National Medicines Information Centre

VOLUME 9
NUMBER 6
2003

ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596 • e-mail: nmic@stjames.ie

UPDATE ON OSTEOPOROSIS

SUMMARY

- **Osteoporosis is the commonest bone disease**
- **Bone mineral density is determined by peak bone mass (achieved by age 30years) and the subsequent rate of bone loss**
- **Significant advances have been made in the management of osteoporosis**

INTRODUCTION

Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture[1]. The estimated lifetime risk for a woman aged 50 years in the UK sustaining an osteoporotic fracture is 14% for the hip, 13% for the distal forearm and 11% for clinically diagnosed vertebral fractures, with the corresponding figures in men 3%, 2% and 2%.[2] Following hip fracture there is a 10-20% reduction in survival with the majority of excess deaths occurring within 12 months.[8]

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Bone is living, growing tissue with continuous remodelling through the activation of bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblasts). Bone formation occurs at a pace faster than resorption during childhood and teenage years until **peak bone mass** (maximum bone density and strength) is reached at 30 years. After that, bone resorption slowly begins to exceed bone formation at a rate of approximately 0.5% per year. During the perimenopausal period and up to seven years after menopause, women may experience a variable and significant increase in the rate of bone loss of up to 3% per year[3]. Oestrogen deficiency is linked to the production of several cytokines responsible for the proliferation and differentiation of osteoclasts: interleukin-1, macrophage colony stimulating factor, interleukin-6 and tumour necrosis factor-a[4]. In the elderly, bone loss tends to be as a result of reduced function and life span of osteoblasts.

Osteoporosis develops where the normal processes of bone formation and resorption become uncoupled resulting in excessive bone resorption, subsequent bone loss and increased bone fragility. If optimal bone mass is not reached during the younger bone-building years, osteoporosis and bone fragility may develop earlier in life. The majority of osteoporotic fractures occur on a background of low-impact injuries or simple falls[1]. **Bone mineral density** (BMD) is the greatest predictor of fracture risk, as it accounts for 70% of bone strength[5] and its key determinants are the amount of peak bone mass achieved and the subsequent rate of bone loss.

RISK FACTORS FOR OSTEOPOROSIS

Many risk factors have been identified and are listed in Table 1. Twenty percent of women who develop an osteoporotic vertebral fracture will sustain a new fracture within the next 12 months.[7] Bone loss with corticosteroids is believed to be most rapid in the first few months of treatment. While the skeletal response varies, high doses are generally associated with greater adverse effects, whereas daily doses of prednisolone less than 7.5mg are less likely to result in bone loss.[6]

Table 1 Risk factors for osteoporosis

Major factors:	**Additional / Minor risk factors:**
Premature menopause	Primary or secondary hypogonadism in men
Long term secondary amenorrhoea	Low dietary calcium intake
Prednisolone (or equivalent) 7.5mg /day or more with an expected use of over 6 months	Vitamin D deficiency
Previous fragility fracture	Excessive alcohol consumption
Low bodyweight	Poor visual acuity
Family history of hip fracture	Long term immobilisation
Cigarette smoking	Other medical conditions – dementia, vertigo, Parkinson's disease, hemiparesis, anorexia nervosa, malabsorption syndromes
	Medications including anticonvulsants, heparin

DIAGNOSIS

Hip measurement of BMD by dual-energy x-ray absorptiometry (DXA) is the gold standard as it has the highest predictive value for hip fracture, the most significant complication of osteoporosis[5]. It can be performed in a few minutes with radiation exposure that is approximately one tenth that of a chest x-ray. Other techniques (ultrasound and computed tomography) have been developed to assess bone mass but DXA has been adopted as the standard reference.

The three key pieces of information obtained from a DXA report are actual bone density, the T score and the Z score. The **T-score** is a comparison of the patient's measured BMD with the mean BMD of a healthy, *young* (20–29 yr old) and sex-matched reference population and is reported as the number of standard deviations (SD) from the mean. A *negative T-score* indicates the person either failed to achieve the optimum peak bone mass or subsequently lost bone mass as a result of the effects of ageing or disease. The World Health Organisation (WHO) definition of osteoporosis is based on T scores and is outlined in Table 2[9]. While values are less well defined for men, the WHO recommend a similar cutoff value for hip BMD (T score >-2.5) be used to make a diagnosis[9].

