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UPDATE ON OSTEOPOROSIS

- **Osteoporosis is a significant cause of morbidity and mortality especially in the elderly population**
- **Evaluation of clinical risk factors is important in the identification of osteoporosis**
- **Patients at risk of osteoporosis should have adequate intakes of calcium and vitamin D**
- **Bisphosphonates are usually the first line treatment of osteoporosis**

INTRODUCTION

Osteoporosis, defined as a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to bone fragility with consequent increase in risk of fracture, is a global disease.[1,2,3] It is a silent disease until complicated by fractures, which are associated with significant mortality and morbidity.[4] Osteoporosis is also an important public health issue as it is estimated that up to 50% of women and 20% of men > 50 years will have a fragility fracture in their remaining lifetime.[1] In Europe osteoporosis accounts for more disability-adjusted life years lost than many non-communicable diseases including rheumatoid arthritis, Parkinson's disease and breast cancer,[5] thereby placing a large financial burden on the individual and the country.[2,6] Osteoporosis is most common in postmenopausal (PM) women, however it also occurs in men where it tends to be under-diagnosed and under-treated.[7]

The hip, vertebral body and distal forearm are the typical sites of osteoporotic fractures, however there is an increased risk of all fractures in osteoporosis.[1,3] Hip fractures, of which 80% occur in women and 90% occur in people >50 years, cause serious disability. They are associated with increased mortality (up to 20%) in the year following the fracture;[8] the prevalence of mortality is higher in men.[7,9] The prevalence of vertebral fractures is similar in men and women, of which many are painless but also associated with morbidity and mortality.[3,7]

PATHOPHYSIOLOGY

The bone mass of an individual in later life is determined by the peak bone mass accrued during intrauterine life, childhood and puberty as well as the subsequent rate of bone loss in adult years. Genetic factors contribute to peak bone mass and environmental factors modulate the genetically determined pattern of skeletal growth.[1] In adult life, the skeleton is continually remodelled in an orderly sequence of bone resorption (by osteoclasts) followed by bone formation (by osteoblasts).[10] A remodelling imbalance occurs when the processes are not matched e.g. with advancing age and menopause. This results in a net loss of bone mass leading to disordered skeletal architecture and increased risk of fractures, many of which occur following low-impact injuries or simple falls.[11]

Secondary causes of osteoporosis include corticosteroid use, rheumatoid arthritis, untreated hypogonadism in men and women, prolonged immobility, organ transplantation, type I diabetes and hyperthyroidism. Up to 60% of osteoporosis in men is due to secondary causes.

DIAGNOSIS

The diagnostic benchmark for osteoporosis, since the 1990's, has been quantitative assessment of bone mineral density (BMD) by central dual energy X-ray absorptiometry (DXA).[1,12,13] The World Health Organisation (WHO), the International Osteoporosis Foundation and the International Society of Clinical Densitometry define osteoporosis based on DXA, applied to the femoral neck, hip or lumbar spine, where the T-score is a comparison of the patient's measured BMD with the mean BMD of a healthy young adult.[5,8,14] Table 1 gives three general descriptive categories for adult men and women using measurements of DXA at the femoral neck. Prospective studies show that the risk of fracture increases progressively with decreasing BMD.[5] Individuals at high risk of osteoporosis and people with a fragility fracture (except women ≥75 years who should be assumed to have osteoporosis and offered treatment) should be referred for BMD.[15] The predictive value of BMD for hip fracture is at least as good as that of blood pressure for stroke and it also provides information on prognosis.[5,16] BMD testing is a vital component in the diagnosis and management of osteoporosis, however there are other factors, which contribute to fracture risk that need to be taken into account.

