Osteoporosis: Causes and consequences

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Postmenopausal osteoporosis is a major international public health problem. Painful and disabling fractures now affect approximately 50% of elderly people, and an increased incidence of fractures is predicted. Consequently there is an urgent need for therapeutic measures to prevent and treat osteoporosis.

Bone mineral density of the spine and hip is correlated with fracture risk. These non-invasive measurements indicate the balance of bone loss via resorption and bone gain via formation. Diet and exercise contribute to building and preserving strong bones.

Osteoporosis may be prevented or treated by agents which retard bone resorption, such as estrogens, calcitonin, and bisphosphonates, and formation-stimulating drugs such as anabolic steroids and fluoride.

OSTEOPOROSIS results from a series of events leading to significant bone loss and fragile, easily fractured bone. This silent disease affects a large number of women, and frequently goes undetected until one or more fractures occur.

Signs of developing osteoporosis are decreased height and 'dowagers hump' as spongy vertebral bone is compressed. In older men and women, fractures tend to occur in the spine, hip and forearm. Fracture incidence is lower in men than women, probably because (a) men have higher peak bone density, (b) men lose less bone during aging, (c) men do not become hypogonadal during normal aging, (d) men sustain fewer falls. Prevalence of fractures is also lower in men, probably due to their lower average life span[1]. Fractures are often painful and disabling in elderly people, and approximately 50% of patients' lives may be permanently altered, since they will never walk unaided after a hip fracture. Approximately 25% of these patients die within six months.

The age-specific incidence of fractures is increasing[2]. The projected number of hip fractures worldwide by 2025 is 1.16 million in men and 2.78 million in women. This will be most apparent in Asia[3]. Most non-hip fractures in the elderly are associated with considerable short-term disability; there are nearly 750,000 non-hip, non-spine fractures each year in the United States alone[4].

Low bone mass is a major contributor to skeletal fragility, but other factors intrinsic to bone and the occurrence of falls and injuries are important. An important and independent risk factor for future fractures is the presence of existing or previous fractures. Gardsell *et al.*[5] showed that previous spine, wrist and hip fractures were independent predictors of future fragility fractures after adjusting for bone mass and falling. Improving muscle strength decreases the chances of falling and may contribute to fracture prevention.

This article reviews the current state of knowledge on osteoporosis.

Bone mineral density

Bone mineral can be measured non-invasively using single- or dual-photon absorptiometry, dual-energy X-ray absorptiometry or quantitative computed tomography. Causes of osteoporosis and fractures are low peak bone density, excessive loss, or both. Multiple prospective studies of postmenopausal women have demonstrated associations between low bone density and fractures[7]. Fracture risk increases progressively, and approximately exponentially, with decreasing levels of bone mineral density. Women with average bone density have twice the fracture risk of women with bone density 1 SD above the mean; those with bone density 1 and 2 SD below the mean are anticipated to have fracture risks approximately two and four times greater than those with average bone density[8]. Bone mineral density of the femoral neck is a strong predictor of future fractures; bone density of the spine and radius are less strongly associated with the risk of hip fractures[9].

In adults, bone mineral density, which indicates bone fragility, is the result of a complex factorial equation involving factors including ethnic origin, diet, timing of menarche and menopause, physical activity and ovarian cyclicity[10]. Recently, Morrison *et al.*[11] published surprising evidence that as much as 75% of the total genetic effect on bone mineral density in postmenopausal women could be predicted by common allelic variants in the gene encoding the vitamin D receptor, which is involved in bone metabolism. African racial origin is associated with stronger bone and increased resistance to osteoporosis[12]. The racial difference becomes manifest at puberty; prepubertal black and white girls had similar vertebral bone mineral density but significant differences favouring greater mass in black girls became apparent as bone mass increased during puberty[13]. Investigations of underlying differ-

ences in hormonal balance and bone metabolism may help in devising strategies to attain higher peak adult bone mass.

