Osteoporosis: prevention and diagnostic work-up

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Prevention of osteoporosis has assumed a paramount role in the decrease of osteoporotic fractures and the associated medical costs. A thorough diagnostic work-up of the patient with osteoporosis helps the physician exclude secondary causes of bone loss and acquire useful data for staging the disease, and contributes to planning the correct therapeutic management.

Osteoporosis is now recognized as one of the most prevalent conditions associated with aging. As the demographics in the USA shift toward an older population, a dramatic increase in the number of osteoporotic fractures is expected in coming years (Consensus Development Conference, 1991; Kanis et al, 1994). Interestingly, 1.66 million hip fractures occurred worldwide in 1990, approximately 1 197 000 in women and 463 000 in men (Cooper et al, 1992). In most cases, hip fractures were related to osteoporosis, with only 10% resulting from severe trauma and 1% from underlying pathology, such as metastatic disease (Melton et al, 1982). The reported figures for osteoporosis-related vertebral and distal radius fractures are 17% and 8%, respectively (Owen et al, 1982; Cooper et al, 1992).

Data have shown that the femur of an elderly person has half the strength and one-third the energy-absorption capacity of that of a younger person (Courtney et al, 1995). Typically, osteoporosis-related hip fractures follow a fall from standing height or lower (Melton et al, 1988). The risk of experiencing at least one fall annually in postmenopausal American women rises from 20% in women aged 60–64 years to 30% in women aged 80–84 years (Cummings and Nevitt, 1989). Yet only 1% of falls result in a hip fracture, probably as a result of the orientation of the fall and the various protective responses (i.e. use of an outstretched arm to break the fall, soft tissue padding over the hip) (Melton and Riggs, 1985). However, the risk of developing a hip fracture is 13-fold greater when the point of impact is directly over the greater trochanter (Hayes et al, 1991).

Half or more of the falls among elderly people are associated with diminished postural control, gait changes, muscular weakness, decreased reflexes or poor vision and hearing. Interestingly, an external protective device designed to cushion the hip has been reportedly able to halve the risk for hip fracture, even among frequent fallers (Lauritzen et al, 1992).

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PREVENTIVE STRATEGIES

Osteoporosis is more amenable to prevention than treatment. Early detection of the condition, however, is required to retard or even inhibit progressive bone loss. If prevention is not undertaken, the estimated costs associated with osteoporosis will more than double in the next 30 years (Cummings et al, 1990).

In general, preventive strategies should be aimed at increasing the individual's peak bone mass, achieved at approximately 20–25 years of age, and maintaining adequate levels of bone mass until late in life.

Increased exercise

Weight-bearing exercise is considered an important component of an osteoporosis prevention and treatment programme. This particular form of exercise forces the person to work against gravity, and includes activities such as walking, jogging, dancing, hiking, tennis and stair-climbing. Examples of non-weight-bearing exercise include swimming and bicycling.

Additional benefits of increased physical activity include:

- Improvement of psychological status, balance and coordination, which may be helpful in the prevention of falls
- Promotion of muscle strength
- Improvement of appetite and nutrition, which are often impaired in the elderly population.

However, trials have shown only a slight increase of bone mineral density (BMD) in adults who

follow an exercise programme, and have proved a lack of effect on BMD in the elderly, and subsequently on risk of fractures (Salamone et al, 1999; Wolff et al, 1999; Karlsson et al, 2002).

Health education

Health education is aimed at improving diet and nutrition. In this regard, adequate intake of calories, calcium and vitamin D is also required for the attainment of peak bone mass. However, in practice it may be easier to prescribe calcium or vitamin D supplements rather than persuade patients to change their dietary habits. The 4-year trial of calcium supplementation conducted by the Mayo Clinic (Riggs et al, 1998) showed that calcium-treated patients had BMD levels only 1% above the control group. Furthermore, it has been shown that supplemental vitamin D may reduce bone loss from the femoral neck, but cannot reduce the rate of hip fracture (Ooms et al, 1995). Researchers have shown that rapid bone loss occurs once supplemental calcium and vitamin D is discontinued (Dawson-Hughes et al, 1999).

Smoking and excessive alcohol or caffeine intake may place patients at increased risk of developing osteoporosis, and should therefore be discouraged. Published data indicate that the risk of vertebral fractures is increased twofold in smokers and in people who consume two or more alcoholic drinks per day (Seeman et al, 1983). Moderate alcohol consumption, however, may not be harmful and may even slightly reduce bone loss in women (Ganry et al, 2000).