Table 1: The definition of osteoporosis by BMD [5,8,14]

Normal	A value for BMD that is within 1 SD of the young adult reference mean (T-score ≥ -1)
Osteopenia (Low bone mass)	A value for BMD > 1 SD but < 2.5 SD below the young adult mean (T-score between –1 and -2.5)
Osteoporosis	A value for BMD ≥2.5 SD below the young adult mean (T-score ≤ -2.5 SD)

Table 2 indicates additional risk factors, which should be included in assessing a patient's risk of fracture.[13] Low body mass is a well recognised risk factor for fractures and the risk is most marked for individuals with a BMI of ≤20 kg/m2. Age contributes to fracture risk independently of BMD and the risk of hip fracture increases 30-fold between 50-80 years. Family history of fragility fractures is a significant risk factor independent of BMD, while fracture risk is doubled in the presence of a previous fracture. The use of corticosteroids is an important cause of osteoporosis and fractures.

Table 2. Risk factors used for assessment of fracture probability [5,13]

Age Sex Low BMI (≤20kg/m2) Prior fragility fracture particularly of the hip, wrist or spine Parental history of hip fracture Current glucocorticoid treatment (any dose, by mouth ≥3months) Current smoking Excessive alcohol use (≥3 units per day)	Secondary causes of osteoporosis including: • Rheumatoid arthritis • Untreated hypogonadism in men and women • Prolonged immobility • Organ transplantation • Type I diabetes • Hyperthyroidism • Gastrointestinal disease • Chronic liver disease • Chronic obstructive pulmonary disease

The International Osteoporosis Foundation, the WHO and the US National Osteoporosis Foundation (NOF) recommend that risk of fracture should be expressed as a short-term absolute risk, i.e. probability over a ten year interval.[5,8] FRAX® is a computer based algorithm (www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability in men and women; it incorporates many of these risk factors to estimate 10-year fracture probability with and without the use of BMD.[5,17] The fracture probabilities derived from FRAX® can be used to enhance management decisions: e.g. the NOF recommends that patients ≥50 years with a DXA diagnosis of osteopenia should be considered for treatment if the probability, over 10 years, of hip fracture is ≥3%, or of a major osteoporotic fracture is ≥20%.[8]

MANAGEMENT

Evidence suggests that osteoporosis is under-diagnosed and under-treated.[18] There is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture.[3] **Current guidelines recommend that fracture risk should be assessed in PM women and men ≥50 years, using the clinical risk factors included in table 2, to determine the need for BMD testing.**[5,8] In general the more clinical risk factors that are present, the greater the fracture risk. Women with a prior fragility fracture may be considered for treatment without the need for further assessment[5,19,20] In men with or without a fragility fracture and in women without a previous fragility fracture, management should be based on the assessment of the 10 year probability of a major osteoporotic fracture, using a recognised assessment tool e.g. FRAX®.[5] A comprehensive management plan should include evaluation of those at highest risk, exclusion of secondary causes of low BMD and selection of the appropriate treatment.[21] It is important that secondary causes of osteoporosis are excluded, particularly in men.

NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological management includes prevention of falls and modification of risk factors including: diet, smoking and excessive alcohol intake.[11,12,22] Important measures aimed at preventing falls include attention to modifiable factors including: correcting decreased visual acuity, exercise, reduced consumption of medication that alters alertness and balance, and improvement of the home environment. While large trials have shown that it is possible to reduce falls, randomised studies have not shown significant decrease in fracture risk. There is controversy on the use of hip protectors to prevent fractures, with recent evidence casting doubt on this preventive measure.[23,24] **Attention to diet is important, because there is a high prevalence of calcium and vitamin D insufficiency in the elderly, particularly those with chronic conditions.** Calcium is necessary for maintaining bone health and vitamin D enhances its absorption. A diet with adequate calcium (>1,200mg daily) and vitamin D (800 IU daily) is recommended for those with risk factors. Adults ≥50 years often only consume 700mg calcium daily, so the use of supplements, including fortified food products, may be required. Immobilisation is an important cause of bone loss and should be avoided whenever possible. **Patient education is important, as adherence to treatment is a major problem in osteoporosis.**

PHARMACOLOGICAL MANAGEMENT

Drugs in osteoporosis act mainly on bone resorption (inhibiting osteoclasts) or on bone formation (stimulating osteoblast activity). Most studies have been conducted on PM women.

