

# Risk factor identification and prevention of osteoporosis in the primary care setting

Patricia De Gabriele

On one of her visits, MB Borg, a 54 year old lady, showed concern about her risk of developing osteoporosis. Lately, she had been listening to a series of radio and TV programmes on this matter where particular emphasis was put on bone density scans. She was preoccupied about being at risk for osteoporosis and wanted to know what she could do to prevent it or even treat it if she was found to suffer from osteoporosis.

## Introduction

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and deterioration of bony microarchitecture. The result is fragile bones and an increased risk for fracture with even minimal trauma. Osteoporosis is a chronic condition of multifactorial etiology and is usually clinically silent until a fracture occurs.<sup>1</sup>

Osteoporosis affects 200 million individuals worldwide.<sup>2</sup> In 1990, there were 1.7 million hip fractures alone worldwide. With changes in population demographics, this figure is expected to rise to 6 million by 2050.<sup>3</sup> Often, osteoporosis is untreated and unrecognized, partially because it is a clinically silent disease until it manifests in the form of fracture, most commonly of the hip, spine and wrist. As populations age, the number of osteoporotic fractures in elderly people will increase.<sup>3</sup>

Osteoporosis creates a huge socioeconomic burden of disease and disability. Identifying high-risk groups in primary care and using preventive treatment can result in a substantial reduction in morbidity and mortality. General practitioners can then help by presenting a unified lifestyle message, advising on fall prevention and providing effective treatment.<sup>4</sup>

## Keywords

Osteoporosis, risk factors, management strategies

**Patricia De Gabriele** MD Dip WH (ICGP)  
Department of Primary Health Care, Floriana, Malta  
Email: rdegabriele@nextgen.net.mt

## Prevalence of Osteoporosis

The World Health Organization estimated the prevalence of osteoporosis in western women (adjusted to 1990 US white women) at any site as 14.8% in women aged 50-59, 21.6% for ages 60-69, 38.5% for ages 70-79, rising to 70.0% in women aged 80 or more.<sup>5</sup>

The likelihood that any individual will suffer from an osteoporotic fracture is relatively high. According to a conservative estimate, more than one-third of adult women will sustain one or more osteoporotic fractures in their lifetime. The lifetime risk of symptomatic fracture for a 50 year old white woman in the UK has been estimated as 13% for the forearm, 11% for the vertebrae and 14% for the femoral neck.<sup>6</sup>

## Risk Factors for Osteoporosis

The risk factors for osteoporosis are well recognised. The key risk factors for fractures (particularly hip fractures) are:

1. Previous low-trauma fracture after the age of 50 years
2. Maternal history of hip fracture
3. Low body mass index (< 19)

A large risk factor study of 7782 women aged 65 years and older (with a mean age of 73.3 years) identified seven variables:

- Age
- BMD T-score
- Fracture after age 50 years
- A parental history of hip fracture especially maternal hip fracture after age 50
- Smoking status
- Thin body type with weight less than or equal to 57 kg (125 lbs)
- Use of arms to get up from a chair<sup>7</sup>

Additional risk factors for osteoporosis include:

- Being female
- Early menopause (age <45 years)
- Use of systemic corticosteroids
- Excess alcohol intake
- Hypogonadism
- Physical inactivity<sup>8</sup>

There are other secondary causes of osteoporosis that are shown in Table 1.

**Table 1: Secondary Causes of Osteoporosis**

<b>Endocrine</b>	<b>Nutritional</b>	<b>Drugs</b>	<b>Others</b>
Thyrotoxicosis	Inflammatory Bowel Disease	Long-term Corticosteroid Use	Rheumatoid arthritis
Cushing's Syndrome	Chronic Liver Disease	Phenytoin	Multiple Myeloma
Hyperprolactinaemia	Coeliac Disease	Phenobarbitone	Metastatic Carcinoma
Hyperparathyroidism	Anorexia Nervosa	Overtreatment with Thyroxine	Renal Disease
Hypogonadism	Vitamin D Deficiency	Diuretics such as Bendrofluazide	