Caffeine consumption is associated with low bone mass and increased fracture risk, likely owing to increased urinary calcium loss. In addition, excessive dietary sodium intake may contribute to bone loss as a result of the obligatory renal calcium loss when sodium is excreted (Need et al, 1991).

Safety measures

The prevention of falls plays an important role in the elimination of fractures and their dreaded complications. In this regard, the institution of simple safety measures can help protect the elderly from falls and subsequent fractures. These measures include:

- Good lighting in every room
- Placement of grab bars or non-slip strips where necessary
- Removal of rugs and items out of walking paths
- Use of handrails and shoes with non-skid soles or low heels
- Placement of commonly used items within easy reach
- Avoidance of heavy lifting.

Effect of other conditions

The risk of hip fractures among patients using long-acting psychotropic medications is greater than that of patients not taking such medications. Because the administration of drugs with sedative effects may slow reflexes or decrease coordination and impair protective responses during a fall, careful adjustment of dosage should be considered where indicated. Clearly, the identification and treatment of derangements that may increase the risk of falls, such as sensory defects, neurological disorders, cognitive impairment and arthritis, is important in the prevention and elimination of osteoporotic fractures.

EVALUATION OF THE PATIENT WITH OSTEOPOROSIS

The clinical evaluation of the patient with osteoporosis can be extremely helpful to the physician in arriving at a diagnosis and planning appropriate therapeutic management. Clinical evaluation is also used to exclude secondary causes of bone loss and to provide useful information for staging the condition. Careful diagnostic work-up includes:

- Medical history
- Bone densitometry
- Laboratory evaluation.

Thorough medical history may reveal past and present illnesses or exposure to risk factors for osteoporosis, such as drugs, nutrition and family history, and can be used to assess the patient's risk for the disease, often directing further diagnostic tests. For example, a detailed history may suggest that low bone mass is secondary to hyperparathyroidism, hyperthyroidism, osteomalacia, hypercortisolism, multiple myeloma or hypogonadism.

It is interesting to note that once the first osteoporotic fracture occurs, the relative risk of a second fracture increases fivefold, regardless of bone mass. In addition, the combination of low bone mass and just one vertebral fracture increases the relative risk of a second fracture 25-fold (Wasnich, 1987).

Because patients sustaining osteoporotic fracture(s) can be asymptomatic, lateral spine radiographs should be routinely included in the diagnostic work-up. A complete blood cell count and a routine analysis of serum biochemical levels (calcium, phosphorus, alkaline phosphatase) may suggest the presence of mineral and electrolyte imbalances, and haematological or other underlying disorders. Renal function can be screened by measuring the serum urea and creatinine levels, whereas hepatic function is assessed using the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma (γ)-glutamyl transpeptidase values.

Measurement of the serum testosterone level to exclude hypogonadism in the male population is part of the investigation for underlying, unrecognized systemic disease.

Patients with hypercalcaemia should undergo a work-up for primary or secondary hyperparathyroidism, which includes the measurement of serum parathormone (PTH) and 25-hydroxyvitamin D levels to evaluate a possible vitamin D deficiency. Serum protein immunoelectrophoresis to detect a monoclonal immunoglobulin spike, urine immunoelectrophoresis to demonstrate the presence of Bence-Jones protein, and bone marrow aspirate should be performed to rule out multiple myeloma. Measurement of serum tri-iodothyronine resin uptake (T_3RU) and thyroxine (T_4) levels is required for excluding the diagnosis of hyperthyroidism.

In asymptomatic, postmenopausal, osteoporotic women, however, results of routine laboratory tests are normal and do not provide information regarding the extent and rate of bone loss, or the prognosis. In patients with osteomalacia or other rare causes of bone loss such as mastocytosis, iliac bone biopsy can provide additional diagnostic information. Bone densitometry cannot differentiate osteomalacia or mastocytosis from osteoporosis, however, as in general BMD is decreased in these conditions. Additional tests, such as biochemical markers, are helpful in assessing bone turnover and may facilitate monitoring of therapy.

BONE BIOCHEMICAL MARKERS

Measurement of the biochemical markers of bone turnover is an evolving clinical tool in the evaluation and treatment of osteoporosis. Biochemical markers include:

- Serum or urine enzymes
- Matrix proteins synthesized by osteoblasts or osteoclasts
- Osteoclast-generated degradation products of the bone matrix.