Calcium and vitamin D supplements Evidence for the use of calcium and vitamin D supplements to maintain optimum BMD in healthy adults with normal dietary intake is limited,[3,4] however a recent systematic review found that the ingestion of calcium or calcium with vitamin D reduced osteoporotic fractures in men and women ≥50 years by 12%.[12] They should be considered for patients in nursing/residential homes and the housebound elderly. Daily intakes of up to 1200mg/day calcium and 800IU vitamin D are recommended, and supplements should be prescribed if dietary intake is inadequate in patients receiving treatment for osteoporosis.[15]

ANTI-RESORPTIVES

Bisphosphonates are potent inhibitors of bone resorption and are the most prescribed medication in the management of osteoporosis.[10,25,26] All the authorised bisphosphonates (alendronate, risedronate, ibandronic acid, zoledronic acid and etidronate) reduce the risk of vertebral fractures.[1,10,27] Alendronate, risedronate and zoledronic acid have also been shown to reduce the risk of non-vertebral fractures including hip fractures.[5,26,28] Post hoc analysis revealed reduced non-vertebral fractures for ibandronic acid.[5,10] Bisphosphonates have been used in trial extensions for up to 10 years, which suggest that bone quality remains normal and that reductions in fracture risk are sustained for as long as treatment

continues.[10] However concern has been expressed about oversuppression of bone turnover, leading to fractures later.[29] Further assessment of prolonged use is required and the optimum duration of therapy remains unclear.[1,31]
The oral bioavailability of bisphosphonates is low and impaired by food. Oral formulations must be taken fasting, sitting upright with a full glass of water, followed by no food for up to 1 hour. This is to reduce the gastrointestinal effects experienced by patients. Compliance with treatment is a problem, particularly in view of these requirements.[22,28,30] This may be improved with weekly/monthly oral dosage regimens. Intravenous formulations (3 monthly and yearly) are also available. Formulations of bisphosphonates in combination with colecalciferol and/or calcium are also available.
Adverse effects: the most common are gastrointestinal including non-ulcer dyspepsia, oesophagitis, oesophageal strictures, gastric and duodenal ulcers. Bisphosphonates are contraindicated in the presence of abnormalities of the oesophagus, and hypocalcaemia. There have been reports of **osteonecrosis of the jaw** (ONJ) reported with their use, particularly with IV formulations given in high doses for metastatic bone disease.[31-33] ONJ has also been associated with bisphosphonate use in osteoporosis;[34,35] the prevalence has been estimated to be ~1/100,000 patient-years, which is similar to the prevalence in the overall population.[33] **Risk factors associated with ONJ** in patients with osteoporosis include history of dental procedures and corticosteroid use.[34,35] Patients with risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene and periodontal disease) should be considered for dental assessment prior to initiation of bisphosphonate treatment.[32,36-40] There have also been reports of **atrial fibrillation** associated with the use of alendronate[41] and zoledronic acid,[5,29] however epidemiological studies show conflicting results.[41-43] A recent systematic review and meta-analysis advised that while there is some data linking bisphosphonates to atrial fibrillation, definite conclusions could not be made and that further investigations are required.[44]

Selective oestrogen-receptor modulators (SERMs) are non-steroidal agents, which act as agonists on bone and reduce the rate of bone loss in PM women.[3,45] Raloxifene has been shown to reduce the risk of vertebral fractures in PM women with low bone mass, however there is no significant reduction in non-vertebral fractures. Other SERMs may be available in the near future.
Adverse effects: raloxifene has been associated with an increased risk of venous thrombosis similar to that for hormone therapy, and with exacerbation of hot flushes.[1,45] An increased risk of death due to stroke has been reported with raloxifene, and it should be used with caution in women with a history of, or risk factors for, stroke. It is contraindicated in women with child-bearing potential, history of venous thromboembolism (VTE) or unexplained uterine bleeding, hepatic impairment and severe renal impairment.