Risk factors for low bone mass are not sufficiently sensitive for diagnosis or exclusion of osteoporosis. Only bone mineral density (BMD) measurement can identify patients who have a low bone mass. However, assessment of risk factors is useful for identifying women at high risk of osteoporosis, heightening clinical awareness of osteoporosis and developing societal strategies for prevention of fracture and treatment of osteoporosis.<sup>10</sup>

The diagnosis of osteoporosis is based on the measurement of BMD. There are a number of clinical risk factors that provide information on fracture risk over and above that given by BMD. The assessment of fracture risk thus needs to be distinguished from diagnosis to take account of the independent value of the clinical risk factors. The independent contribution of these risk factors can be integrated by the calculation of fracture probability with or without the use of BMD. Treatment can then be offered to those identified to have a fracture probability greater than an intervention threshold.<sup>6,11</sup>

Identification of an individual's risk profile would also form the basis of the decision to test for BMD.<sup>12</sup> In a study made by Kanis JA et al., it was found that the most efficient assessment scenario was the use of clinical risk factors with the selective use of BMD scanning.<sup>13</sup> The osteoporosis self-assessment tool (which might take the form of a questionnaire based on risk factor assessment) may be the most useful means for the busy clinician to identify postmenopausal women who would most benefit from BMD testing.<sup>14</sup>

An example of such questionnaire can be viewed by linking to [www.home.um.edu.mt/med-surg/mmj](http://www.home.um.edu.mt/med-surg/mmj)

MB could be assessed with regards to her risk of developing osteoporosis with an appropriately designed questionnaire<sup>15</sup> aimed at identifying possible risk factors for osteoporosis and referred for bone mineral density scan accordingly.

### **Prevention of Osteoporosis**

Independent of the bone density scan result, advice should be given to MB Borg by her family doctor on measures that need to be taken to prevent osteoporosis.

- A healthy balanced diet, rich in calcium, is crucial for strong and healthy bones. Absorption of calcium from the intestine may be reduced by bran, bran-based cereals and chapattis. Urinary calcium excretion may be increased by high dietary intake of sodium, protein and caffeine. Table 3 shows the main dietary sources of calcium.

- Vitamin D is also important to help absorb calcium from food. The skin can usually make enough vitamin D when exposed to daylight. Most people get enough from exposing their hands, arms and face for a few minutes a day, and they get that from normal daily activities – sunbathing is not recommended. However, the use of sunblock creams prevents this effect of sunlight. Thus, individual patients may need calcium and vitamin D supplements.
- A rough guideline for patients would be that it is sensible to try to eat 3-4 portions of calcium a day. Examples of a portion are:
  - a glass of milk (about 200ml) – as a drink on its own, on cereal, or in hot or cold drinks
  - a small pot of yoghurt
  - a portion (50g) of cheese or cheese spread
  - a handful of nuts or seeds
  - two slices of bread or four crackers or crisp breads
  - a serving of green vegetables (such as spinach, broccoli or cabbage)
  - a portion (100g) of fish with edible bones (such as tinned salmon or pilchards)<sup>17</sup>
- Eating a balanced diet with at least 5 portions of fruit and vegetables a day should ensure that the patient gets enough of other important nutrients too. Examples of a portion are:
  - one large fruit (such as an apple, banana or pear)
  - two medium fruits (such as a satsuma, kiwi fruit or plum)
  - a handful of small fruit (such as grapes or strawberries)
  - one tablespoon of dried fruits
  - one small glass of fruit juice
  - two tablespoons of vegetables
  - a small bowl of salad<sup>17</sup>
- Activities such as climbing stairs, brisk walking or dancing – known as ‘weight-bearing’ exercise – help make bones stronger. Doing 30 minutes five days a week is ideal, but every little bit helps. Certain exercises also help the patient's balance, making it less likely for them to fall. Keeping active is also good for the rest of the body, such as the heart and circulation.

