Osteoporosis, Diagnosis and Management

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Bone is a very active tissue, with continuous formation and breakdown (resorption) proceeding throughout life. In order for bone mass to be maintained, the processes of formation and resorption must be equal. When resorption exceeds formation over a sufficient length of time, bone mass is lost and the result is osteoporosis. Osteoporosis can be defined as systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

The single most potent cause of osteoporosis is oestrogen deficiency following the menopause. It is a condition of great social and economic importance and is a major cause of disability and morbidity, probably responsible for most of the 1.5 million fractures occurring annually in elderly females in the USA.

Clinical Features

Patients with osteoporosis may have no symptoms, but when present, the major symptom is bone pain due to fracture, whether radiologically visible or not. Osteoporosis itself (unlike osteomalacia) is not associated with pain in the absence of fracture. Common fractures are those of the wrist, femoral neck or vertebrae. Vertebral crush fractures are the hallmark of the clinical diagnosis of osteoporosis, and are associated with the sudden onset of severe localized pain, often precipitated by muscular effort or trauma. Pain may radiate anteriorly and is often exacerbated by movement and relieved by rest. The pain may improve over a period of several weeks, but can persist for many months, and further episodes of crush fracture cause pain recurrence. Chronic low-grade back pain may ensue and osteoporosis complicated in this way is probably one of the most common causes of low back pain in the community. Bone tenderness is sometimes present, but neurological complications are surprisingly uncommon. In some patients, vertebral fractures can occur with little or no pain and can simply manifest themselves as progressive loss of height and increase in kyphosis—the development of the ‘dowager’s hump’. Vertebral collapse is a common problem...
particularly in the elderly, and differentiation between collapse due to osteoporosis and underlying malignant disease can sometimes be difficult radiologically. In established osteoporosis the clinical signs are usually those of the spinal lesion. There may be a marked dorsal kyphosis, usually with a measurable loss of height due to collapse of the vertebral bodies. In very severe cases the lower ribs may eventually come into contact with the iliac crest and cause pain. Osteoporosis may also occur as a result of several other diseases, and symptoms and signs of these associated conditions may be present in such secondary osteoporosis. It is important clinically in assessing new patients with osteoporosis to consider the possibility that the bone loss may be secondary to one of the diseases listed in Table 1, and appropriate tests should be carried out where indicated. Osteoporosis is rarely fatal, but in the severe progressive form of the disease which is sometimes seen in young adults, in patients with multiple myeloma and in patients with corticosteroid-induced osteoporosis, death can result from the respiratory consequences of multiple vertebral and rib fractures.

**Significance of Osteoporosis**

Osteoporosis is taking on great significance for the costs of medical care which it generates, and much effort in the last several years has been directed towards identifying those at risk for the condition, and instituting measures for its prevention. This attitude is reflected in the definition of the disease, which defines it in terms of low bone mass and susceptibility to fracture, rather than defining the condition when an end-stage is reached, at which time treatment is virtually ineffective.

Death will follow in 10% of hip fracture subjects within one year of the fracture event, and over 50% of survivors will be incapacitated, many of them permanently. Spine fractures cause significant pain and deformity and long-term limitation of activity. The progressive aging of the world’s population predicts a great increase in the economic burden imposed by osteoporosis.

**Bone Mass, and Factors Influencing it**

Bone mass is the major determinant of the risk of osteoporotic fracture, and measurement of bone mass essentially occupies in this field of medicine the same place as the measurement of blood pressure in the prediction of stroke. Bone mass increases during childhood and adolescence,
monozygotic twins is significantly less than the variance of dizygotic twins. Lifestyle factors can influence bone mass, including cigarette smoking and alcohol abuse, both of which contribute to low bone mass. A sedentary lifestyle and inadequate calcium intake while young, also contribute to low bone mass. In pre-menopausal women oestrogen deficiency results in bone loss that can lead to osteoporosis. This occurs particularly in anorexia nervosa, in elite athletes and ballet dancers who exercise over prolonged periods to the point of amenorrhea, and subjects with hyperprolactinemia. Thyroid hormone excess, primary hyperparathyroidism, and glucocorticoid excess, either in Cushing's disease or from therapeutic use, can lead to bone loss (see Table 1).

**Diagnosis**

**Bone mass measurement**

Osteoporosis needs to be identified by the low bone mass which is the major predictor of subsequent fracture. Therefore the measurement of bone mass is vital to the early diagnosis of osteoporosis and its effective treatment. Methods need to be rapid, reliable, inexpensive, have a low error and low radiation dose, their fracture prediction capability must be validated, and there must be the capacity to measure multiple sites and assess both trabecular and cortical bone.

