




TREATMENT OF OSTEOPOROSIS

Summary

-  Prevention is the key issue in the management of osteoporosis.
-  HRT is the agent of choice for prevention of postmenopausal osteoporosis.
-  Bisphosphonates and Calcitonin are effective alternatives to HRT for treatment of osteoporosis.

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.^{1,2}

It is a major health and economic problem and data from many countries have shown an increasing prevalence of osteoporotic fractures that is thought to be related to an increasing ageing population. The estimated financial cost to the exchequer in Ireland is approximately £10 million per year.³

Bone is a metabolically active tissue which is continually undergoing a process of resorption (involving osteoclasts) and formation (involving osteoblasts). Under normal circumstances this process maintains the biochemical competence of the skeleton by replacing bone that has accumulated fatigue damage. In addition bone remodelling plays a role in mineral homeostasis and the maintenance of normal serum calcium levels.⁴ Osteoporosis results when an imbalance occurs between these two processes. This results in a reduction in bone mineral density (BMD) and thus an increased risk of fractures.^{5,6} The bones most commonly affected are the vertebral bodies, the distal end of the radius and the neck of femur.

RISK FACTORS:

Bone mass increases during the first twenty years of life, peaks in the third or early in the fourth decade and declines thereafter. Factors that contribute to the development of osteoporosis include as follows:

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| • Physical | Genetic factors, ethnic origin, low bone mass, thin body type, advanced age. |
| • Lifestyle | Cigarette smoking, high alcohol intake, sedentary lifestyle, excessive exercise, inadequate calcium intake. |
| • Disease | Cushings syndrome, hyperparathyroidism, hypogonadism, anorexia nervosa, hyperprolactinaemia, malabsorption, multiple myeloma. |
| • Drugs | Corticosteroids, Heparin, Thyroxine (in excess). ^{5,7,8} |

INVESTIGATIONS:

Early detection can be made by measuring BMD and so predicting the risk of fracture. The method of choice being dual energy x-ray absorptiometry (DXA) although population-based screening is not currently recommended. The first presentation of osteoporosis is often with a fracture sustained after an injury due to minimal trauma. Other investigations include spinal radiography and screening for secondary causes e.g. serum calcium, thyroid stimulating hormone concentration.

PREVENTION:

Prevention of osteoporosis is the key issue in the management of osteoporosis. The aim in prevention is to increase peak bone mass and to reduce the subsequent rate of bone loss. Preventative measures can be broken down into two categories:

- ❖ Lifestyle modifications
 - increase calcium and vitamin D intake (↑consumption of fortified milk)
 - increase weight bearing exercise - 3 x 20 minute sessions per week (note excessive exercise may lead to amenorrhoea and then bone loss)
 - decrease alcohol intake
 - stop smoking
- ❖ Pharmacological intervention
 - HRT at the menopause

Because peak bone mass is achieved between the ages of 25 and 35 years it is suggested that both exercise and adequate calcium intake be encouraged at a much earlier age.⁴

TREATMENT:

The aim of treating established osteoporosis is to alleviate the patient's symptoms and to reduce the risk of further fractures.⁷

HORMONE REPLACEMENT THERAPY (HRT):

HRT is recommended for the prevention of osteoporosis in women with a premature menopause and in postmenopausal women. At the menopause bone turnover increases and bone resorption exceeds bone formation. Greatest bone loss occurs in the first three to six years post menopause; however oestrogen related bone loss may continue for up to 20 years.⁶ HRT reduces bone remodelling activity in postmenopausal women and reduces the rate of bone loss via binding to oestrogen receptors in the bone. Epidemiological studies suggest that HRT is associated with a reduction of about 50% in the risk of hip fracture and probably a similar if not greater reduction in other osteoporotic fractures.^{2,6} Efficacy is dependant on the dose of oestrogen delivered and not on the route of administration. Doses equivalent to 0.625mg of conjugated equine oestrogens are recommended. Maximal effect is seen if treatment is initiated early in the post menopausal period. There is still debate about the duration of therapy required to give maximal reduction of risk because discontinuation of treatment is followed by immediate resumption of bone loss. The current consensus is to treat for as long as possible and preferably for at least 5-10 years.^{2,6}

The decision to take HRT is a complex issue. Factors that need to be considered include:

- Beneficial cardioprotective effects
- Risk of endometrial hyperplasia and thus the need for a progestagen
- Slightly increased risk of breast cancer

For further information please refer to NMIC Bulletin 1996:2(1) and manufacturers product data sheet.