- It is advisable to maintain a good posture by keeping the head held high, chin in, shoulders back, upper back flat and lower spine arched. This helps avoid stress on the spine. When sitting or driving, a rolled towel should be placed in the small of the back. While reading or doing handwork, leaning over should be avoided. When lifting, bending should be done at the knees, and not at the waist. Then, lifting should be done with the legs, keeping the upper back straight.
- Smoking increases the risk of osteoporosis so the patient should be advised to quit if she smokes.
- Sensible drinking doesn't seem to increase the chance of developing thin bones, but long-term heavy drinking might.<sup>18,19</sup> For this and other reasons, it's not wise for women to drink more than 14 units of alcohol per week (no more than 2–3 units per day), or for men to drink more than 21 units per week (no more than 3–4 per day). Typically, a 175ml glass of wine or a pint of ordinary strength beer is about 2 units, and a measure of spirits is one unit.

### Treatment for Osteoporosis

Having established that those at highest risk of osteoporotic fractures should be targeted for treatment, this should be preceded by assessment of BMD by DEXA scan in the vast majority of cases. People with two or more vertebral fractures (including painless fractures) are considered to be at such high risk of further fracture that treatment can be started without measuring BMD.<sup>9</sup> The goals of treating osteoporosis are:

- To prevent fractures
- To stabilize or achieve an increase in bone mass
- To relieve symptoms of fractures and skeletal deformity
- To maximize physical function.

Treatment should include:

1. Lifestyle and nutritional advice (as described before)
2. Drug therapy
3. Assessment and management of risk of falls, particularly in the elderly

### Drug Treatment Options

There are a range of drug treatment options. Guidance on the preferred options changes regularly with the identification of new treatment modalities, and the discovery of adverse effects of existing medications. The current UK guidelines are summarised in Table 2.

The most commonly used options for which there is good evidence are detailed below.

- **Hormone Replacement Therapy (HRT)**  
HRT stops bone loss in early, late and elderly postmenopausal women by inhibition of bone resorption resulting in a 5-10% increase in BMD over 1-3 years.<sup>20</sup> When HRT is stopped

bone loss resumes at the same rate as after the menopause. The results of a meta-analysis of 13 randomised placebo-controlled trials of HRT use suggest a 33% reduction in vertebral fracture<sup>21</sup>. A meta-analysis of 22 randomised trials of HRT use suggested a 27% reduction in non-vertebral fractures in a pooled analysis, with a 40% reduction for hip and wrist fractures.<sup>21</sup>

HRT was the treatment of choice in early postmenopausal women (within 5 years of the onset of the menopause) until recently. While recent RCTs<sup>22,23</sup> confirm the benefit of HRT in prevention and treatment of osteoporosis, concerns about the balance of risks and benefits have led the Medicines Boards in Europe to recommend that HRT should be used for the shortest possible time and no longer recommend it as first choice for the prevention of osteoporosis.

- **Bisphosphonates**

The bisphosphonates are synthetic pyrophosphate analogues which 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 their ability to resorb bone. The commonest drugs used are etidronate, alendronate and risedronate.

Etidronate is given in a cyclical pattern with the regimen beginning 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. However, it reduces the risk of vertebral fracture only.<sup>9</sup>

**Table 2:** Treatment options for osteoporosis<sup>9</sup>

<b>Treatment options</b>	<b>Notes</b>
<b>First-line treatment</b>	
Alendronate or risendronate	Risedronate not licensed for use in men Do not use bisphosphonates in people who are unable to adhere to dosing instructions
<b>Second-line treatment</b>	
Raloxifene, calcitonin or cyclical etidronate HRT Calcium and Vitamin D	Recommended for treatment of diagnosed OP in postmenopausal women HRT should be used for those in whom benefits outweigh risks Calcium and vitamin D may be used alone in elderly (80+), frail or housebound
<b>Adjunct treatment</b>	
Calcium and Vitamin D	Consider as adjunct treatment if dietary intake suboptimal. Dose will depend on dietary intake

