

Postmenopausal osteoporosis: epidemiology, pathophysiology and treatment

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INTRODUCTION

Osteoporosis is an important age-related disease constituting a major health problem in most developed societies especially among postmenopausal women who are expected to live well into the **80s**. An estimated total of about 75 million people in the USA, Europe and Japan are afflicted by the disease. It is often the underlying cause of spine, wrist and hip fractures. Spinal fracture leads to pain and loss of height but a hip fracture may result in disability or as a consequence of long-lasting immobilisation even death. The financial cost to governments of such fractures is enormous and runs into the region of US\$ **18 billion**¹ and **500 pounds sterling**² each year in the United States of America and the United Kingdom respectively.

Bone mass increases rapidly in growing children and adolescents, reaching a peak in adults between the second and third decade. After the age of 35-40 years, bone mass begins to decline. Men lose bone mass at approximately the same rate over their lifetime; in women however, the rate of bone loss increases dramatically after menopause or **oophorectomy**.³ The bone mass in women after the age of 50 is only two-thirds of that found in **men**.⁴ These two factors - lower initial adult bone mass and a more rapid rate of bone loss, combine to produce a high incidence of osteoporosis in older women.

Postmenopausal osteoporosis can be prevented and treated. While most other therapies stabilise rather than restore bone mass, it is now widely accepted that the best prevention and treatment method in postmenopausal women is hormone replacement therapy. It is the only treatment shown unequivocally to prevent loss of bone mass and to reduce the risk of fracture. In addition, it may be used for stabilising bone mass in established osteoporosis in postmenopausal women.

DEFINITION

Osteoporosis can be defined as a disease characterised by:

1. low bone mass
2. microarchitectural deterioration of bone

tissue leading to enhanced bone fragility, and

3. a consequent increase in fracture risk (particularly of the spine, wrist and **hip**).⁵

Using this definition, patients may be diagnosed as osteoporosis even where fracture has not yet occurred and so osteoporosis is often termed a "silent" condition which can be categorised further into:

Primary osteoporosis

1. Postmenopausal osteoporosis (Type I)
2. Age-associated osteoporosis (Type II)
3. Idiopathic osteoporosis (affects premenopausal women and middle-aged and young men)

Secondary osteoporosis (caused by an identifiable agent or disease)

PATHOPHYSIOLOGY

Once an adult reaches maturity, skeletal growth ceases. Yet there is continuous replacement of old bone with new throughout life. The underlying mechanism of bone loss is a disturbance of this bone remodelling process. There is increased cellular removal of bone and relatively decreased replacement of bone and consequent reduction in the biomechanical competence of the **skeleton**.⁶ The remodelling process occurs at discrete areas of activity along the bone surface. There are 5 phases to bone remodelling:

1. **Activation:** An unknown signal attracts precursor cells (**preosteoclasts**) to a potential remodelling site. Preosteoclasts fuse to form osteoclasts, the multinucleated giant cells responsible for bone removal or resorption.
2. **Resorption:** Osteoclasts erode bone, **forming** a cavity on the **bone** surface in cancellous bone **and** a tunnel in cortical bone. Osteoclasts then **disappear**. Their fate is unknown.
3. **Reversal:** Mononuclear cells of unknown lineage appear to prepare the surface for bone formation.

4. **Formation:** Osteoblasts, derived from mesenchymal cells are recruited to the surface of the cavity to replace as exactly as possible the recently removed bone. The newly synthesised matrix (osteoid) is mineralised by formation of calcium hydroxyapatite crystals between the collagen fibrils.
 5. **Quiescence:** Bone tissue remains dormant, lined by resting osteoblasts until the next cycle of bone remodelling begins.
- The entire remodelling process occurs over approximately 4-8 months with a range of 3 months to 2 years.

