Correlation between osteoporosis and cardiovascular disease

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Summary
Several evidences have shown in the last years a possible correlation between cardiovascular diseases and osteoporosis. Patients affected with osteoporosis, for example, have a higher risk of cardiovascular diseases than subjects with normal bone mass. However, the heterogeneous approaches and the different populations that have been studied so far have limited the strength of the findings. Studies conducted in animal models show that vascular calcification is a very complex mechanism that involves similar pathways described in the normal bone calcification. Proteins like BMP, osteopontin, osteoprotegerin play an important role at the bone level but are also highly expressed in the calcified vascular tissue. In particular, it seems that the OPG protect from vascular calcification and elevated levels have been found in patients with CVD. Other factors like oxidative stress, inflammation, free radicals, lipids metabolism are involved in this complex scenario. It is not a case that medications used for treating osteoporosis also inhibit the atherosclerotic process, acting on blood pressure and ventricular hypertrophy. Given the limited amount of available data, further studies are needed to elucidate the underlying mechanisms between osteoporosis and cardiovascular disease which may be important in the future also for preventive and therapeutic approaches of both conditions.

KEY WORDS: osteoporosis; cardiovascular disease; vascular calcification

Cardiovascular disease and osteoporosis are important causes of morbidity and mortality in the elderly. Traditionally these two conditions were considered unrelated and their coexistence has been attributed to independent processes exclusively related to age. However an increasing number of biological and epidemiological evidence has provided support for a link between the two conditions that have been shown to share common pathophysiological and genetic risk factors (1-5).

The possible link between cardiovascular disease and osteoporosis stimulates today to analyse not only the evidence of a possible association, but also to identify common pathogenetic pathway.

To date studies to identify them are numerous, but the great heterogeneity of the population makes it difficult to perform a correct meta-analysis. However the majority of these studies have shown that individuals with cardiovascular disease have a higher risk of experiencing bone loss and thus greater predisposition to risk of fracture. On the other hand there is growing evidence that individuals with low bone mass have higher mortality for cardiovascular events compared to patients with cardiovascular disease with normal bone mass.

Vascular calcification and bone mineralization share a number of interesting anatomical and pathophysiological common features. In fact the calcification of the arterial tissue is not just a passive process of precipitation or absorption of phosphate and calcium but it is a highly organized and regulated by mechanisms similar to those involved in bone mineralization (6-9).

Vascular calcification is an active process, regulated by factors known to be primarily involved in the osteogenesis process. These include the BMP (Bone morphogenetic protein), the ALP (alkaline phosphatase), the OPN (osteopontin) and the MPG (Gla protein of matrix) (10, 11).

Calcification is a consequence of bone formation triggered by Osteoblast-like cells. Vascular smooth muscle cells able to differentiate into Osteoblast-like cells, were shown to form nodules and mineralize spontaneously. In vitro, these osteoblastic cells produce hydroxyapatite, an important mineral in bone formation.

The transformation of vascular smooth muscle cells in Osteoblast-like cells is promoted by several factors and stimuli such as: BMP, Rank-L, oxidative stress, inflammation, oestrogen deficiency. These osteoblastic cells produce ALP, osteocalcin and other important factors to mineralization (10).

The BMP is a powerful growth factor on Osteoblast differentiation and also seems to be an important mediator of vascular calcification. This has been highlighted (10, 12), in the atheromatous plaques, where the endothelial cells, foam cells and smooth muscle cells exhibit greater BMP2 and
BMP4 expression. 

In vitro it has been seen that there are several factors that can cause cardiovascular disease such as oxidative stress, oxidized LDL, the TNF-alpha can up-regulate the expression of BMP in endothelial cells.

The OPG is a glycoprotein which accumulates in extracellular matrix of bone tissue where it binds to calcium and hydroxypatite. The OPG, which is expressed in the bone tissue, is also found in atherosclerotic arteries and its elevated serum levels are associated with vascular calcifications.

The ALP is located on the osteoblasts surface and is often used as a marker of bone turnover. It is an enzyme that catalyzes the hydrolysis of esters. Inflammation and oxidative stress induce an increase in ALP in smooth muscle cells in vitro. This increase is associated with an increase in mineralization.

The OPG expressed in vascular and bone tissue is produced by osteoblasts by different factors including BMP, inflammation, estrogens, vitamin D and oxidative stress.

OPG knock-out mice shows an early onset of osteoporosis and increased vascular calcification. In vitro studies shows as the OPG may be important for endothelial cells survival and inhibition of calcification; it appears that the OPG protect from vascular calcification and elevated levels have been found in patients with CVD.

The antibody RANK-L (Denosumab), which inhibits the OPG in experimental animal, prevents calcium deposition at vascular level (10, 13).

Several hypotheses have been proposed to explain the link between the two conditions. One concerns the coexistence of osteoporosis and cardiovascular disease in relation to common etiologic factors besides age, such as smoking, physical activity, alcohol consumption, menopause, hypertension, etc., which can simultaneously promote or inhibit atherosclerosis and bone demineralization. This may partly explain the association between the two diseases, however in many epidemiological studies, the association between osteoporosis and cardiovascular disease remains even after the removal of some of these risk factors (14).