Alendronate differs from etidronate in that the dosage needed to inhibit resorption is much lower and therefore it can be given continuously. A dose of 10mg per day is usually used although 70mg once weekly has a good safety profile and the same efficacy as 10mg daily in increasing BMD and reducing bone turnover. In one randomised controlled trial of alendronate versus placebo, alendronate resulted in a BMD increase of 8.8% in vertebrae and 6.9% in the femoral neck and reduced all fractures from 18 to 13%.<sup>24</sup> Another randomised controlled trial of alendronate plus calcium versus calcium and placebo showed a 48% decrease in new vertebral fractures, a decrease in the progression of vertebral deformities and a significant reduction in height loss.<sup>24</sup> A further multicentred randomised controlled trial of more than 2,000 women followed for three years showed that alendronate increased average BMD while halving the rate of vertebral fractures.<sup>24</sup> The FIT trial showed that alendronate reduced the relative risk of hip fracture by 50% in women with established osteoporosis.<sup>25</sup> Thus, alendronate reduces the risk of both vertebral and non-vertebral fractures.<sup>9</sup>

Risedronate prevents postmenopausal bone loss. In one study of 2,400 patients with vertebral fractures it reduced the cumulative incidence of patients with new vertebral fracture by 41% over three years and by 65% after the first year.<sup>21</sup> It is taken at a dose of 5mg per day. There is evidence that it reduces the risk of both vertebral and non-vertebral fractures.<sup>9</sup>

The commonest side-effects of bisphosphonates are gastrointestinal disturbance causing nausea, constipation and diarrhoea. Oesophageal erosion, inflammation and ulceration can also occur. These drugs must be taken on an empty stomach with a minimum of 200mls of water on awakening, at least half an hour before food, drink and other medications. The patient should not lie down for at least 30 minutes after taking these agents. Hypocalcaemia and other disturbances of calcium metabolism must be corrected before any bisphosphonate therapy is initiated. Bisphosphonates are particularly useful for the treatment of older postmenopausal women.

- **Selective Oestrogen Receptor Modulators (SERMS)**

SERMS act as oestrogen agonists or antagonists depending on the target tissue.

Tamoxifen (first generation SERM) is an oestrogen antagonist in breast tissue but a partial agonist in bone and cholesterol metabolism and the endometrium. Because of its side effects, including increased risk of thromboembolic disease and hepatic and endometrial tumours, it is not used for the prevention or treatment of osteoporosis.

Raloxifene (second generation SERM) has a tissue specific effect and competitively inhibits the action of oestrogen in the breast and the endometrium while acting as an oestrogen agonist on bone and lipid metabolism. The

MORE (Multiple Outcomes of Raloxifene Evaluation) study, a three year randomised controlled trial of raloxifene use in more than 6,800 women, showed a decreased the risk of vertebral fracture by 50% at 60 or 120mg/day.<sup>26</sup> The risk of non-vertebral fractures was unchanged. Raloxifene increased BMD at the femoral neck by 2.1 to 2.6% yearly. Unfortunately it was also shown to increase the risk of DVT.<sup>26</sup> The ongoing RUTH study will ascertain whether or not the decrease in LDL cholesterol and fibrinogen seen in individuals taking raloxifene can result in a reduction in coronary heart disease in the high-risk population of postmenopausal women.

SERMS may be most useful in the treatment of older postmenopausal women. In younger women they can cause menopausal symptoms like flushing and sweating.

- **Calcium and Vitamin D<sup>27</sup>**

Calcium alone: Calcium intake is important for the maintenance of bone mass. Dietary supplementation of calcium is inexpensive and may increase BMD up to 1% over two years. Postmenopausal women need 1 – 1.5g elemental calcium daily. Ideally, calcium intake should be via ingestion of calcium rich foods (see Table 3). Supplementation should take dietary intake into account. Gastrointestinal side effects are mainly reported such as constipation and diarrhoea. Hypercalcaemia is rare at dosages of less than 2g/day.

A meta-analysis of 16 observational studies involving over 38,000 postmenopausal women with a mean age of 60-80 years, with a mean dietary calcium intake of 168-786mg/day showed that for every 300mg/day increase in dietary calcium intake there was a 4% fall in the odds of experiencing a hip fracture. However, four small randomised controlled trials involving 531 postmenopausal

**Table 3:** Composition and serving size of calcium containing foods<sup>6</sup>

<b>Food</b>	<b>Serving size</b>	<b>Calcium per serving (mg)</b>
Milk	1 cup	290-300
Cheddar/other hard cheese	1 oz	220
Yogurt	1 cup	240-400
Ice cream	1/2 cup	90-100
Cottage cheese	1/2 cup	80-100
Parmesan cheese	1 tbsp	70
Powdered non-fat milk	1 tsp	50
Sardines in oil (with bones)	3oz	370
Canned salmon (with bones)	3oz	170-210
Broccoli	1 cup	160-180
Egg	1 medium	55
Calcium-fortified food	1 serving	Varies
Baked beans	4 oz	45
Dried apricots	2 oz	52

women provided conflicting evidence on whether calcium alone had a protective effect against fractures.

