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Review Article

Role of Vascular Factors in Osteoporosis

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Osteoporosis is a silent epidemic in the world today. With the increase in the elderly population, there will be an increase in the prevalence of osteoporosis, and so the need for focused preventive strategies should become a public health priority. Prophylactic therapy and risk-factor reduction is important, as this is likely to be cost effective. There are scientific observations that point out that vascular dysfunction seen with aging may be related to the pathogenesis of osteoporosis. Here we review this relationship from a different angle. We think aggressive control of vascular risk factors in addition to the known existing osteoporosis risk factors may help to reduce the morbidity and mortality associated with this disease.

OSTEOPOROSIS is a major public health problem. It is the most common type of metabolic bone disease, and it affects one woman in four and one man in eight above the age of 50 years. It is the most important cause of spine and hip fractures in elderly men and women. Osteoporosis is a multifactorial disorder with many pathogenic processes that eventually contribute to the bone loss leading to osteopenia. Among the multiple risk factors, nutritional, hormonal, and lifestyle factors are recognized as important.

Blood Supply to the Bone

Blood supply is recognized as a vital basis of bone growth and remodeling. In mature bone, the most widely accepted concept of perfusion is that of a centrifugal flow through cancellous and cortical bone, arising from nutrient medullary vessels (1). There are two distinct vascular pathways in cortical bone: one containing longitudinal vessels supplies the haversian system (osteon); the other supplies blood through transverse vessels into the principal vascular and nutrient system (2).

Factors Controlling Microvascular Flow in Bone

Peripheral vascular resistance and the perfusion pressure gradient are two main factors controlling the rate of flow through the microvascular bed. Other factors are hormonal, neural, and metabolic. Extensive innervations of bone vessels with unmyelinated C-fibers suggest an autonomic function of these nerves (3). This is further supported by the data showing that variations in vascular resistance by sympathetic stimulation as well as responses to vasoactive drugs suggest the presence of intraosseous vascular alpha and beta adrenoreceptors (4,5). The response pattern of bone blood vessels to norepinephrine and adenosine was found to be similar to that seen in skeletal muscles (6). Bone and periosteum are innervated by both sympathetic and sensory fibers. Using protein gene product 9.5, a general neural marker, Hukkanen and colleagues showed that most nerve fibers in bone marrow, periosteum, and cortex are closely associated with blood vessels (7). Studies performed on isolated arteries from animal bone and human bone indicate that alpha-1 receptors are responsible for the constrictive adrenergic response in bone (8).

It has been suggested that blood vessels play an ''active'' role in the process of osteogenesis, rather than just the passive role of providing substrates for this process (9). Recent studies suggested a role for endothelium and nitric oxide (NO) in normal skeletal homeostasis, further supporting our view (10,11). Thus factors affecting the integrity of the blood supply to the bone affect the process of osteogenesis.

Vascular Risk Factors and its Possible Association With Osteoporosis

Several risk factors associated with osteoporosis, such as age, postmenopausal state, hypertension, diabetes, smoking, alcoholism, and physical inactivity are also risk factors for vascular diseases. At present, to our knowledge there are no clinical studies that have systematically explained the association between biochemical markers of vascular risk factors (lipid profile, homocysteine, lipoprotein, fibrinogen, C-reactive protein) and osteoporosis.

Smoking

Epidemiological evidence links smoking to osteoporosis. Few studies have shown a loss of bone mineral density in smoking postmenopausal women and older men (12).

Hypertension

Studies have shown that high blood pressure is associated with abnormalities of calcium metabolism. The mechanism by which this occurs is due to a defect in the kidney's ability to handle calcium (13,14). In another study by Cappuccio and associates (15), higher blood pressure in elderly white women was associated with an increased bone loss in the femoral neck.