BISPHOSPHONATES:

Bisphosphonates are carbon substituted analogues of pyrophosphate an endogenous physiological inhibitor of bone mineralization.² They bind strongly to hydroxyapatite crystals of bone and are retained in the bone for a lengthy period. During the process of resorption they are released locally and taken up by osteoclasts thereby inhibiting the osteoclasts ability to resorb bone.^{1,2,9}

Disodium etidronate has recently been licenced for the treatment of established osteoporosis. The dosage of etidronate that inhibits bone resorption also impairs the mineralization of newly synthesized bone and hence etidronate must be administered in a cyclical pattern.^{2,5,6} The regimen begins with 14 days therapy of etidronate 400mg daily taken two hours before and two hours after food, followed by 76 days of calcium carbonate 500mg. At present it is recommended that this regimen is adhered to for 3 years, although the optimum duration of treatment has not yet been established.¹⁰ Adverse effects of etidronate tend to be mild and include nausea, dyspepsia and diarrhoea.

Other bisphosphonates (alendronate) inhibit bone resorption at concentrations much lower than those that impair mineralization and thus unlike etidronate it may be given continuously. Alendronate is indicated for the treatment of post menopausal osteoporosis at a dose of 10mg once a day. Deficiencies of calcium and vitamin D intake should be corrected before initiating treatment with alendronate.

In a three year placebo controlled clinical study of alendronate the rate of new vertebral fractures was 48% lower in the treatment group than in the placebo group.^{9,11,12} The recently published Fracture Intervention trial found similar results and in addition a significant reduction in the risk of hip fractures among postmenopausal women was noted.¹⁸ Adverse effects were found to be mild and generally did not require discontinuation of therapy. There have been reports of oesophageal inflammation, erosion and ulceration with alendronate. For this reason it is recommended that alendronate is taken with a full glass of water (>200ml) and the patient should not lie down for at least 30 minutes after taking alendronate.¹² If concurrent calcium supplementation is required it should not be taken at the same time of day as alendronate.

CALCITONINS:

Calcitonin is a peptide hormone synthesized and secreted by the C-cells of the thyroid. It has a direct action on osteoclasts thus inhibiting bone resorption. Several species of calcitonin exist with salmon calcitonin the most potent and the only variety licensed in Ireland. For the treatment of postmenopausal osteoporosis 100 units by subcutaneous or intramuscular injection is recommended. Studies have suggested that calcitonin may also possess analgesic properties and so may be of additional benefit for those patients with significant acute or chronic pain from osteoporosis.^{2,4,5,6} The main adverse reactions reported include nausea, vomiting, tingling of hands and facial flushing. Its use is limited due to its high cost in relation to other therapeutic options available and its availability only as a parenteral formulation in Ireland which may lead to poor compliance.^{8,14} An intranasal formulation of calcitonin is available in other countries.

CALCIUM:

Calcium intake is important for the maintenance of bone mass. Calcium supplements decrease the risk of osteoporotic fractures in men or women whose calcium intake is deficient i.e. <400mg/day.¹⁵ The aim is to achieve a total intake of 1000-1500mg/day. The intake ideally should be via ingestion of calcium rich foods such as dairy products (a glass of milk contains approximately 300mg of calcium).¹ Therefore supplementation need only add to dietary intake which usually means that an individual will require a supplement of 400-600mg/day.²

In the early postmenopausal period the use of calcium supplementation confers little protection against the rapid bone loss but should be given to women who decide not to take HRT. ^{9,16} Bone loss in elderly women whose dietary calcium intake is below 400mg daily can be retarded by increasing their calcium intake to at least 800mg/daily.¹⁶

Calcium carbonate (Calcichew^R equivalent to calcium 500mg) is relatively inexpensive, well tolerated and contains more calcium per gram than other forms of calcium.⁸ Gastrointestinal side effects are mainly reported e.g. constipation, diarrhoea.

VITAMIN D AND METABOLITES:

Vitamin D increases calcium absorption in the gastrointestinal tract.¹² Care should be taken especially in the elderly to ensure adequate vitamin D status. Cutaneous production of vitamin D in response to sunlight falls with advancing age leading to a decrease in calcium absorption and parathyroid hormone mediated