#### *Vitamin D alone*

Vitamin D increases calcium absorption in the GI tract. Data from one randomized controlled trial involving 2,564 men and women with either age-related or postmenopausal osteoporosis using daily oral supplements of vitamin D<sub>3</sub> 400IU alone for 3 years had no protective effect against hip or any other non-vertebral fracture.

#### *Calcium plus vitamin D*

One randomized controlled trial of 2,790 elderly women (mean age 84 years) with age-related or postmenopausal osteoporosis showed that daily oral supplements of calcium 1.2g plus vitamin D<sub>3</sub> 800 IU for 3 years helped prevent hip and non-vertebral fractures. Another randomized placebo-controlled study involving 445 younger ambulant men and women (average age 71 years) taking oral supplement of calcium 500mg plus vitamin D<sub>3</sub> 700 IU for 3 years reduced the incidence of non-vertebral fractures. Combined calcium and vitamin D is the treatment of choice in elderly, housebound patients and is usually well tolerated and can be given indefinitely.

- **Calcitonin**

Calcitonin is a peptide hormone synthesised and secreted by the C-cells of the thyroid. It has a direct action on osteoclasts thus inhibiting bone resorption. Treatment with calcitonin causes a short-term decrease in bone resorption. The usual dose is 100 IU calcitonin salmon preparation either intramuscularly or subcutaneously three times per week. Calcitonin may also possess analgesic properties and may be of additional benefit to patients with acute or chronic pain due to osteoporosis.<sup>28</sup>

The PROOF (Prevent Recurrences of Osteoporotic Fractures) study, a 5 year double blind randomised placebo controlled study of 1255 postmenopausal women with osteoporosis showed that intranasal salmon calcitonin 200 IU per day seemed to reduce the rate of vertebral but not peripheral fractures by about 30% compared with placebo.<sup>29</sup> Unfortunately a large percentage of the study participants were lost to follow up. The main adverse reactions include nausea, vomiting, tingling of hands and facial flushing. Its use is limited due to its high cost.

- **Strontium ranelate**

Strontium ranelate is a new first-line therapy recently licensed in Europe. It is indicated in the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral and hip fractures in patients with or without a previous history of fractures.<sup>30</sup> It is the first antiosteoporotic treatment to simultaneously increase bone formation and

decrease bone resorption. It increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture. It reduces bone resorption by decreasing osteoclast differentiation and resorbing activity. This rebalances bone turnover in favor of the formation of new and stronger bone and provides early and sustained antifracture efficacy.<sup>30-33</sup>

Results from phase III clinical development have shown that strontium ranelate is effective at all major osteoporotic sites, including the vertebrae and hip, however over 3 years of treatment. In the TROPOS study, it was shown that strontium ranelate increased femoral neck bone mineral density by 8.2% after 3 years. It also reduced the relative risk of nonvertebral fracture by 16% (P=0.04) over 3 years compared with placebo<sup>34</sup>. It is also effective regardless of the severity of patient's disease, whether they have osteoporosis or osteopenia and whether or not they have a previous fracture. Strontium ranelate is the first antiosteoporotic agent to show conclusive efficacy in patients 80 years of age and over.<sup>30</sup> The combined effects of strontium distribution in bone and increased X-ray absorption of strontium as compared to calcium, leads to an amplification of BMD measurement by DEXA scans. Thus, care must be taken when interpreting BMD changes during treatment.

- **Teriparatide**

Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include stimulation of bone formation by direct effects on osteoblasts indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney. Teriparatide is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone. This can be used in the treatment of established osteoporosis in postmenopausal women who are at high risk for having a fracture.<sup>35</sup> However, it has been shown to bring about a significant reduction in the incidence of vertebral, but not hip, fractures. The drug is also approved to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. This product is usually used when the patient is resistant to other anti-osteoporotic treatments.