Lipids

A study by Yamaguchi and colleagues pointed out that low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were inversely and positively correlated with vertebral fractures in postmenopausal women (16). Animal, epidemiological, and clinical studies have shown that lipid-lowering agents such as statins increase bone mineral density and reduce fracture rate (17–20). However, this is not a consistent finding, and some studies have shown no benefit with statin use (21). Chung and coworkers reported that diabetic men using statins showed an increase in bone density compared with diabetic men not requiring this therapy. No significant effect was found in diabetic women (22). In the study of the effect of pravastatin by Reid and associates, fracture prevention was not shown (23). Aminobisphosphonates, which are used in the treatment of osteoporosis, are potent antiresorptive agents that cause osteoclast apoptosis by inhibiting the farnesyl diphosphate synthase enzyme in the mevalonate pathway, which is involved in the synthesis of cholesterol (24). Statins decrease cholesterol synthesis by inhibiting the first step in the same biochemical pathway affected by aminobisphosphonates, and this is their currently proposed mode of action on the bone.

Diabetes

Postmenopausal women who have diabetes or in whom diabetes develops are at higher risk for hip fracture than unaffected postmenopausal women (25). Bone histology studies in humans, as well as in experimental studies, show evidence that decreased bone formation is one major mechanism leading to reduced bone mass. Microangiopathy in the bone tissue has also been discussed as a possible reason for diabetic osteopenia. Some studies found an increased fracture risk especially in older women with type I diabetes; however, other studies did not support this finding (26).

Alcohol

Studies have shown that alcoholism leads to osteopenia and an increased incidence of skeletal fractures (27,28). Alcohol has been shown to decrease bone formation by decreasing osteoblast number, osteoid formation, and osteoblast proliferation (29). Population studies suggest the coronary protective effect of a moderate alcohol intake of 1–3 ounces per day, especially red wine, in decreasing vascular disease. With similar consumption the same protective effect has also been seen in bone. However, heavy alcohol consumption is clearly a risk factor for atherosclerosis. Heavy alcohol intake increases blood pressure and increases triglycerides, which are clearly risk factors for vascular disease. Moderate to heavy alcohol consumption is not only associated with heart and vascular disease, but has also been shown to be positively correlated with a low bone mineral density (30).

Apolipoprotein E

Some authors have shown that the apolipoprotein E4 allele is associated with a low bone mass and hip fractures in postmenopausal women (31–33), whereas others have not reported this association (34).

Coffee

Caffeine causes a temporary increase in blood pressure, which has been thought to be harmless in people with normal blood pressure. Studies are suggesting, however, that regular, heavy coffee drinking (an average of 5 cups per day) can boost blood pressure, and there is growing evidence that a high intake of coffee may be harmful in people with hypertension and may even increase their risk for stroke. Drinking coffee also increases excretion of calcium, which may also affect blood pressure. A caffeine intake of greater than two cups of coffee per day is associated with an increased risk of hip fractures (35,36).

Mortality

According to a study done in the UK, low bone density at the hip is a strong and independent predictor of all-cause and cardiovascular mortality in elderly men (37).

Could Risk Factors for Osteoporosis Also be Risk Factors for Vascular Dysfunction?

Vascular osteonecrosis is defined as the death of cell components of bone (osteocytes and bone marrow cells). It is not a specific entity but rather the final common pathways of various conditions that impair the blood supply to the bone—hence the frequently used term *avascular necrosis*. The chief causes of nontraumatic osteonecrosis of the femoral head are treatment with corticosteroids, sickle cell disease, and chronic alcohol abuse. It is also a well-known fact that sickle cell disease can also cause vaso-occlusive problems or crisis. Secondary osteoporosis is common with steroid use. The bone cells may be affected by a metabolic disorder, and their nutrition may be compromised by a purely local reduction in blood supply to a level that is not, in itself, incompatible with cell survival. Under such circumstances, any additional adverse factors may be fatal to the bone cells. These factors may be cytotoxic agents such as ethanol or substances such as cortisone, regardless of whether the hypercortisonism is exogenous or endogenous. The agents concerned may directly affect the cells or their precursors; equally, they may act through capillary endothelial lesions to produce vascular insufficiency. Adults with osteonecrosis who have heritable thrombophilia and/or hypofibrinolysis may facilitate thrombotic blockage of venous drainage of bone, subsequent increase in bone venous pressure, reduced arterial perfusion, anoxia, and subsequent ischemic bone death (osteonecrosis) (38). In addition, glucocorticoids can induce hypertension, and there is evidence that glucocorticoids potentiate atherosclerosis and thromboembolic events. Furthermore, systemic effects of high-dose steroid use include hyperlipidemia and steroid-induced diabetes. From this evidence we can postulate that steroids and alcohol may cause osteoporosis through a vascular mechanism.