Bone anatomy

Most bone is cortical bone, which is the dense outer shell of the skeleton. In contains perforations called Haversian canals which allow the passage of cells and nutrients. Trabecular or cancellous bone is encircled by cortical bone and is a network of bony spicules called trabeculae. Trabecular bone comprises 20% of the skeleton and is found in the vertebral bodies and distal ends of long bones such as the radial head and to a lesser extent in the hip. Trabecular bone is a supporting structure which leaves significant room for hematopoietic marrow tissue[14]. The preferred objective of osteoporosis treatment and prevention is to increase the strength of trabecular bone and thereby to increase resistance to fractures.

Bone metabolism and physiology

Bone undergoes a constant cycle of resorption and formation. Each bone remodelling unit consists of osteoclasts and osteoblasts. Resorption is carried out by osteoclasts, which originate in the bone marrow. Precursor cells from the bloodstream collect at bone resorption sites and fuse to form multinucleated osteoclasts which invade the bone surface and erode it, dissolving the mineral and matrix. Osteoblasts, the cells which form new bone, then arrive and lay down collagen and minerals. Osteoblasts are derived from precursor cells in the blood and migrate to areas where bone has been eroded by osteoclasts. Many osteoblasts become trapped in the bone matrix and survive as osteocytes. These osteocytes, which are found in mineralized lacunae, are stimulated by PTH and inhibited by calcitonin to control the dissolution of bone calcium. Calcium is rapidly conducted from these lacunae to the bone surface and to extracellular fluids.

Bone resorption and formation are tightly coupled processes which are kept in balance in healthy people, the net result being a constant amount of bone mineral in the body. This balance may be upset to favor a single process by diseases such as postmenopausal osteoporosis, hyperthyroidism, hyperparathyroidism, and Paget's disease. The rate of bone turnover can be indirectly assessed by measuring levels of urinary degradation products of bone collagen (pyridinoline and deoxypyridinoline) and collagen (hydroxyproline) and serum levels of osteocalcin, a specific bone protein[15]. Biochemical parameters help to monitor response to drug therapy and to differentiate rapid bone losers, who have a greater need for therapy, from slow losers.

Diet

Adequate dietary intakes of calcium and protein are essential for attainment of adequate peak bone mass and subsequent reduction of bone loss. It is not known whether high dietary calcium accelerates bone growth to peak mass or permits achievement of a higher mass. Estimates of optimal calcium intake for women are as follows: ages 2–8: 1000 mg/day; ages 9–17: 1600 mg/day; ages 18–30: 1100 mg/day; postmenopause: 1500 mg/day[16].

Increasing daily calcium intake from 80% of the recommended daily allowance to 110% by administering calcium citrate malate resulted in significant increases in vertebral spine and total body bone mineral density in adolescent girls. The increase per year among the supplemented group translates into an 1.3% gain in skeletal mass per year during adolescent growth, which may provide added protection against fractures[17].

The lifetime intake of caffeinated coffee is directly correlated with decreased bone mineral density in older postmenopausal women; the deleterious effect of caffeine was offset by milk consumption[18]. Vitamin D supplements can offset the wintertime bone loss in postmenopausal women in northern latitudes who are subject to variations in sunlight exposure[19].

Exercise

Exercise plays an important role in preventing osteoporosis by enabling an individual of any age (childhood to geriatric) to achieve greater bone mass. Inactivity and lack of weight bearing (mechanical loading, gravitational force) especially prolonged immobility due to illness, cause bone loss[20].

Mechanical forces modulate bone mineral density around an individual's genetically determined level, with increased regular vigorous loading and weight-bearing exercise resulting in bone mass improvements[21,22]. Bone mass is adjusted via a feedback loop; increased strains caused by muscular pull and gravity regulate the balance of bone loss and formation to increase bone mass; below-normal strains produce a signal to alter the balance in favor of bone loss. There is a constant relationship between muscle mass and skeletal mass because total muscle mass.bone mass ratio remains fairly constant throughout life; the tendency to become sedentary as we age therefore may undermine the health and strength of our bones.

Once osteoporosis develops, activity levels are likely to decrease because of pain, disability, and fear of further fractures. Carefully designed exercises are still useful in potentially reducing the rate of later fractures, and improving the self-image of the stooped individual by lessening the dowager's hump.

