Osteoporosis: bare bone facts

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Osteoporosis has become increasingly recognised as a major health care problem as it is the cause of more than 2.3 million fractures annually in Europe and USA alone. These fractures place an enormous medical and personal toll on the individual and a major economic burden on the nation. Osteoporosis can be prevented, and once diagnosed, can be treated. The aim of prevention and treatment of osteoporosis is to prevent the occurrence of future fractures. Lifestyle changes should be encouraged in high risk patients. Pharmacological interventions include the bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy (HRT), calcitonin, teriparatide, calcium and vitamin D supplements, and calcitriol.

Osteoporosis is a silent systemic skeletal disease which commonly leads to fractures that can occur in the absence of trauma or following minimal trauma.[1] Fractures commonly associated with this disorder are those involving the thoracic and lumbar spine, distal radius and proximal femur.[2]

Osteoporosis was defined by the World Health Organisation as "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".[3]

Classification of osteoporosis

Osteoporosis can be defined as being either primary or secondary in origin.[4] Primary osteoporosis is said to exist where there are no other contributory diseases present. In women, 70% of all osteoporosis cases are defined as being primary, although the vast majority of these are due to post-menopausal oestrogen deficiency.[5] In men, however, only 46% of osteoporosis sufferers have no known predisposing illness but a further 16% are known to have hypogonadism.[5]

Secondary osteoporosis is said to exist where a pre-existing disease can be identified as leading to the development of osteoporosis. However, in some cases this may be iatrogenic i.e. through drug administration.[4] Table 1 gives a summary of causes of secondary osteoporosis.

Factors affecting bone mineral density

- **Physical activity:** The first evidence of an association between physical activity and bone mineral density (BMD) came from studies of the effect of inactivity on bones, particularly the osteopenic effects of weightlessness in astronauts during space flights.[6] Physical activity has also been recognised as influencing the attainment of peak bone mass in childhood and adolescence.[6]

- **Calcium** is one of the most important constituents of bone and adequate intake and absorption are required to ensure that enough calcium is available to fulfil the needs of the growing skeleton. The absorption of calcium from the diet relies on two mechanisms. With a high calcium intake most calcium is absorbed passively from the gut. However, with low intakes, calcium absorption relies on an active transport system in the intestinal mucosa which is vitamin D dependent. Therefore a low calcium intake combined with a low vitamin D availability would greatly impair the amount of calcium available for bone formation. The maximal effect of a calcium supplement appears to occur with a dosage of approximately 1000mg per day which should take into account dietary intake.[6] High calcium intake is needed in childhood to achieve the optimum peak bone mass and therefore help prevent subsequent osteoporosis.[5]

- **Vitamin D** is necessary for the normal absorption of calcium from the intestine, and hence a deficiency of this vitamin is a risk factor for osteoporosis. Low vitamin D status is attributed to low dietary intake, decreased skin exposure to the sun, or impaired synthesis of vitamin D in the skin.[6]

- **Caffeine:** dietary caffeine induces a negative calcium balance through increased urinary loss.[6]

- **Smoking:** the adverse effect of smoking on bone is likely to be mediated through changes in endogenous oestrogen metabolism; oestrogen production is decreased and metabolic clearance has been reported to be increased in smokers, but this has not been confirmed in all studies.[6] In addition, smoking is known to lead to an earlier menopause and hence to earlier post-menopausal status and earlier onset of the phase of rapid bone loss.[5] Smoking has also been associated with lower BMD in males.

- **Alcohol** is directly toxic to bone as it reduces bone cell proliferation and activity. As well as having a direct effect on bone, heavy alcohol consumption is also associated with poor nutrition, decreased calcium intake, reduced mobility and low vitamin D, all of which will have a compounding effect on reducing bone mass through their own individual actions.[5]

- **Gynaecologic variables**, such as oral contraceptive use, parity, breastfeeding, age at menarche, and menstrual cycle irregularities have all been associated with BMD.[6] Women with late onset of menarche have been reported to have significantly reduced peak bone mass and increased fracture risk. The effects on bone of oligomenorrhea and periods of amenorrhea have been documented mainly in cross-sectional studies which reported lower values for BMD than in control populations.[6]

- **Genetic factors** are clearly important in the determination of peak bone mass and this appears to be the stage at which they exert most effect, but they could also be determinants of fracture risk which are in part independent of BMD.[5]

- **Thin body type:** it is well recognised that thin individuals have lower bone mineral density than heavier individuals, and there may be multiple reasons for this.[5] Increased weight will put more stress on the skeleton and help maintain BMD in a similar way to exercise.

- **Race:** Afro-Carribean women have a higher BMD than white women at all ages due to a higher peak bone mass and slower rate of loss. White women have a 2.5-fold greater risk of getting osteoporosis.[3]

Table 1

Causes of secondary osteoporosis[4,5]

Endocrine abnormalities
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Diabetes mellitus
Hypogonadism (in males)

Drugs
Glucocorticoids
Anticonvulsants
Heparin therapy (long term)

Neoplastic conditions
Multiple myeloma
Bone metastases

Others
Anorexia nervosa
Alcoholism
Chronic liver disease
Inflammatory bowel disease
Rheumatoid arthritis
Renal disease
Vitamin D deficiency
Malabsorption syndromes:
- Post gastrectomy
- Coeliac disease

Who should be treated?