Osteoporosis and Endothelial Dysfunction

Endothelial dysfunction has been identified as an early marker of vascular disease, and it appears before athero-

sclerosis. It has been described in diabetes, hyperthyroidism, and hyperparathyroidism (39–42), which has been associated with the causation of osteoporosis. Patients with osteoporosis may also have several of these traditional vascular risk factors, many of which have also been associated with endothelial dysfunction. It looks as though endothelial dysfunction may play a role in the causation of osteoporosis, but the causal relationship has yet to be determined.

Nitric Oxide and Osteoporosis

In animal studies, the inhibition of NO production in rats was followed by marked bone loss (43). Estrogen receptors have been reported on bovine bone endothelial cells (44). Another study found that inhibition of NO synthase (NOS) activity in rats produced similar changes in bone mass to those seen after oophorectomy and that these effects were prevented by giving NO donors such as nitroglycerine (45). In a study in human subjects (postmenopausal women), neuronal NOS expression was lower (46). On the basis of these studies we can speculate that similar mechanisms occur with estrogen in relation to bone circulation, and estrogen deficiency seen in postmenopausal women could alter the endothelial function of bone microcirculation. Nevertheless, the study of endothelial function and its manipulation may be an exciting area of research and will (one would hope) yield promising, clinically relevant results in osteoporosis.

Could There be a Role for Autonomic Dysfunction in Osteoporosis?

The autonomic nervous system regulates the activity of innervated tissues throughout the body, including the musculoskeletal system. Autonomic dysfunction is common in the elderly population. At present, to our knowledge there is no published study on the role of autonomic dysfunction in osteoporosis, even though there are studies in reflex sympathetic osteodystrophy and rheumatoid arthritis, both of which can cause secondary osteoporosis. In the condition of reflex sympathetic osteodystrophy or Sudeck atrophy there is autonomic dysfunction with involvement of the sympathetic nervous system. In its early stages there is patchy osteoporosis and later diffuse osteoporosis (47). A sympathetic component is suggested by the relative success of sympathectomy in treating some of the manifestations of rheumatoid arthritis (48,49). It is also possible that the autonomic system may be affecting the digestive system, which may interfere with the absorption of calcium in the elderly population. A recent study by Hunt and colleagues showed that estrogen replacement therapy improves baroreflex regulation of vascular sympathetic outflow in postmenopausal women (50).

Are We Already Treating Vascular Dysfunction When We Treat Osteoporosis?

Vitamin D and Its Anticoagulant Effect

The hormonally active form of vitamin D is 1,25-dihydroxyvitamin D3 [1,25(OH) 2D3], which is a principal regulator of calcium homeostasis. It also affects hormone secretion, cell differentiation, and proliferation by a mode of action that involves stereospecific interaction with an intracellular vitamin D receptor (51). It has numerous other physiological functions including inhibition of proliferation of cancer cells, effects on hormone secretion, suppression of T-cell proliferation, cytokine production, and an anticoagulant effect. Analogs of 1,25(OH) 2D3 with anticoagulant activity may serve as adjunctive antithrombotic agents in monocytic leukemia and atherosclerotic disease (52,53).

Hormone Replacement Therapy

The hormonal components of oral contraceptives exert major effects on plasma lipoprotein metabolism that suggest hormone replacement therapy (HRT) in postmenopausal women may have an impact on lipoprotein metabolism as well (54). HRT may be beneficial in postmenopausal women for a variety of reasons (55). Treatment with 0.625 mg/d of conjugated equine estrogen and 2.5 mg/d medroxyprogesterone in postmenopausal women was recently reported to have a significantly greater effect on reducing LDL cholesterol (LDL-C) and apolipoprotein B in LDL pattern B postmenopausal women compared with LDL pattern A women (56). This reduction in LDL-C was accompanied by a significant reduction in small dense LDL, an increase in HDL2b, and an increase in lipoprotein lipase. For postmenopausal women with the LDL pattern B disorder, HRT may be considered as a possible therapeutic maneuver.