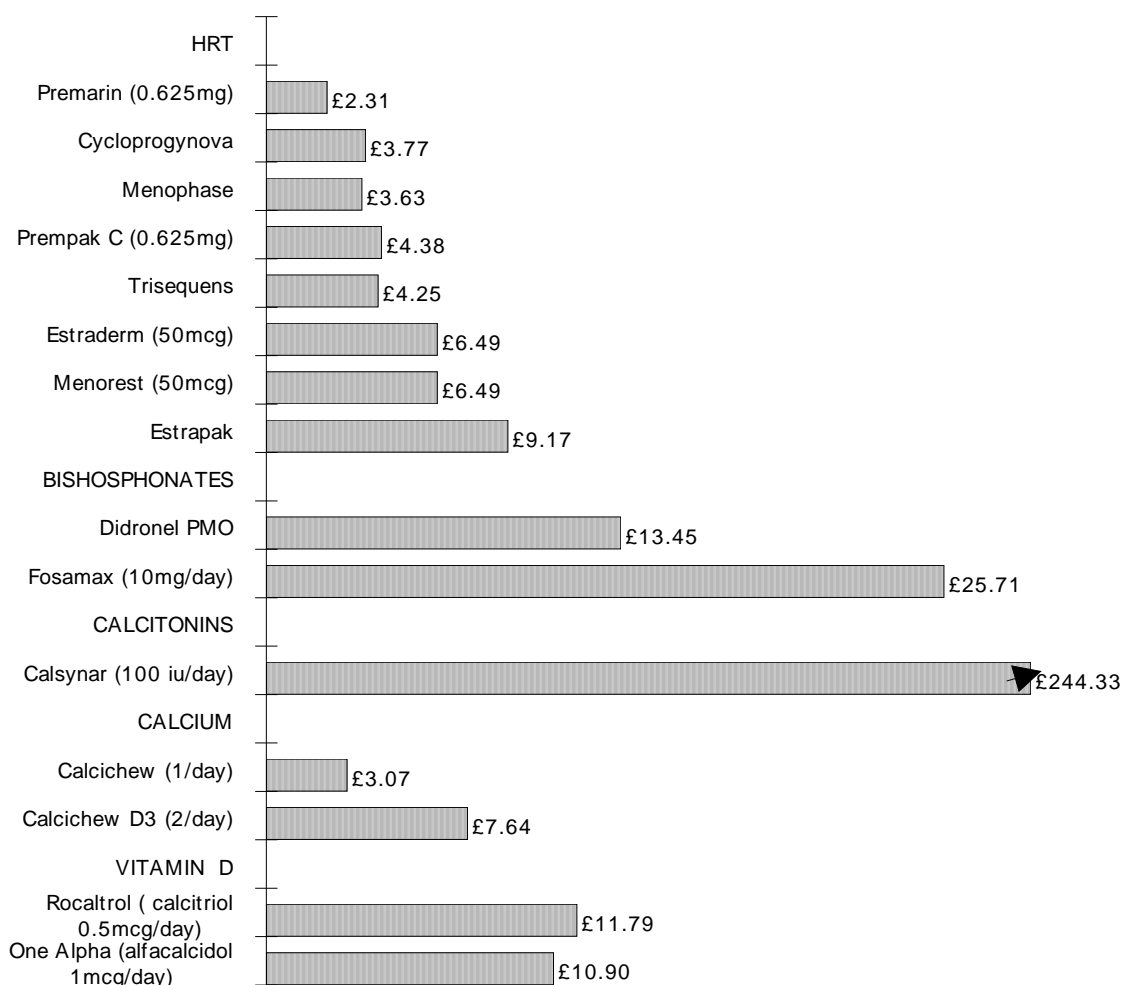
bone loss.^{1,15} There is evidence to suggest that vitamin D supplementation can reduce the risk of fracture. A study involving over 3,000 elderly women treated with 1.2g elemental calcium and 800 units cholecalciferol (vitamin D₃) daily was associated with a significant decrease in the risk of hip fractures and other non-vertebral fractures.¹⁷ Another study comparing calcitriol therapy to calcium supplementation over a 3 year period found a reduced incidence of new vertebral fractures with calcitriol 0.25microgrammes twice daily compared to calcium alone.

Parent vitamin D appears to be a safer option than calcitriol since hypercalcaemia and hypercalciuria are more likely to occur with the latter therapy.¹⁹ There is no convincing evidence that oestrogen benefits women over the age of 75 years. Supplementation with calcium (500mg-1000mg/day) and vitamin D (400iu-800iu/day) such as Calcichew D₃ (1-2 daily) is the treatment of choice for such patients.⁶ Dietary supplementation using calcium and vitamin D fortified milk could also be employed, one glass contains 60% of the recommended daily allowance of these agents.

CORTICOSTEROID INDUCED OSTEOPOROSIS

It is well established that osteoporosis is one of the major complications of corticosteroid therapy. The mechanism by which corticosteroids exert their osteoporotic effect is thought to differ from that associated with postmenopausal osteoporosis. Corticosteroids cause rapid bone loss within the first 6 - 12 months of therapy. Bone loss is dose dependant and varies both between individuals and according to skeletal site. As yet there are no definite recommendations for the most effective agent for prevention or treatment of corticosteroid - induced osteoporosis.

Costs based on one months supply (MIMS Jan 97)



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FURTHER REFERENCES ON REQUEST