If drugs were 100% efficacious, 100% safe and cost-free, and patients were 100% compliant, the answer would be to treat everyone and early.[2] Knowledge on an individual's absolute risk is central to making treatment decisions. The imperative to intervene increases with advancing age, lower BMD and previous fracture, as each of these contributes independently to fracture risk.

Most therapeutic agents currently used to treat osteoporosis inhibit bone resorption. Two exceptions include teriparatide, which promotes bone formation, and strontium ranelate, which has a dual mode of action.[7] Selection should take into consideration the evidence for efficacy of different interventions, the long term effects of agents and the differing modes of action.

Calcitriol

Calcitriol has been shown to decrease bone loss in women with osteoporosis, but study results differ.[7] A decrease in vertebral fracture frequency has been demonstrated but no protective effect has been shown for hip fracture.[8] Calcitriol is licensed in the UK for the treatment of postmenopausal osteoporosis.[9]

Table 2

Advice and patient education

Advice to patients:
- Eat a healthy balanced diet with adequate calcium and Vitamin D intake
- Avoid high alcohol intake
- Eat a diet rich in fruits and vegetables
- Do not smoke
- Keep an active lifestyle, including weight bearing exercise
- Keep a healthy weight for height
- Maintain a good posture

Educate patients on:
- The dangers of falling, including information about periods of greatest risk i.e. rising too quickly after eating or resting
- Awareness and reduction of home hazards – increasing home safety includes optimal lighting, elimination of slippery or hazardous home surfaces and ensuring adequate hand supports

Calcitonin

Calcitonin is a peptide hormone with antiresorptive properties in bone.[10] It decreases further bone loss at vertebral and femoral sites in patients with documented osteoporosis but has a questionable effect on fracture frequency.[11] Calcitonin produces an analgesic effect with respect to bone pain.[12] The increase in bone density resulting from this therapy is significantly less than that achieved by alendronate or oestrogen, and may be limited to the spine, but it still has value in reducing the risk of fracture.[11] It can be administered either by subcutaneous injection, intramuscular injection or as a nasal spray.[7,9]

Strontium ranelate

Strontium ranelate stimulates bone formation and reduces bone resorption and is the first of a new class of osteoporotic treatments. In the UK it is licensed for the treatment of postmenopausal osteoporosis.[7] The Scottish Medicines Consortium has advised (July 2005) that strontium ranelate should be restricted to use when bisphosphonates are contra-indicated or not tolerated and then only in women aged over 75 years with a previous fracture and low bone mineral density or in other women at equivalent risk.[9] Avoidance of calcium-containing foods and tablets within two hours of taking the strontium ranelate is important to avoid drug interactions and loss of efficacy.[13] Clinical trials did not provide evidence of an increased incidence of upper gastrointestinal side effects and the main side effect of diarrhoea is reported to be short-lived. An increased risk for thrombosis has been noted which is being investigated by the manufacturers.[7]

Teriparatide

Teriparatide, a recombinant, fragment of parathyroid hormone, has been shown to stimulate new bone formation by direct effect on osteoblasts.[14, 15] It is the first licensed anabolic drug used to reduce the risk of vertebral fractures in established osteoporosis.[7] Teriparatide is available as a subcutaneous injection[9] and is usually used when the patient is resistant to other antiosteoporotic treatments.[9, 17]

Selective oestrogen receptor modulators

Raloxifene is a nonsteroidal benzothiophene compound[8] with tissue-specific oestrogen agonist and antagonist actions.[8,, 16] It has beneficial effects on the skeleton and blood lipid levels, but does not stimulate breast or uterine tissue.[16] The drug has been shown to increase the risk of venous thromboembolism to the same degree as oestrogen.[7] One advantage of raloxifene is its antagonistic action in the endometrium – when taken over two years, raloxifene did not affect endometrial depth.[7]

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate which adsorb onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.[9] Nitrogen-containing bisphosphonates, such as alendronate, risedronate and pamidronate, may suppress bone resorption by a different mechanism from that of etidronate or clodronate, which do not contain nitrogen.[16] Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronic acid or risedronate sodium are considered the drugs of choice for these conditions, but disodium etidronate may be considered if these drugs are unsuitable or not tolerated.[9] Bisphosphonates are poorly absorbed by the intestine and their absorption is further reduced by food, especially if it contains calcium. They should, therefore, be taken in the fasting state 30 to 60 minutes before a meal and only with water.[3]

It is important to note that bisphosphonates do not work optimally when there is underlying vitamin D deficiency.[7]

Table 3

Treatment of Osteoporosis[9,13, 18-22]*

Post-menopausal osteoporosis	Glucocorticoid-induced osteoporosis
1st line ***Oral Bisphosphonates***	
Alendronate 10mg daily or 70mg once weekly	*Alendronate* For postmenopausal women not on HRT: 10mg once daily Other patients: 5mg once daily
Etidronate 90-day cycles of 400mg disodium etidronate for 14 days followed by 76 days of 500mg elemental calcium	
Risedronate 5mg daily or 35mg weekly	*Risedronate* 5mg daily
2nd line	
Strontium ranelate - 2g daily	*HRT* (dose depends on preparation used)
3rd line *Raloxifene* - 60mg daily	

* A number of other drugs which are available on the local market are commonly used for the treatment of osteoporosis. However, since their use is unlicensed for the treatment of postmenopausal and glucocorticoid-induced osteoporosis such drugs were not mentioned in this table.