A study by Mendelsohn and Karas has shown that estrogen enhances bioavailable endothelial-derived NO (57). Simoncini and associates demonstrated that estrogen receptor isoform ER alpha binds to the P85 alpha regulatory subunit of phosphatidylinositol-3-hydroxylkinase (PI3K). Estrogen-enhanced ER alpha was associated with PI3K activity, leading to the activation of endothelial NOS, independent of gene transcription (58).

Bisphosphonates

The aminobisphosphonates are potent antiresorptive agents that cause osteoclast apoptosis by inhibiting the farnesyl diphosphate synthase enzyme in the mevalonate pathway, which is involved in the synthesis of cholesterol. At the present time, there is no evidence of bisphosphonates affecting lipid metabolism.

Osteoporosis Affects far More Women Than Men, Whereas Atherosclerotic Vascular Disease Is the Opposite. How Can We Explain This?

Osteoporosis in men is not rare; nor are its consequences. The state of affairs is reminiscent of a few decades ago, when heart disease was considered to be primarily a disorder of men. With very little attention given to heart disease in women, it was also assumed that what would be learned about male heart disease would automatically apply to female heart disease. Such erroneous assumptions have also been made in the field of osteoporosis. We are slowly learning about osteoporosis in men. According to a National Institutes of Health report, osteoporosis can strike at any age. More than 2 million American men suffer from osteoporosis, and a million more are at risk. Each year 80,000 men suffer a hip fracture, and one third of these men die within a year.

Female hormones protect against heart disease before menopause. Similarly, increased baseline bone mass in men is protective to some extent against early osteoporosis. This increase in bone mass differs in men from different ethnic groups. More osteoporosis is seen in Asian males. Osteoporosis, as defined by current WHO criteria, appears to be less common in men than in women. Men have larger skeletons, and bone loss starts later in life and progresses more slowly. They do not experience the rapid bone loss that affects women when their estrogen production drops as a result of menopause. However, declining testosterone levels may cause bone loss that is similar to the bone loss that occurs in women at the time of menopause.

In spite of the theoretical relationship of bone loss to andropause, osteoporosis is seen in men under 60 years of age. Could be this related to the relatively common prevalence of atherosclerosis in this population? Some of the studies in which subjects under the age of 60 years had osteoporosis are as follows. Orwoll and colleagues (59) studied the effect of 10 mg of alendronate or placebo, given daily, on the bone mineral density of 241 men aged 31–87 years who had osteoporosis. In their cross-sectional population-based study, Bendavid and associates found that 17.0% of men aged 55–64 years were osteopenic at one skeletal site, 16.5% were osteopenic at two sites, and 13.6% were osteopenic at three or more sites. This cross-sectional study strongly suggested that age-related bone loss occurs in middle-aged men (60). Similar data were found in a study by Cohen-Solal and colleagues (61), who studied 38 middle-aged men with severe idiopathic osteoporosis (mean age 50 $\pm$ *SD* 11 years), presenting with vertebral or peripheral bone fractures as a result of primary osteoporosis. Osteoporosis affects millions of men throughout the world, yet it is underdiagnosed, underresearched, and underreported in men.

Clinical Significance

Osteoporosis is the main cause of bone fractures in postmenopausal women and the elderly population, and it causes deformity, pain, and loss of independence. In the United States, approximately 1.5 million fractures occurs per year and cost 10 billion dollars per year. In the UK, approximately 100,000 hip fractures occur per year and cost an estimated 600 million pounds per year. Because of the increase in the elderly population and the resultant increase in the prevalence of osteoporosis, the need for focused preventive strategies should become a major public health priority.

Prophylactic therapy and risk-factor reduction are important at this point in the population management of osteoporosis. We hope studies on vascular risk factors may provide valuable information about factors contributing to this devastating disease. Aggressive control of vascular risk factors in addition to the existing therapies may help to reduce the morbidity and mortality associated with osteoporosis.

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