Table 2 WHO diagnostic criteria for osteoporosis

• ***Normal***	*BMD value within 1 SD of young adult mean (T score above –1)*
• ***Osteopenia***	*BMD value between –1 SD and –2.5 SD below young adult mean (T score between -1 and -2.5)*
• ***Osteoporosis***	*BMD value at least –2.5 SD below the young adult mean (T score below -2.5)*
• ***Severe osteoporosis***	*T score below -2.5 SD plus one or more fragility fractures*

Z-scores compare the patient's BMD with the mean for a healthy normal person matched for *age*, rather than to the young adult mean. While not of diagnostic value, they express a patient's risk of sustaining an osteoporotic fracture relative to their peers. While the prevalence of osteoporosis increases with increasing age, a case finding strategy based on the presence of strong risk factors (Table 1) or a history of a fragility fracture rather than routine screening of the general population is recommended.

PREVENTION AND TREATMENT

Optimal prevention and treatment of osteoporosis requires modification of risk factors, smoking cessation, attention to dietary calcium and vitamin D intake, and promotion of weight-bearing physical activity, in addition to pharmacologic intervention.

NON-PHARMACOLOGICAL MEASURES

Smoking cessation

Evidence Cigarette smoking is associated with decreased sex hormone concentrations, lower body weight, early menopause, decreased calcium absorption, reduced BMD and up to an 80% increase in the risk of fractures. [10]

Practical advice All smokers should be strongly encouraged to stop.

Exercise

Evidence Exercise plays an important role in the acquisition of bone mass in youth. Exercise programmes in pre-menopausal women demonstrate a positive bone benefit. While exercise alone is not adequate to prevent the rapid bone loss associated with oestrogen deficiency in early menopause, it is an important component of prevention and treatment programmes. The effects of activity tend to be most pronounced in those who are the least active. Exercise assists in building and maintaining bone density and reducing the risk of falls by enhancing balance, flexibility and strength.[11,44]

Practical advice High impact and weight-bearing activities such as running, jumping, soccer and volleyball appear to be the most beneficial to the younger skeleton. Activities such as walking, jogging, weight training, dancing, tennis, cycling, gardening and low impact aerobics help to offset age-related bone loss and decrease fracture risk.

Other measures

Falls account for 90% of hip fractures with the risk of falling increasing with age.[1,12] Effective *prevention of falls* involves identifying and modifying where possible intrinsic, extrinsic, and environmental risk factors.[12] Examples of such risk factors are cataracts, medication (e.g. benzodiazepines) and inadequate lighting inside and outside the home. Systematic reviews of the use of *external hip protectors* have shown that they reduce the relative risk of hip fracture in frail elderly women. Not all trials have found that they are efficacious and compliance is an issue.[13,14] *Treatments that predispose to osteoporosis,* e.g. chronic corticosteroid therapy should be minimised and patients taking them assessed for other risk factors of osteoporosis and advised appropriately. *Early surgical management of hip fractures* is essential to decrease mortality rate and to improve perioperative morbidity.

PHARMACOLOGICAL THERAPIES

Calcium and Vitamin D

Evidence Adequate calcium intake is necessary for attaining peak bone mass and maintaining bone health. Calcium requirements change during life, the greatest demands are during childhood and adolescence when the skeleton is growing rapidly and the initial few years after the menopause when a significant increase in bone resorption may occur. Vitamin D is essential for the intestinal absorption of calcium. Supplementation with calcium / calcium plus vitamin D reduces fracture incidence by 30-50% in subjects with low calcium intakes. The efficacy of supplements in healthy elderly people with adequate dietary intake and normal BMD is not established. [15,16]

Practical advice A National Institute of Health (NIH) consensus conference on optimum elemental calcium intake recommends 1000-1500mg/day for adolescents, 1000-1500mg/day for adults up to age 65 years, 1500mg/day for older women and 1000mg for older men[17]. The daily requirement of Vitamin D is 400-800 IU daily. Typical dietary sources of calcium are dairy products, such as milk, yoghurt, cheese and ice cream; dark green, leafy vegetables such as broccoli and bok choy; sardines and salmon; tofu and almonds. Many foods are now fortified with calcium e.g. orange juice, cereals and breads. Many menopausal women consume only 600mg of elemental calcium daily and thus require some form of supplement. It is best absorbed if taken more than once a day in doses of 500mg. Mild gastrointestinal side-effects include constipation, bloating and cramps.

Bisphosphonates

Evidence Bisphosphonates are synthetic pyrophosphate analogues and act by inhibiting osteoclastic mediated bone resorption. Due to this non-specific inhibition of bone resorption, bisphosphonate therapy is also suitable for treatment of steroid-induced osteoporosis, male osteoporosis, Paget's disease, hypercalcaemia, skeletal metastatic disease and potentially other conditions characterized by disproportionate bone resorption. Their half-life in bone is several years. Etidronate (Didronel®) was found to increase spine BMD by approximately 4% with a reduction of vertebral fracture rate at 2 years but this was not significant after 3 years of treatment.[18]

Alendronate (Fosamax®) was the first of the newer agents to be approved. In the Fracture Intervention Trials (FIT), which enrolled over 6000 postmenopausal women with low femoral neck BMD, patients received alendronate 5mg daily during the first 2 years and 10mg in the third and fourth years or matching placebo and supplemental calcium and vitamin D if necessary. Women with at least 1 preexisting vertebral fracture at baseline had the risk of all clinical fractures reduced by 50%.[19,20] In women with low BMD but no preexisting vertebral fracture, a 4–8% increase in BMD over 3 years and a 14% decrease in the risk of all clinical fractures were documented.

