/RANK system, such as modulation of cell survival, mineralization and inflammation, make it an interesting candidate mediator in the progression and destabilization of atherosclerotic lesions (29). Mice with a deletion of *OPG* gene develop arterial calcification as well as osteoporosis with multiple fractures (30). The mechanism by which OPG regulates calcification is not well known. OPG injected into adult mice deficient in OPG reversed the osteoporosis phenotype but did not diminish arterial calcification and only the *OPG* transgene in the OPG deficient mice rescued both arterial calcification and osteoporosis (31, 32). Nevertheless, Price et al. (33) tested the efficacy of osteoprotegerin as an inhibitor of arterial calcification in two animal models. In the first model arterial calcification was induced by treatment with the vitamin K antagonist, warfarin and in the second model arterial calcification was induced by treatment with toxic doses of vitamin D. The authors concluded that doses of osteoprotegerin that inhibit bone resorption are able to potently inhibit the calcification of arteries that is induced by warfarin and by vitamin D (33). On the other hand the widened hypertrophic chondrocytes layer in most knockout mice is focally altered by the invasions of highly vascularized proliferating cell tissue (34). However RANKL and RANK transcripts could only be demonstrated in calcified arterial lesions of OPG-deficient mice but not in wild-type mice and they have not been shown to be directly involved in human vascular diseases (35). Kim and colleagues (36) reported that RANKL activates vascular endothelial cells and induces adhesion molecule expression, endothelial tube formation and angiogenesis *in vivo* (36). In addition RANKL increases vascular permeability with leukocytes extravasation, increased permeability and angiogenesis. These processes are mediated by eNOS. It is noteworthy that the effects of RANKL are not exclusively eNOS/NO-dependent. In fact, a NOS inhibitor or eNOS deletion significantly diminishes, but does not completely abolish the effects of RANKL (37). Evidences from several sources suggests that NO can mediate bone loss and these data open new connections between the fields of vascular biology , inflammation and bone metabolism.

Matrix Gla-proteins (Mgp)

Mgp are part of the family of mineral-binding proteins, including osteocalcin, that contain γ-carboxylated glutamate residues. Under carboxylated Mgp has bee isolated from calcified atherosclerosis plaques of aging rats (38). Mice with a disrupted *Mgp* gene have an extensive calcification in the aorta and its branches led to their rupture and hemorrhage. In addition these animals showed disrupting chondrocytes columns, short stature, osteopenia and fractures (38, 39).

Fetuin-A/calcium phosphate mineral phase complex

Fetuin is member of the cysteine superfamily of cysteine protease inhibitors. It is synthesized in the liver and in present in the bone, tooth and serum . The knockout mice for *Fetuin* gene showed a low mineralized bone, cartilage calcification and extraskeletal calcifications (40). The physiological consequence observed in the fetuin knockout mice are the increase of systolic and diastolic blood pressure, severe nephrocalcinosis, secondary hyperparathyroidism and osteoporosis (40).

Conclusions

Many factors influence the biological linkages in humans that regulate osteoporosis and atherosclerosis with calcification. Combined therapies now available may enhance bone density and limit atherosclerosis progression. A greater understanding of the biological linkages may lead to new dual-purpose therapies that may ultimately prevent the adverse outcomes of osteoporosis and atherosclerosis.

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