The benefits of exercise are confined to the region where the exercise is practised, for instance, walking will not increase bone density of the radius[23] and bone mass frequently differs between dominant and non-dominant arms, in parallel with muscular strength. Whole body exercise is therefore necessary throughout an individual's lifespan to build up bone mass until menopause or andropause and slow bone loss after that time.

Bone loss induced by severe estrogen deficiency and progesterone insufficiency, as in amenorrheic girls or menopausal women, is not entirely compensated for by vigorous exercise; marked bone loss occurs as a consequence of the amenorrhea which frequently occurs in women during intense exercise training and weight reduction[24].

Medical management of osteoporosis

Osteoporosis may be prevented or treated by agents which retard bone resorption, such as estrogens, calcitonin, and bisphosphonates, and drugs such as anabolic steroids and fluoride which stimulate bone formation.

Hormone replacement therapy

The effectiveness of estrogen replacement therapy in preventing and treating osteoporosis in postmenopausal women has been demonstrated in a number of clinical trials and epidemiological surveys. Protective effects on vertebral bone mineral density have been demonstrated for conjugated equine estrogens[25,26], micronized estradiol[27], estrone sulphate[28,29], estradiol pellets[30], and transdermal estradiol[31,32].

Estrogens may act directly on human bone cells through a classical receptor-mediated mechanism. Eriksen *et al.*[33] demonstrated nuclear binding of estradiol in human osteoblast-like cells in culture and identified messenger RNA for the human estrogen receptor. Pretreatment with estradiol increased the specific nuclear binding of progesterone in certain cell strains of these osteoblast-like cells, indicating that estrogens stimulated progesterone receptor synthesis in bone cells, similar to receptor induction in other estrogen target tissues.

Many postmenopausal women stop taking estrogen therapy after a few months to a few years. Bone loss accelerates after estrogen withdrawal, either at the time of ovarian failure or upon discontinuation of estrogen treatment[34,35]. In women who discontinue estrogens, the amount of bone 'bought' may be a multiple of the duration of estrogen use and the rate of bone loss in the slow loss phase which follows the rapid bone loss seen immediately after estrogen withdrawal.

In amenorrheic women, severe deficiency of estrogen possibly enhanced by progesterone and androgen deficiency often leads to trabecular bone loss and osteopenia[36]. Progesterone alone prevented oophorectomy-induced bone loss in rats and increased bone formation parameters in rats[37]. Gallagher *et al.*[38], in a two-year study comparing conjugated estrogens and medroxyprogesterone acetate separately and in combination in postmenopausal women, observed a synergism between the hormones and potentiation of a low dose of estrogen by progestogen.

Anabolic steroids

Anabolic steroids significantly increase bone mineral density and testosterone supplementation prevents osteoporosis in hypogonadal men. Anabolic androgenic steroids are postulated to have a direct effect on osteoblasts or their precursors and/or resorption-inhibiting effects. Anabolic steroids given as monotherapy induce an unfavourable lipoprotein profile and should not be given as long-term therapy. When combined with estrogens, however, lipoprotein changes are generally beneficial (Watts *et al.*[39], submitted for publication).

Androgens combined with estrogens as menopausal hormone replacement therapy consistently increase bone mineral density. This has been observed for testosterone[40], methyltestosterone[39], and nandrolone[41]. Nandrolone combined with estrogens and progestins increased bone mineral density in postmenopausal women significantly over three years of treatment[41]. Treatment with nandrolone alone also increased bone mineral in a small clinical study[42]. Stanozolol increased bone mineral density by 4.4% over 29 months in 21 patients compared with 17 placebo-treated patients in whom bone mineral density did not change[43]. Anabolic steroids such as nandrolone may attenuate accelerated post-withdrawal bone loss; Erdtsieck *et al.*[41] observed that a statistically significant elevation in bone mineral persisted at the end of one year of hormonal washout following two years of treatment with nandrolone + estrogen + progestogen compared to estrogen + progestogen.

Calcitonin

Calcitonin directly suppresses the activity of osteoclasts and also inhibits their recruitment. It has been isolated from a number of animal species and injectable salmon and human calcitonin are commercial products.