There have been major advances in development of methods for measurement of bone mass in recent years. The most commonly used are dual-energy X-ray absorptiometry (DXA), which has largely replaced dual photon absorptiometry (DPA) as the optimum method to estimate axial, proximal appendicular and total body bone mass, and single photon absorptiometry (SPA) and single X-ray absorptiometry (SXA), which are applicable to peripheral appendicular bones. Measurement of bone mass at any site is able to predict fracture at all sites, but is not a measure of bone density or a response to treatment at those other sites. A recent study showed that DXA measurements of the proximal femur predict hip fracture risk better than do measurements at other sites, and there is increasing agreement that measurement at more than one site should be aimed at. Quantitative computed tomography (QCT) has been adapted to measure bone mass, with comparison of standard reference material. Because of the radiation exposure and the fairly high precision error, QCT of the spine is not widely used but ultrasonography is under development; SPA is used to assess bone mineral at peripheral sites such as the radius or the calcaneus. Bone mineral is expressed as grams of mineral per centimetre of bone (bone mineral content, BMC) or as grams per centimetre square (bone mineral density, BMD). SPA can be used to measure preferentially the cortical or cancellous compartment, depending on whether measurement is made at the mid- or the distal and ulnar distal radius. The calcaneus consists mainly of cancellous bone.

In addition to being inexpensive, SPA has the advantage of a low radiation exposure, but the accuracy error is low (about 5%) as a result of variations in soft tissue thickness around the bone. The precision error is 1–2% at the mid-radius but is higher at the distal radius. Measurements made by SPA of the radius and calcaneus, although in a global sense they might be predictors of fracture expectations in a population, do not provide an indication of the bone mineral content of the spine or the proximal femur, which are the main sites of osteoporotic fracture. Therefore, SPA measurements are of limited use in assessing an individual subject, or in monitoring treatment.

DXA is a major technological improvement on the principles introduced several years earlier with DPA. This improvement has been achieved by using an X-ray tube to generate the dual-energy photons. DXA has excellent precision (approximately 1%), low radiation exposure (less than 3 MREM) and a shorter scan time.

The National Osteoporosis Foundation (USA) has recently recommended indications for the clinical uses of bone mass measurement:

1. in oestrogen-deficient peri-menopausal women, to help the physician and patient make decisions about hormone replacement therapy;
2. in patients with radiological abnormalities or osteopenia, to obtain information useful in making decisions about further diagnostic evaluation and therapy;
3. in patients receiving long-term glucocorticoid therapy, to diagnose low bone mass in order to adjust therapy;
4. in patients with asymptomatic primary hyperparathyroidism, to diagnose low bone mass in order to identify those at risk of severe skeletal disease.

There are certainly going to be further indications, some of which are applied already, such as the use of BMD measurements to monitor the efficacy of treatments of osteoporosis and indeed of osteomalacia, and measurements also in patients with gastrointestinal malabsorption
or chronic renal failure, in whom bone loss is common.

Of all these indications, the most important is the use of BMD measurements in determining the need for oestrogen replacement at the time of the menopause. General screening of all women is not recommended because it is extremely expensive, and of course not all women are at risk for development of osteoporosis. Bone mass measurements nevertheless should be undertaken in patients with specific problems, especially if decision whether or not to prescribe hormone replacement therapy depends on the value of the bone mass in that individual at the menopause. If the decision has already been made to use hormone replacement therapy in an individual for another reason, there is no need for BMD measurement in that individual.

**Biochemical measurements**

Although there is much interest in the clinical use of risk factor analysis, these are of little use when applied to individuals. Bone mass measurements are undoubtedly extremely important and indeed, have revolutionized the clinical approach to osteoporosis, but there continues to be an effort to develop biochemical assays which are of use in predicting fracture risk or of monitoring treatment.

Measurement of plasma levels of alkaline phosphatase and of osteocalcin (bone-gla-protein, BGP) are used to reflect bone formation, whereas urinary hydroxyproline and calcium in fasting state reflect bone resorption. Some improvements have been made in these methods. Total serum alkaline phosphatase is not specific for bone, and recently methods have been developed for measuring the bone isoenzyme. A radioimmunoassay of the amino-terminal peptide of type 1 collagen has been developed and clinical data are emerging which suggest that this is promising in the assessment of bone formation. Serum assays for osteocalcin are being used as a sensitive and specific marker of osteoblastic activity, particularly useful in osteoporosis.