Oestrogens

Maintaining adequate oestrogen levels remains the most important way of maintaining adequate bone density in women.[11] Evidence indicates that oestrogens reduce bone turnover and prevent bone loss.[16] Calcium supplementation amplifies this effect. Oestrogen receptors have been demonstrated on osteoblasts and on other cells in the bone microenvironment but the precise mechanism of oestrogen action is still unclear.[16] The risks and benefits of oestrogen combined with progestogen treatment are complex and require the individual assessment of each woman.[3] The CSM has advised that Hormone Replacement Therapy should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT.[9]

Conclusion

Many patients are not being given appropriate information about prevention, are not having appropriate testing to diagnose osteoporosis or establish osteoporosis risk, and once diagnosed too many patients are not being prescribed effective therapies.[1] Table 2 gives a summary of the appropriate advice and education which should be given to patients.

The prevention of osteoporosis is life-long. The risk is reduced if a healthy lifestyle is maintained, whilst those at risk of developing osteoporosis should be targeted and given the correct preventive treatment. Once osteoporosis is diagnosed following a fracture, treatment should be given. Choice of therapy should be made following a full discussion with the patient, in which the benefits and side-effects are outlined, so that the patient can make an informed choice about his/her treatment.

Practice Points

- The prevention of osteoporosis begins with the acquisition of optimal bone mass during growth. Anything hindering the acquisition of bone mass such as malnutrition, should be identified and dealt with during childhood
- Lifestyle advice should be provided for optimal bone health to those at risk of osteoporosis
- When present, secondary causes of osteoporosis should be treated/managed
- The most appropriate treatment of osteoporosis for each particular patient should be determined
- Strategies which aim to reduce the risk of falls should be explored

References

1. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation; 2003 Apr. 37 p.
2. Chisholm D, Zajac J D. Treatemnt of osteoporosis: why, whom, when and how to treat. Med J Aust 2004; 180(6): 298-303.
3. Scottish Intercollegiate Guidelines Network Management of Osteoporosis June 2003
4. Tanna N Osteoporosis and its prevention. Pharm J 2005 vol 275 521-524.
5. Liggett NW, Reid DM. The incidence, epidemiology and aetiology of osteoporosis. Hospital Pharmacist 2000 Vol 7 No 3 62-68.
6. Guthrie JR, Dennerstein L, Wark JD. Risk Factors for osteoporosis: A review. Medscape
7. Tanna N. Osteoporosis and its treatment. Pharm J 2005; 275:581-584.
8. Christodoulou C, Cooper C. What is osteoporosis? Postgrad Med J 2003; 79: 133-138.
9. Mehta D. (Ed.) British National Formulary 51st Edition, March 2006. Available at: http://www.bnf.org.uk (Last accessed 10th May, 2006).
10. Micromedex® Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com (cited: 05/03/2006).
11. South-Paul J. Osteoporosis: Part II. Nonpharmacologic and Pharmacologic Treatment. Am Fam Physician 2001; 63(6):1121-8.
12. American Medical Association (AMA). Osteoporosis Management: The online series. Accessed at http://www.ama-cmeonline.com/osteo_mgmt/.
13. Servier Laboratories Ltd. Protelos® (strontium ranelate) Summary of Product Characteristics November 2004. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=15410 (Last accessed 10th May, 2006).
14. National Institute for Clinical Excellence. Bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Technology Appraisal 87. London: National Institute for Clinical Excellence; January 2005.
15. Reginster JV. New agents for the treatment of osteoporosis. Medscape January 2003.
16. World Health Organisation (WHO). Prevention and Management of Osteoporosis. WHO Technical Report Series 2003.
17. De Gabriele P. Risk factor identification and prevention of osteoporosis in the primary care setting. Malta Medical Journal 2006; 18(01): 40-45.
18. PRODIGY Knowledge (2006) Osteoporosis-treatment and prevention of fragility fractures. Sowerby Centre for Health Informatics at Newcastle Ltd. (SCHIN) http://www.prodigy.nhs.uk/osteoporosis_treatment/view_whole_guidance [Accessed 25th May, 2006]
19. MSD Fosamax® (alendronate sodium) Summary of Product Characteristics March 2006. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed 29th May, 2006).
20. Procter and Gamble Pharmaceuticals UK Limited. Actonel® (risedronate sodium) Summary of Product Characteristics February 2005. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).
21. Procter and Gamble Pharmaceuticals UK Limited. Didronel PMO® (etidronate disodium) Summary of Product Characteristics July 2003 Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).
22. Eli Lilly and Company Limited. Evista® (raloxifene hydrochloride) Summary of Product Characteristics. June 2004. Acessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).