Risedronate (Actonel®) similarly reduces bone loss. An American study of 2458 women with prevalent vertebral fractures found that risedronate 5mg reduced the risk of vertebral fractures by 41% and the cumulative incidence of nonvertebral fractures by 39% compared to placebo.[21] A parallel multinational study of 1226 women with severe osteoporosis found that risedronate 5mg reduced the risk of new vertebral fractures by 49% and the risk of nonvertebral fractures by 33% versus placebo.[22] The Hip Intervention Program (HIP) study found that in the younger women (70-79 years), risedronate therapy reduced the risk of hip fracture by 40%, but there was no significant decrease in hip fracture risk seen in older women.[23]

As bisphosphonates have a long duration of action, weekly preparations of alendronate 70mg and risedronate 35mg have been shown to have good safety profiles with the same efficacy as the daily preparations.[24,25]

Practical advice Bisphosphonates are the first line therapies for the prevention and treatment of osteoporosis. Their oral bioavailability is low (1-3%) and is impaired by food, calcium, iron, coffee, tea and orange juice. There are rare reports of severe oesophagitis with alendronate ingestion. For maximum absorption with minimum side-effects, tablets must be taken after an overnight fast (first thing in the morning), sitting upright, with a glass of water, and food avoided for 30 minutes. Weekly administration may improve long-term compliance. The optimal duration of bisphosphonate use is currently unknown.

Selective oestrogen receptor modulators (SERMs)

Evidence Raloxifene (Evista®) is the only SERM licensed for the treatment and prevention of osteoporosis. The MORE project found that treatment with raloxifene 60mg for 3 to 4 years increased spinal BMD by approximately 3%, femoral neck BMD by roughly 2% and reduced the risk of new vertebral fractures by at least 40%.[26,27] No significant effect on nonvertebral fracture rate was observed. It is encouraging that a reduction in the relative risk of oestrogen-receptor positive breast cancer (no effect on oestrogen-receptor negative disease) has been noted with 4 years of raloxifene treatment.[28]

Practical advice Vertebral fracture risk reduction is similar to that obtained with bisphosphonates. Due to the lack of effect on nonvertebral fracture risk, raloxifene would not be considered first choice for patients at high risk of hip fracture. Side effects, although uncommon, include leg cramps and venous thromboembolic disease.

Parathyroid hormone (PTH)

Evidence Continuous infusion of PTH promotes bone loss, but daily, subcutaneous injection of PTH has an anabolic effect, stimulating bone formation by increasing the number and action of osteoblasts. Teriparatide (Forsteo®) is a recombinant human parathyroid hormone fragment 1-34 (rhPTH (1-34)), which stimulates bone formation and reverses the bone loss in osteoporosis. In postmenopausal osteoporotic women treated with daily 20mg subcutaneous injections of rhPTH (1-34) for 18 months, spinal and hip BMD increased by 9% and 2.8% respectively. Vertebral fracture risk was reduced by 65% and nonvertebral fracture risk by 53%.[34] A study of 437 men with idiopathic or hypogonadal osteoporosis given teriparatide found a significant increase in spinal BMD compared to placebo.[35] In long-term toxicological studies, high doses of rhPTH induced osteosarcoma in rats. In clinical studies of over 1000 patients, treatment with rhPTH for up to 3 years has not increased the frequency of tumours in bone or other tissues.

Practical advice Teriparatide is a daily, subcutaneous 20mg injection, supplied in a disposable pre-filled 28-day pen. It should be stored in the refrigerator (2-8°C). Side effects while uncommon include leg cramps and dizziness. Due to its cost and the need for daily subcutaneous injections, its use will be primarily in those with severe osteoporosis. While there has been no increase in bone tumours in humans treated with rhPTH to date, it should not be prescribed for anyone with an increased risk of developing bone tumours (Paget's disease, prior radiation therapy to bone) or for longer than 18 months.