Involved in the progression of two conditions there are common pathophysiological mechanisms which include inflammatory cytokines, endogenous sex hormones, oxidized lipids and dyslipidemia, vitamin K and vitamin D deficiency, low calcium intake, oxidative stress and diabetes in both condition of insulin resistance and lack of insulin production (15-17).

The role of lipids in the association between osteoporosis and cardiovascular disease is controversial today. In mice, the oxidized lipids cause vascular calcifications and inhibit the differentiation of osteoblasts. In mice dyslipidemia is always associated with an increases bone resorption mediated by osteoclasts which leads to osteoporosis (11).

Estrogen deficiency is a major risk factor for osteoporosis and cardiovascular disease. After menopause, estrogen levels decrease dramatically resulting in formation of osteoclasts and bone turnover increase with subsequent rapid bone loss. In addition, the decline in production of estrogen causes secretion of pro-inflammatory cytokines such as IL-6, IL-1, TNF-alpha (18, 19).

In postmenopausal women the risk of cardiovascular mortality, stroke-related increases for each DS decrease bone mass (20).

Inflammation, important in the atherogenic process, involves the release of markers such as pro-inflammatory cytokines and the PCR which are involved in the process and which influence atherosclerosis and bone metabolism by increasing bone resorption through an induction of osteoclastogenesis or even inhibiting the way of OPG (21).

Radicals have an important effect on the osteoclasts differentiation. Oxidative stress is associated with hypertension, atherosclerosis as well as with BMD. Oxidized LDL promotes vascular smooth muscle cells differentiation into osteoblasts, which is inhibited by antioxidant effects.

The free radical Nitric Oxide (NO), is a powerful vasodilator that helps keep the vascular tone and would inhibit collagen and bone loss. Knock-out mice have low bone mass, decreased BMD and reduced the number of osteoclasts which suggest that NO could be involved in osteogenesis (22). The endothelial synthase eNOS, isoform, is present in high concentrations level in bone and play an active role in osteoblast activation and inhibition of bone resorption. Patients treated for one year with NO show an increasing bone mass. Finally the nitroglycerin has proved to be a powerful medicine to enable the osteoclastogenesis and to increase bone mass (22-24).

Atherogenesis and bone loss have in common genetic factors such as mutations in genes related to the osteoprotegerina, the Gla protein of matrix and the apolipoprotein E (ApoE). Mice lacking the osteoprotegerina gene have a greater ability to develop early vascular calcification, osteoporosis, increased risk of CVD and cerebral hemorrhages. Similarly, mice lacking protein Gia of matrix gene showed vascular calcifications, osteopenia and fractures. ApoE genotype was associated with atherosclerosis, end stage renal disease, reduced BMD, risk fracture, hypertension and vascular diseases (1, 11, 25).

Polymorphism in the gene for IL-6, a cytokine involved in bone metabolism and cardiovascular diseases, has shown to be associated with reduced bone mass in postmenopausal women and with increase of PAO, while in men was associated with an increased incidence of cardiovascular disease. Polymorphism of the vitamin D receptor is associated with risk of both vertebral fractures and MI (26).

Other hypotheses suggest a causal relationship between the two conditions. A reduced blood flow supply predisposes to atherosclerosis and could influence the intrasosseous blood circulation. This in turn impairs bone metabolism in the joint and results in osteoporosis. There is evidence that in the case of asymmetrical peripheral arterial disease, the hip bone mineral content in the affected limb is lower than that of the contralateral limb.

Limited physical activity in patients with cardiovascular disease could be consequently responsible for bone loss.

It is also speculated that progressive bone loss is due to deposits of salts, calcium and phosphate in the arterial wall. It has been shown than in patients with femoral neck fracture, spraying blood vessels proximal femurs are often atherosclerotic.

Finally evidence that some medications such as statins, insulin, antihypertensives and bisphosphonates are effective on both osteoporosis and cardiovascular disease, suggests a common pathophysiological basis.

Experimental studies in mice have shown that bisphosphonates, widely used as treatment of osteoporosis and prevention of risk of fracture, also inhibit the atherosclerotic process, acting on blood pressure and ventricular hypertrophy (27).
Correlation between osteoporosis and cardiovascular disease

Raloxifene, a selective modulator of estrogen receptors, useful in preventing osteoporosis and fracture risk, seems to have a positive effect on LDL cholesterol levels and risk of coronary heart disease, especially in postmenopausal women in which improves vascular endothelial function. In this connection it should be remembered that mevalonate, common to both diseases, leads to the synthesis of both cholesterol and prenylated proteins which activate the osteoclast cells. His inhibition induced by statin or bisphosphonates reduces the synthesis of cholesterol and protein prenylation (18, 19, 28).

Statins reduce cardiovascular mortality by regression of atherosclerotic plaque and decrease LDL cholesterol levels in patients with dyslipidemia, are also associated with greater bone mineralization in rats and patients with osteoporosis in which is also observed a reduced incidence of fractures. In conclusion, the association between osteoporosis and cardiovascular disease, not just age dependent, could allow an early identification of those at high risk. Further elucidation of the mechanisms underlying the link between osteoporosis and cardiovascular disease are crucial to understanding the basis for preventive and therapeutic approach of both conditions (1, 17).

References