Calcitonin is an endogenous polypeptide hormone that inhibits bone resorption. It is administered by injection or nasal application.[3,21] It modestly increases BMD at the lumbar spine and humerus and reduces the risk of vertebral fracture, however its effect on non-vertebral fractures remains equivocal.
Adverse effects: most frequent are rhinitis and nasal discomfort. Use is contraindicated in patients with hypocalcaemia.

Hormone therapy (HRT) was once considered the primary therapy for PM women with osteoporosis. Oestrogens reduce the accelerated bone turnover induced by the menopause and decrease the risk of vertebral and non-vertebral fractures by about 30%.[3] Due to the unfavourable risk/benefit balance seen in the older PM women in the Women's Health Initiative study (30% risk of heart disease and breast cancer and 40% increased risk of stroke), **the use of HRT for osteoporosis prevention is restricted to short-term use for younger PM women with menopausal symptoms at high risk of fracture.**[5]

Calcitriol (1,25-dihydroxycholecalciferol) is the active form of vitamin D and is approved for the treatment of established PM osteoporosis. It acts mainly by inhibiting bone resorption.[5] It has been shown to reduce vertebral fracture risk in PM women but its effect on non-vertebral and hip fractures has not been established. It is contraindicated in patients with hypercalcaemia, and calcium and creatinine levels need to be monitored.

OTHER AGENTS

Strontium ranelate has antiresorptive properties and possibly increases bone formation.[5,46] It has been shown to reduce vertebral and non-vertebral fractures.[47] A post hoc analysis showed a significant reduction in hip fractures in women >74 years. Its absorption is reduced by food and milk and ideally should be taken at bed-time, at least 2 hours after eating.
Adverse effects: the most common are nausea and diarrhoea, usually reported at the beginning of treatment. It should be used with caution in patients at increased risk of VTE; there have been reports of VTE, even though a causal relationship has not been established.[3,47] Cases of severe hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal has been reported with its use. Patients should be informed to stop strontium immediately and permanently when a rash occurs and to seek medical advice. There have also been recent reports of alopecia occurring with use of strontium.[48]

Parathyroid hormone (PTH) increases bone remodelling and increases bone formation (anabolic agent).[21] Treatment with either the intact molecule (recombinant PTH 1-84) or the 1-34 N-terminal fragment (teriparatide) reduces vertebral fractures.[5,49,50] Teriparatide has also been shown to reduce non-vertebral fractures (not hip fractures) in PM women and has efficacy in men and glucocorticoid induced osteoporosis.[1,3,49] BMD reduces rapidly after discontinuation unless followed by an antiresorptive agent.
Adverse effects: the most common adverse effects are nausea, limb pain, headache and dizziness. Transient slightly increased serum calcium has been observed in some normocalcaemic patients. Contraindications include severe renal impairment, pre-existing hypercalcaemia and metabolic bone disease other than primary osteoporosis.[5,49,50]

MANAGEMENT OF OSTEOPOROSIS IN GENERAL PRACTICE

All patients with confirmed osteoporosis should be offered treatment, and **an intake of adequate calcium and vitamin**