TABLE 1.
Biochemical markers of bone turnover used routinely in clinical practice

Bone formation markers	Serum alkaline phosphatase
	Serum osteocalcin (bone *Gla* protein)
	Serum procollagen I extension peptides
Bone resorption markers	Urinary calcium and hydroxyproline
	Urinary hydroxylysine glycosides
	Plasma tartrate-resistant acid phosphatase
	Urinary collagen pyridinium crosslinks
	N- and C-terminal crosslinked telopeptides of type I collagen

Examples of bone biochemical markers

The two main categories of markers include markers of bone formation and markers of bone resorption. *Table 1* lists the markers used routinely in clinical practice. Bone formation markers are usually obtained in serum, whereas bone resorption markers are mostly collagen breakdown products obtained in urine (Price and Thompson, 1995).

Total alkaline phosphatase level in serum is still the most widely used bone formation marker in clinical practice (i.e. to assess and monitor Paget's disease of bone). Among bone resorption markers, urinary hydroxyproline was until recently the most commonly used index of bone resorption. However, the collagen crosslinks assay is reportedly a more sensitive marker of bone resorption than hydroxyproline (Price and Thompson, 1995). Bone resorption markers have a low sensitivity and specificity, thus biochemical markers that reflect bone matrix formation with higher sensitivity have superseded them.

Osteocalcin and bone-specific alkaline phosphatase are emerging as the most sensitive and specific indices of bone formation. However, serum osteocalcin is not as elevated as might be expected, and correlates poorly with total serum alkaline phosphatase and with the bone-specific enzyme in Paget's disease of bone.

The propeptides of type I collagen represent total type I collagen synthetic activity in all tissues in the body, not just in bone formation; therefore, their use is not widespread. An assay for the serum collagen pyridinium crosslinks has been recently cleared for clinical use by the Food and Drug Administration, but sufficient data on its performance in the postmenopausal population are missing. Osteoporotic patients have significantly increased bone formation and bone resorption markers compared with the normal population (about three standard deviations above the mean). Indeed, resorption markers show greater increase than do formation markers.

Bone markers may be used in conjunction with BMD to assess the rate of bone turnover, thereby differentiating fast from slow bone losers. In addition, because changes in biochemical markers owing to treatment may be detected after 3–6 months, monitoring the early effects of anti-resorptive therapy can be achieved with the use of markers. On the other hand, it may be necessary to wait up to 2 years after initiating therapy to determine whether treatment is effective, based on BMD measurements by dual-energy X-ray absorptiometry.

There are certain limitations to the broad use of biochemical markers in clinical settings. Bone markers show a high variability among individuals (20–35%) and high temporal variation (5–10%) (Bollen et al, 1995). Resorption markers may also be affected by circadian rhythm, dietary factors, calcium intake, age, gender and anthropometric variables, as well as geography and ethnicity (Bollen et al, 1995). It is in this regard that most bone markers exhibit a diurnal rhythm, with a peak in the early morning and lower levels in the afternoon. Conceivably, measurement of bone resorption markers in the first void urine specimen in the morning may reflect peak activity, whereas a serum sample for bone formation markers would not. It is clear that optimal sampling requires rapid processing of the sample, and reproducible timing.

Urinary collagen pyridinium crosslinks are currently considered the best markers for assessing bone resorption, and like urinary hydroxylysine glycosides they offer the advantage of being independent of dietary sources.

Clinicians are more familiar with BMD than bone markers, however. To place the variability of bone markers in perspective with that of BMD, it is noteworthy that 2–11 years may be needed to assess the rate of bone loss or response to treatment. Average bone loss rates determined by serial BMD measurements typically range between 0–3% per year at the spine, proximal femur, forearm and the calcaneus (Greenspan et al, 1998). On the other hand, the long-term, intraindividual, BMD variation ranges from 2–4%.

Studies on bone biochemical markers

Some studies suggest that a faster rate of bone loss predicts increased fracture risk independently of BMD. In fact, decreased BMD measured in the spine and increased bone turnover have approximately equal power to predict fracture rate (Riggs et al, 1996; Riis et al, 1996). A prospective cohort study of elderly (older than 75 years) French women showed that increased levels of the carboxy-terminal telopeptide of type I collagen, above the upper limit of the premenopausal range (e.g. mean plus two standard deviations), were associated with an increased risk of hip fracture even after adjusting for femoral neck BMD (Garnero et al, 1996).