In measurements of resorption, fasting urinary calcium and hydroxyproline have been the most commonly used marker, but they lack sensitivity. A considerable improvement has been provided by the measurement of urinary pyridinium cross-links. Pyridinoline (Pyr) and deoxypyridinoline (D-Pyr) are reducible cross-links which stabilize the collagen chains within the extracellular matrix. Unlike hydroxyproline, these cross-links are not metabolized in the body and are not subject to dietary influence. Pyridinium cross-link excretion correlates well with bone turnover rates as measured by other means. The best results are produced by measuring this marker relative to creatinine on an early morning spot urine sample. Recent results have resulted in simple common direct urinary immunoassay methods. Such assays will have many clinical applications, both for diagnosis and the monitoring of therapy of metabolic bone disease.

There is no single, ideal marker of either formation or bone resorption. All of the markers mentioned above need to be characterized further, and different markers are likely to reflect different events of bone metabolism. Using a panel of various markers is likely to provide more information on bone formation and resorption, and such an approach should improve the assessment of bone turnover in osteoporosis. Certainly, the use of biochemical markers is helpful in discriminating between patients with high and low bone turnover, and this is of particular importance because these two subgroups are likely to require different therapies.

**Prevention and Treatment of Osteoporosis**

The single most important approach to management of osteoporosis is its prevention. Once serious bone loss has occurred there is no proven method to restore healthy bone tissue and normal bone architecture to all skeletal sites. Prevention requires attention to public health measures from the earliest stages of life, aimed at ensuring maximal accumulation of normal bone tissue during the years of skeletal growth, and reducing or eliminating bone loss after the skeleton matures.

**Adolescence and young adults**

Adequate calcium nutrition is essential for the development and maintenance of a normal skeleton. The National Osteoporosis Foundation recommended that daily intakes of elemental calcium are 1200 mg/day between the ages of 1 and 24, 1600 mg/day for women who are pregnant or breast-feeding, aged 19 and under, and 1200 mg/day for those who are pregnant or breast-feeding aged 20 and over. Weight-bearing exercise, including walking, jogging etc. contributes to bone health, and the deleterious effects of cigarette smoking and excessive alcohol need to be stressed.
Serious illness in childhood is detrimental to normal bone mass development, and of course pre-menopausal oestrogen deficiency states such as anorexia nervosa or excessive athleticism or prolactinoma can all lead to individuals reaching a lower than otherwise peak bone mass. A lower extremity stress fracture may be the first clue to osteoporosis in a young woman who is an elite athlete or ballet dancer. In addition to these more striking examples, there is increasing evidence that milder states of pre-menopausal hormone deficiency as indicated by episodic menstrual disturbances, may also be associated with bone loss.

Recent genetic studies identify clearly the very strong genetic component in the development of low peak bone mass. A polymorphism in the vitamin D receptor gene has been identified, with expression of one allele associated with low bone mass in pre-menopausal women, and of another allele with a higher bone mass. This discovery is an extremely promising one, and even offers an entirely new approach to the identification of those at risk for the development of osteoporosis from a very early age.

**Menopause**

The loss of bone following the menopause is undoubtedly a major contributor to the net life-time loss of bone. There is no evidence that increasing calcium intake in the peri- or early post-menopausal period will alter either the peak bone mass or the accelerated spinal bone loss of the post-menopause. The only way to modify the latter with surety is with oestrogen replacement therapy. It is likely that other inhibitors of bone resorption, including calcitomin and bisphosphonates, would be capable of inhibiting the resorption associated with oestrogen withdrawal from the menopause, but none is as effective as oestrogen.

**Elderly**

Following the menopausal loss, there is a gradual and progressive loss of bone tissue that accompanies aging in women and this also occurs in men. In some of these subjects this is associated with a decline in efficiency of intestinal calcium absorption, and therefore calcium supplements are indicated in those elderly subjects who exhibit this. There is little evidence that exercise can modulate the bone loss accompanying aging. However, exercise is strongly recommended on other grounds, particularly for the improvement of agility and therefore making falls less likely.

**Specific Treatments**

**Oestrogens**

Oestrogen is the agent of choice in preventing post-menopausal bone loss because it is the only treatment which unequivocally reduces fractures. It is also effective in reducing bone loss among women long after the menopause. All women at risk for osteoporosis should be considered for oestrogen therapy if there are no contraindications, and as indicated above, bone densitometry is extremely valuable in predicting this risk in women who are considering oestrogen therapy.

The effects of oestrogen or oestrogen-progestin therapy on bone are independent of age and menopausal age. In early post-menopausal women, hormone replacement therapy reduces bone loss, with 0.625 mg/day required of conjugated oestrogen, or 2 mg of 17β-estradiol. In addition to oral therapy, new delivery systems are available in which oestrogen can be given as a skin patch, in which 50 μg/day delivery is required.