Osteoporosis results from a basic abnormality in this bone remodelling:

1. At menopause, there is an increased activation of remodelling sites due to the reduction of the hormone oestrogen resulting in decrease of both trabecular and cortical bone. The greatest proportion of bone loss occurs in cancellous bone which is found in the vertebral bodies and metaphyses of long bones, thus accounting for the high incidence of fractures at these sites. So as ovarian function gradually declines, there is an equally gradual increase in the rate of bone loss.⁷
2. Bone resorption is increased, resulting in deeper resorption cavities which may perforate trabecular plates.
3. With increasing age, formation of new bone tissue declines causing a permanent bone deficit at each remodelling cycle.

The exact mechanism by which oestrogen influences bone remodelling is not clear. An original hypothesis by Heany suggested that absence of oestrogen rendered the skeleton more sensitive to the bone resorbing effects of parathyroid hormone.⁸ Specific receptors for oestrogens have also been identified in cells of the osteoblast lineage and the reduction in ovarian oestrogen will affect bone mass.^{9,10} Oestrogens may also control the synthesis and secretion of a variety of growth factors within bone, especially **transforming growth factor beta** (TGF- β) and the insulin-like growth factors.¹¹

WOMEN AT RISK

Factors that predispose towards postmenopausal osteoporosis are those that induce (1) a low peak bone mass, and (2) excessive postmenopausal and age-related bone loss.

These factors include genetic, endocrine and lifestyle components:

1. Caucasian and Asian women who are thin or petite with a previous family history of the disease
2. Women who experience an early menopause
3. Women with low premenopausal oestrogen levels
4. Insufficient calcium intake in the diet
5. Cigarette smoking may interfere with oestrogen metabolism premenopausally and render postmenopausal HRT less effective¹²
6. Alcohol abuse
7. Sedentary lifestyle

DIAGNOSIS

1. **X-rays** can detect osteoporosis when about 30% bone loss has occurred causing fractures and decreased radiodensity, accentuation of primary and loss of secondary trabeculae in vertebral bodies, and **thinning** and accentuation of the cortices.
2. **Radiogrammetry** in which the thickness of the cortex of metacarpal or phalangeal bones is measured on standard radiographs of the hand. This is useful in large study populations to predict fractures.¹³
3. **Radiographic absorptiometry** measures the density of phalanges or metacarpals and compared with the density of an aluminium reference wedge using either an optical densitometer or videodensitometer.
4. **Single photon absorptiometry (SPA)** measures the photon attenuation of the measured site (radius) and converted to bone mineral content BMC in grams. SPA is confined to appendicular skeleton.
5. **Dual photon absorptiometry (DPA)** is used for bone mass measurements in the central skeleton or total body bone mineral content and fat content assessment. Bone mass estimates are given as BMC in grams or as BMD in grams/sq cm.
6. **Dual x-ray absorptiometry (DXA)** is the modern upgraded version of DPA where the radioisotope source is replaced by an X-ray source. This enables bone density to be measured at the hip or spine with greater precision. DXA technology has **gained** widespread acceptance and distribution.
7. **Quantitative computed tomography (QCT)** is the only method that can estimate bone density separately in the **trabecular** and cortical bone compartments and the only

method giving a true density (in mg/sq cm) estimate. Usually the vertebral body is the site of measurement.

8. **Ultrasound** measurement of bone density is confined to the appendicular skeleton and **made** at the **os calcis** and the patella. The advantage of ultrasound is its absence of radiation.
9. **Neutron activation analysis** is a method of measuring total body calcium by irradiating the body with thermal neutrons and examining the spectrum of g-rays that results. The availability of this method is limited.
10. **Urinary hydroxyproline** is a product of collagen breakdown and approximately 10% of the total production is excreted in the urine as the peptide-bound form. **Pyrilinks-D** is a highly sensitive urine test that measures deoxypyridinoline (Dpd) a cross **link** of type I collagen present in bone. It is excreted unmetabolised in urine and is highly sensitive specific marker of bone resorption. It can help to identify bone loss early in menopause.