Van Daele et al (1996) observed that collagen crosslink values above the median for the cohort were associated with up to a 10-fold increased risk of hip fracture, independently of BMD. These collagen crosslinks have been reportedly able to predict fracture risk with the same magnitude that blood pressure and serum cholesterol predict the risk of stroke and coronary artery disease, respectively. However, bone-specific alkaline phosphatase and osteocalcin were unable to predict hip fracture risk, which is puzzling given that bone formation rate (measured by histomorphometry) predicts vertebral fracture risk, and bone-specific alkaline phosphatase predicts vertebral and non-vertebral fracture risk (Garnero et al, 1996; Riggs et al, 1996; Van Daele et al, 1996).

It has been shown that bone resorption markers are inversely correlated with BMD of the proximal femur, spine and forearm. However, osteoporotic women are more likely to have high bone turnover. In this regard, a history of osteoporotic fracture(s) of the hip, spine or distal forearm may be associated with reduced hip BMD and with increased bone resorption markers. The mechanisms by which increased bone turnover increases the fracture risk include acceleration of bone loss, microarchitectural changes owing to perforation of trabeculae, loss of structural elements of bone, and reduced bone strength owing to enlarged remodelling spaces (Riggs et al, 1996).

Cosman et al (1996) showed that bone loss rates at the spine and hip determined over 2 years were 1% per year greater on average in women with bone markers one standard deviation or more greater than the mean of premenopausal levels, compared with those with lower levels. It becomes conceivable that bone biochemical markers may be used to predict the rate of bone loss, thus complementing BMD measurement.

In a prospective 2-year study, Chesnut et al (1997) found that for every 30% decrease in aminoterminal telopeptide of type I collagen, there was a 2.6-fold increase in vertebral BMD in response to hormone replacement therapy. Greenspan et al (1998) reported that a 30% decrease in aminoterminal telopeptide of type I collagen from baseline to 6 months was associated with a BMD increase of 2.8–4.1% at the hip and 5.8–6.9% at the spine at 2.5 years in the alendronate group.

Riggs et al (1996) suggested that decreased bone turnover is the predominant mechanism for the reduction in risk of vertebral fractures in osteoporotic patients receiving the anti-resorptive treatment. After the initiation of anti-resorptive therapy, there is a significant reduction in bone resorption markers within 4–6 weeks, and in bone formation markers in 2–3 months. Failure to show the expected reduction in resorption markers may indicate non-compliance with therapy, or the need for a change in the therapeutic regimen.

Bone markers may be used to influence treatment decisions and adjust therapy dosage. Bone markers decrease in a dose-dependent manner fol-

lowing therapy with oestrogen, calcitonin or alendronate. Availability of serum determination of bone formation markers makes them convenient to obtain. In addition, bone formation markers do not need to be normalized to a creatinine measurement (unlike urine bone resorption markers); therefore, these markers can be more reproducible.

CONCLUSION

The prevention of osteoporosis is of particular importance. Although treatment of the disease may reduce bone loss, it is difficult, if not impossible, to restore the biomechanical competence of the skeleton (Parfitt, 1987). The potential applications of bone biochemical markers include:

- Diagnosis of osteoporosis
- Identification of high-turnover osteoporotic patients who will mostly benefit from anti-resorptive therapy
- Prediction of risk fracture
- Monitoring of the patient for a timely and appropriate response to treatment.

Finally, bone markers can be used in the clinical investigation of new therapeutic agents to monitor their effects and mechanisms of action. The major limitation in using bone markers for diagnosing osteoporosis, however, is the poor correlation they show to BMD changes (r=0.2; Consensus Development Conference, 1991). HM

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KEY POINTS

- More than 90% of hip fractures are related to osteoporosis.
- Prevention of falls and subsequent fractures can be achieved by making a safer environment for the elderly at home.
- Weight-bearing exercise and sufficient calcium and vitamin D intake may be helpful in the attainment of peak bone mass.
- A careful diagnostic work-up helps the physician exclude secondary causes of osteoporosis and acquire useful data for staging the condition. In addition, detailed diagnostic work-up is crucial in selecting appropriate medical treatment, often allowing dreadful complications to be avoided.
- Bone biochemical markers are helpful tools in the assessment of bone turnover, efficacy of medical treatment and patient compliance to therapy.