D should be ensured. The choice of which agent to use is determined by several factors including the individual patient, their medical history, the severity of the osteoporosis, the risk of adverse effects from the treatment and costs. Trials have not been designed and powered to detect differences in the magnitude of fracture reduction between different treatments, and more studies are required in this area.[4,5] A bisphosphonate is used as first line treatment in many cases.[15,19,20] Strontium ranelate or raloxifene are alternatives for PM women, if bisphosphonates are not suitable due to contraindications or intolerance. The high cost of PTH peptides restricts their use to those at very high risk. Alendronate, risedronate and teriparatide are approved for the treatment of osteoporosis in men.[5,7] **The duration of treatment with antiresorptive agents is uncertain.**[8,10] Treatment with PTH peptides should not exceed 24 months.[49,50] Patients should be followed up for compliance with treatment and for assessment of fracture risk. The majority of patients can be managed in primary care; **investigation and/or referral** should be considered if there is evidence of continued bone loss on treatment, if treatment with PTH is being considered and in men with osteoporosis.[15]
An Irish study from 2007 showed that 8% of all patients who were initiated on one treatment for osteoporosis were later switched to another therapy.[25] The study found that up to 70% of patients on treatment for osteoporosis were >70 years and there was a high level of prescribing of the once weekly bisphosphonates alendronate and risedronate. It also found that the longer that patients were prescribed prednisolone, the greater the likelihood of them being prescribed a bisphosphonate; however 50% of patients on long-term steroids did not receive prophylaxis for osteoporosis.

Table 3 summarises the authorised indications, dosages and costs for the antiresorptive and anabolic agents used in Ireland. (Full details of the prescribing information for each product should be referred to in the Summary of Product Characteristics (SmPC) before prescribing, available on www.imb.ie or www.medicines.ie).

Table 3. Authorised indications, dosages and costs of agents used in osteoporosis

Drug	PM Osteoporosis	Male Osteoporosis	Corticosteroid Induced Osteoporosis	Dosage	Monthly costs#
Alendronate‡ *Fosamax*®[37,38] *Generic formulations*†	+ *See SMPC*	+ *See SMPC*	+ *See SMPC*	Daily PO Weekly PO *Daily/weekly*	€27.74 €29.97 €14.33 - €24.53
Risedronate‡ *Actonel*®[39,40]	+	+	+ in PM women	Daily PO Weekly PO	€28.34 €30.84
Ibandronic acid *Bonviva*®[51,52]	+			Monthly PO 3 monthly IV	€27.73 €103.89 (3 mthly)
Zoledronic acid *Aclasta*®[53]	+	+		Yearly IV	€499.84 (for 1 year)
Etidronate *Didronel PMO*®[54]	+		+	14/90 days with calcium PO	€54.94
Raloxifene *Evista*®[45]	+			Daily	€25.41
Calcitonin *Miacalcic*®[55]	+			Daily - nasal	Not available
Calcitriol *Rocaltrol*®[56]	+			Daily PO	€22.73
Strontium ranelate *Protelos*®[47]	+			Daily PO	€32.91
Teriparatide *Forsteo*®[49]	+	+	+	Daily SC	€454.58
Parathyroid hormone *Preotact*®[50]	+			Daily SC	€415.29
Hormone replacement therapy	+*			Various preparations	

 # monthly costs according to MIMS Ireland April 2009
‡ combination products with colecalciferol +/- calcium are also available
† generic formulations weekly/monthly authorised – check www.imb.ie for full details of authorised products and their indications
** use restricted to those at high risk of future fractures who are intolerant of, or have contraindications to, other medicinal products*

SUMMARY

Osteoporosis is associated with increased risk of fractures with significant mortality and morbidity, particularly in the elderly population. Good evidence supports the treatment of patients with osteoporosis to prevent further bone loss. Individual patient risk factors should be taken into account when assessing a patient's fracture risk. Lifestyle modification is an important part of the management of a patient. All those at risk, and with confirmed osteoporosis, should modify their risk factors and ensure an adequate intake of calcium and vitamin D. The choice of which medication to use should be based on the individual patient. Bisphosphonates are the most common first-line treatment however gastrointestinal adverse effects may result in potential problems, including a patient's compliance. Patient education is important to ensure optimal adherence to long-term treatment.

List of references available on request. Date of preparation: April 2009

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