PREVENTION AND TREATMENT

It is now widely agreed that osteoporosis is for the most part a safely preventable and treatable condition. The main aim of any therapy for osteoporosis is to prevent fractures. Primary prevention attempts to increase peak bone mass by diet and exercise. Secondary prevention aims to prevent bone loss after the menopause by use of **drugs**.¹⁴

I Non-drug therapies

1. Calcium – Adequate calcium **in** the diet is essential for normal bone growth and attainment of peak bone mass. However, a high calcium intake will not prevent accelerated bone loss after the menopause. Calcium supplements are used to support other therapies.
2. Vitamin D – **It** plays a major role in calcium absorption and incorporation into bone. Patients require supplements where there may be deficiency e.g. the housebound and elderly.
3. Physical exercise – Weight **bearing** exercise like walking (rather than swimming) contributes to the development and maintenance of bone mass. Exercise in the elderly is beneficial in increasing blood

supply to muscle, bone and neural tissue. This improves muscular function and agility, thereby reducing the likelihood of falls.

II Pharmacological therapies

There are two types of medication that can reduce or reverse bone loss in postmenopausal women. These are drugs that (1) stimulate bone formation – fluoride, anabolic steroids, parathyroid hormone, and (2) inhibit bone resorption – hormone replacement therapy (HRT), **calcitonin** and biphosphonates.

1. Fluoride – is used to treat established osteoporosis. It stimulates the osteoblasts and causes an increase in cancellous bone mass. However at high doses, it leads to the **disease** called fluorosis resulting in fragile bones. Recent studies have shown that it actually increases the rate of non-vertebral **fractures**.¹⁵ Gastrointestinal side effects and **arthralgias** are the main adverse effects seen.
2. Anabolic steroids – are used to treat osteoporosis in the elderly by obtaining a positive calcium **balance**.¹⁶ They can **increase** bone mass but long term **usage** is limited by side effects such as **virilisation**, as well as adverse effects on **lipid** and carbohydrate metabolism and liver function.
3. **Parathyroid** hormone – is under investigation as a potential therapeutic stimulator of bone formation. It has been shown to increase bone mass when given in low doses.
4. Calcitonin – is a long chain polypeptide hormone used principally in established osteoporosis because it decreases further bone loss by inhibiting bone resorption by a direct inhibitory action on the activity of osteoclasts. Whether there is a decrease in fracture frequency has not yet been established. Calcitonin exerts an analgesic effect in patients with acute bone pain due to fracture. Also it prevents trabecular bone loss during the **first** few years after the menopause but is rarely used prophylactically because it has to be given parenterally. Nasal sprays are also available.
5. Biphosphonates – are a class of drugs which reduce bone loss and vertebral fracture rate during the early years of administration in established postmenopausal osteoporosis. In two double-blind placebo controlled studies, Etidronate given orally at **400 mg/** day for 2 weeks followed by 10-13 weeks

of calcium supplementation reduced vertebral fractures by **50%** compared to patients receiving **calcium**.^{17,18}

- Hormone Replacement Therapy – HRT remains the treatment of choice for the prevention and treatment of postmenopausal **osteoporosis**.¹⁹ It prevents osteoporosis and reduces the risk of bone loss independent of **age**.^{20,21,22} Oestrogen by inhibiting bone resorption, reduces bone loss at all skeletal sites. The earlier the therapy begins, the better the outcome in terms of conservation of bone mass since bone mass lost is not **regained**.²³ Recent epidemiological data predict that if oestrogen is given for at least **5** years early in the climacteric period, subsequent hip and wrist fractures may be reduced by about **50%** and vertebral fractures by up to **80%**.²⁴ The addition of a progestogen does not seem to impair the response of the skeleton to **oestrogen**.⁷ In addition to preventing bone loss, HRT has other important beneficial effects like relieving vasomotor symptoms, **urogenital** atrophy, skin changes and psychological problems as well as reducing the risk of cardiovascular disease in the long term.

CONCLUSION

Restoration of the osteoporotic skeleton is difficult. Factors that may aggravate bone loss or increase risk of fractures should be eliminated. Maximising peak bone mass and preventing menopausal bone loss are the most important means of preventing osteoporosis. HRT is the gold standard for the prevention and treatment of osteoporosis. Combined with calcium supplements and some exercise regimens, HRT is a simple and safe therapy.

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