There is very strong evidence that oestrogen therapy reduces the risk of cardiovascular disease that women experience after the menopause, and this effect may be related to the beneficial effects of oestrogen on lipid metabolism. Indeed, the population benefits of oestrogen therapy are greater for the cardiovascular effect than for the bone effect. The increased risk of uterine cancer with the use of oestrogen is virtually abolished with the administration of progestagen. For oestrogen alone there is a 2–15 fold increased risk of endometrial cancer which is prevented by progestin. Thus cyclical therapy with a progestin is given to non-hysterectomized women who are receiving oestrogen therapy. Continuous combined therapy can also be given to older women long after the menopause, and with this regimen bleeding can be minimized or eliminated. It is not yet known whether progestin use modifies the cardiovascular benefit provided by oestrogen.

There is still argument whether oestrogen treatment is associated with an increased risk of breast cancer. Current evidence is that there might be a statistically higher risk of breast cancer in those on oestrogen therapy, but there is no evidence for an increased mortality. Nevertheless oestrogen replacement therapy should probably not be prescribed for women with a history of
breast cancer themselves, or with a strong family history of breast cancer. Furthermore oestrogen-treated women should receive regular gynaecological and breast examinations, including mammography before and regularly during treatment.

The benefits of oestrogen therapy clearly outweigh its risks in women who are susceptible to osteoporosis. However, low bone mass is only one of several indications for the use of oestrogen therapy in women at the menopause, and it is not considered that all women should have oestrogen replacement therapy.

Finally, it is of interest to note that certain oestrogen antagonists are showing promise in the prevention of bone loss. It is uncertain what are the implications of this for the protective effect of oestrogen against cardiovascular disease, or whether the oestrogen antagonists/partial agonists will be associated with the same endometrial cancer risk. It will also be very important to determine whether these drugs have specific molecular interactions with bone cells which allow them to favour a bone effect.

Calcitonin

Calcitonin is an inhibitor of bone resorption which has been studied extensively in osteoporosis. It has been shown to be capable of slowing the bone loss at the menopause, in studies either of injectible or of intranasally administered calcitonin. It is clearly not as effective as oestrogen, but may be one of the alternatives to consider in those women who cannot or will not take hormone replacement therapy.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate which are powerful inhibitors of bone resorption. They have been shown to reduce bone loss in the post-menopausal state and in patients treated with steroids. Large clinical trials are currently under way to determine effects of bisphosphonates on fracture incidence.

The bisphosphonates are extremely stable compounds which accumulate in bone, and long-term observations will need to be made to ensure that this has no damaging effects.

Vitamin D

Adequate vitamin D nutrition is particularly important in the elderly, in whom calcium absorption may be deficient even with normal vitamin D metabolism, and especially since many elderly people might be deprived of sunlight and even nutritionally deficient. In Asian populations, treatment of osteoporosis with the active form of vitamin D or its analogues has improved bone mass and reduced fracture incidence. This may relate to the very low calcium intake of these populations. The place of vitamin D in therapy prevention needs to be looked at very carefully again especially in the light of the vitamin D receptor polymorphism data referred to earlier.

Fluoride

There is continuing interest in arriving at a therapy for osteoporosis which is capable of increasing trabecular bone mass. Fluoride is the most powerful single agent known to be capable of this because of its ability to increase osteoblast cell population through a mitogenic effect on osteoblast precursors. Fluoride has been proposed in the treatment of vertebral crush fractures because of the massive increase in bone density of the axial skeleton that radiologically characterizes skeletal fluorosis. The stimulating effect of fluoride salts on bone density has been shown in a number of studies, but a few problems have emerged. Uncertainties persist about the quality of the newly synthesized bone, and in a major study funded by the NIH in the 1980s, despite great increases in axial bone mass, there was a tendency towards increasing cortical fractures. When this data was analysed further, the fractures were associated with the highest doses of fluoride.

Side-effects of fluoride are common, particularly gastrointestinal effects of anorexia and nausea, and periarticular pain.

The use in Europe of monofluorophosphate, a highly soluble fluoride salt which forms with calcium carbonate a soluble salt readily absorbed in the duodenum and small intestine, has been successful in reducing gastrointestinal side-effects. The compound also has a high bio-availability, and may be preferable to other widely used forms. Clearly the therapeutic window in the use of fluoride is narrow, but it should not be ignored as a potentially useful treatment in subjects with low bone mass.

Other agents

Anabolic steroids are used in some patients with advanced disease, but their side-effects of hair
growth and voice changes and lipoprotein changes limit their use in prolonged treatment courses.

Further Reading