Daily intramuscular salmon calcitonin at a relatively high dose (100 IU) has been shown to prevent bone loss and slightly increase bone mineral density in women with osteoporotic fractures[44]. In healthy women in early menopause, a much lower dose (20 IU) of synthetic human calcitonin, given subcutaneously three times a week, was as effective as estrogens in preventing spinal trabecular bone loss[45]. Intramuscular administration of

calcitonin is inconvenient and often unacceptable, and consequently intranasal calcitonin is being developed by pharmaceutical companies. Two studies of intranasal salmon calcitonin suggest that it may be efficacious in both the prevention and treatment of postmenopausal osteoporosis[46,47].

Bisphosphonates

Bisphosphonates are stable analogs of pyrophosphate which bind to the bone surface, are incorporated into bone mineral, and inhibit osteoclastic activity. Disodium etidronate has been shown to increase vertebral bone mineral density in women with postmenopausal osteoporosis in placebo-controlled studies conducted in Europe and the US[48,49]. The incidence of fractures was significantly decreased in the European study which enrolled patients with less severe osteoporosis. Fracture incidence improved over the first two years of treatment in the US study, but there was an apparent increase in fractures in the third year and treatment has been extended for additional long-term observations. There is concern that long-term exposure to these drugs may suppress turnover to such a great extent that remodelling ability may be lost (senescent bone); however available animal and clinical data do not support this hypothesis[50].

Alendronate and tiludronate are new and better tolerated bisphosphonates which are currently under clinical investigation in large trials of osteoporosis prevention and treatment.

Fluoride

Fluoride appears to stimulate new bone formation by a direct action on osteoblasts. Both fluorosis and the therapeutic use of fluoride increase the numbers of osteoblasts, possibly by a direct mitogenic effect[51]. The induction of synthesis of abnormal woven bone rather than normal lamellar bone indicates that osteoblast function may be impaired by fluoride under certain conditions[52]. Sodium fluoride increased vertebral bone mineral density[53] and may either increase[54] or decrease[55] the incidence of new fractures. Differences between positive and negative studies may be attributed to the doses used and criteria applied to designate fractures. A major problem is the heterogeneous response to fluoride since only 30 to 40% of patients will exhibit an anabolic response[56].

Upper gastrointestinal side-effects are common, particularly with non-enteric-coated tablets. Approximately 25% of patients will develop pseudo-arthritic pains in the lower limbs, which usually disappear after a few weeks of therapy and may be avoided when resuming treatment by starting with a lower dose and carefully monitoring serum fluoride and alkaline phosphatase.

Combined treatment and AFDR

Activate, depress, free and repeat (AFDR) regimens or coherence therapy theoretically provide a means of increasing bone density to a greater extent than single treatments. Each cycle begins with a drug which stimulates bone formation, followed by an agent which depresses bone resorption. A free or untreated period follows, during which bone remodelling is postulated to increase. Then the cycle is repeated. Studies have used phosphate as the activating agent in combination with calcitonin or etidronate[49,57].

Vitamin D and derivatives

Effects of vitamin D and calcitriol (1,25-dihydroxy-vitamin D) on postmenopausal osteoporosis are variable, because of the narrow therapeutic–toxic ratio of calcitriol. In a multicenter placebo-controlled clinical trial of oral calcitriol in women with postmenopausal osteoporosis, a center in New York reported a non-significant decrease in fracture rate in the calcitriol group[58] while a center in Seattle[59] observed a slight increase in fractures in the calcitriol group. This discrepancy has been explained by differences in dose titration and calcium intake by patients between centers, leading to variable responses.

Calcium

Adequate calcium intake by young adults is needed to attain higher peak bone mass, which will protect against development of postmenopausal osteoporosis. In older postmenopausal women, calcium supplementation had positive effects on bone[60]. Calcium intake cannot counteract the rapid bone loss in early menopause, which is primarily due to estrogen withdrawal. Estrogen-dependent loss is self-limited[61], and bone loss once again becomes susceptible to environmental factors by three to six years after the onset of menopause[16]. Calcium and vitamin D may be beneficial at this stage.

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