Hormone replacement therapy (HRT)

Evidence The role of oestrogen deficiency in the development of osteoporosis has been recognised since the 1940s. HRT exerts an antiresorptive effect and while of proven efficacy in the prevention and treatment of osteoporosis, there is growing evidence that the risks associated with continuous use of HRT outweigh the benefits on BMD and fracture risk. In the Women's Health Initiative (WHI) study, hip and vertebral fracture risk were reduced by 34% and risk of all fracture by 24%, but there were increases in the risk of coronary heart disease, stroke, invasive breast cancer and venous thromboembolic disease.[29] The Million Women Study, investigated the effects of specific types of HRT on breast cancer risk and found that users of oestrogen-progesterone preparations showed a 50% increase of the risk of developing breast cancer, with oestrogen-only preparations having a 30% increased risk and tibolone users had a 45% increase in risk, compared with non-users.[30] Recent studies have suggested that continuous HRT use may also be associated with an increased risk of ovarian cancer.[31]

Practical advice The Irish Medicines Board (IMB) and The Chief Medical Officer (CMO) in the UK have both recently issued a safety message that HRT should not be used as first line therapy for long-term prevention of osteoporosis in women over 50 years of age and that it should only be used for those who are intolerant of other approved therapies.[45] Current HRT users and potential new users should be advised about the benefits (relief of vasomotor symptoms, reduced fracture risk) and risks (cardiovascular disease, venous thromboembolic disease and breast and ovarian cancer) and alternative options explored.

COMBINATION OF AGENTS

Bisphosphonates and oestrogen

A combination of bisphosphonates with HRT induced an increase in BMD slightly greater than that achieved with either treatment alone, but there no evidence of a greater reduction of the risk of fracture.[36,37] Based on the recent published data concerning HRT, these combinations cannot be recommended.[29,30]

Bisphosphonates and SERM

A combination of alendronate and raloxifene produced a slightly greater increase in BMD than that of either treatment alone (5.3% versus 4.3% and 2.1%). The study was not designed to assess the impact on fracture risk reduction.[38]

Bisphosphonates and teriparatide

Recent clinical studies have shown that alendronate impairs the anabolic activity of PTH and thus the combination cannot be recommended.[39,40] If PTH therapy is being considered for patients with severe osteoporosis, it seems that bisphosphonates should be discontinued prior to its initiation.

OTHER AGENTS

Calcitonin is an endogenous inhibitor of bone resorption mediated by the suppression of osteoclasts. In one study, treatment with nasal calcitonin 200 IU daily for 5 years produced a 1.2% increase in spinal BMD and a 36% reduction in the risk of vertebral fracture.[32] There was no evidence of benefit on nonvertebral fracture risk. Calcitonin is also thought to have analgesic properties.[33] It is currently unavailable in Ireland.

Fluoride is known to stimulate osteoblast recruitment and activity. There are mixed results regarding its effect on the skeleton, and it remains an investigational agent in this disease.[41]

Strontium There is experimental evidence that this reduces bone resorption and may stimulate bone formation[42]. A rise in BMD and a reduction in the frequency of vertebral fractures have been suggested by results of a phase II trial.[43]

CONCLUSION

The general recommendations for all at risk and those with confirmed osteoporosis include ensuring adequate calcium and vitamin D intake, smoking cessation and regular exercise. Postmenopausal women with osteoporosis with or without vertebral fracture or non-vertebral fractures should be offered treatment[44]. Which treatment should be prescribed when faced with a patient in the clinic? A person's individual risk factors and T score, the specific benefits, extra-skeletal effects and the costs of the available proven medications need to be considered.[13,44] If the aim is to reduce the risk of vertebral fracture, the choice is between a bisphosphonate or a SERM. If the aim is to reduce the risk of vertebral and nonvertebral fracture, bisphosphonates are first choice and the availability of weekly formulations may increase patient compliance. For those with severe osteoporosis and at high risk of or those with multiple fractures, rhPTH may be an alternative option to the bisphosphonates and SERMs. Future research priorities include deciding what it the optimal duration of treatment, head to head trials of the active agents and discovering the best sequence of using the available proven medications.[13,44]

Table 3 Monthly GMS Cost of commonly used preparations (November 2003)

Name, strength, pack size	€	Name, strength, pack size	€
Calcium 500mg x 100	10.09	Raloxifene (Evista®) tablets 60mg x 28	29.89
Alendronate (Fosamax®) tablets 10mg x 28	32.64	cHRT (oral) Oestradiol2mg + Norethisterone 1mg x 28	6.77
Alendronate (Fosamax®) tablets 70mg x 4	35.26	Oestrogen (oral) 0.625-1.25mg x 28	17.81
Risedronate (Actonel®) tablets 5mg x 28	33.34	Tibalone (Livial®) 2.5mg x 28	17.81
Risedronate (Actonel®) tablets 35mg x 4	36.28	PTH (Forsteo®) Pen – 28day use	454.58

References available on request. Date prepared: Dec. 2003