## **Conclusion**

As seen in the presented case, the family doctor is in the best position to provide information on prevention and treatment of osteoporosis. Moreover, the family doctor plays a major role in identifying patients at high risk of developing osteoporosis and directing management accordingly.

## References

1. Hobar C. Osteoporosis. [www.emedicine.com](http://www.emedicine.com) (December 2005)
2. Lin JT, Lane JM. Osteoporosis: a review. *Clin Orthop*. 2004 Aug; (425): 126-134
3. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser. 2003;921:1-164, back cover
4. Davenport G. *Rheumatology and Musculoskeletal Medicine*. BJGP Vol 54;503: 457-464 [Medline]
5. World Health Organization. Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis. WHO Technical Report Series 843. Geneva: WHO, 1994
6. Anonymous. Osteoporosis. Clinical Guidelines for Prevention and Treatment. London: Royal College of Physicians, 1999
7. Black DM, Steinbuch M, Palermo L et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporosis International* 2001; 12: 519-528
8. Peel N., Eastell R. ABC of Rheumatology: Osteoporosis. *BMJ* 1995; 310: 989-992 (15 April)
9. PRODIGY Guidance. Osteoporosis treatment and prevention of falls. National Health Service: Practical Support for Clinical Governance. [www.prodigy.nhs.uk/guidance.asp?gt=Osteoporosis%20treatment](http://www.prodigy.nhs.uk/guidance.asp?gt=Osteoporosis%20treatment) October 2003
10. AACE Osteoporosis Guidelines. *Endocrin Pract* 2003; 9 (No. 6)
11. Kanis JA et al. Assessment of fracture risk. *Osteoporos Int*. 2004 Dec 23; [Epub ahead of print]
12. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation; 2003 Apr. 37
13. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporosis Int*. 2005 Mar; 16(3):229-38
14. Wehren LE et al. Beyond Bone Mineral Density: can existing clinical risk assessment instruments identify women at increased risk of osteoporosis? *J Intern Med* 2004 Nov; 256 (5):375-80
15. De Gabriele P. Osteoporosis – Risk Factor Identification in my Practice. Project for ICGP Diploma in Women's Health, 2005.
16. American Association of Clinical Endocrinologists. *Endocrine Practice* 2001; Vol 7 No 4: 293-312.
17. USDA Nutrient Data Laboratory, 2000
18. New SA, Bolton-Smith C, Grubb DA, Reid DM. Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. *American Journal of Clinical Nutrition* 1997; 65: 1831-1839
19. Scane AC, Francis RM, Sutcliffe AM, Francis SJD, Rawlings DJ, Chapple CL. Case-control study of the pathogenesis and sequelae of symptomatic vertebral fractures in men. *Osteoporosis International* 1999; 9: 91-97
20. Cummings SR et al. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359:1761-67.
21. Delmas P. Treatment of postmenopausal osteoporosis. *Lancet* 2002; 359:2018-26.
22. Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *NEJM* 2003; 349: 523-4.
23. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-427.
24. ABC of Rheumatology: Osteoporosis. *BMJ* 1995; 310: 989-992.
25. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of the effect of alendronate on fractures in women with pre-existing vertebral fractures. FIT research group. *Lancet* 1996 ; 348 : 1535-41.
26. Ettinger B, Black DM, Mitlak BH. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with Raloxifene: results from a 3-year randomised clinical trial. *JAMA* 1999 ; 282 : 637-45.
27. Lifestyle advice for fracture prevention. *DTB* 2002; 40: No 1.
28. Treatment of Osteoporosis. National Medicines Information Centre 1997. Vol 3 No 1.
29. Reginster JY, Derojy R, Leerare MP. A double-blind placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine bone loss. *Am J Med* 1995 ; 98 : 452-8.
30. European Summary of Product Characteristics of Protelos®.
31. Marie PJ, Ammann P, Boivin G, et al. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif Tissue Int*. 2001;69:121-129.
32. Ammann P. Strontium ranelate: mode of action and benefits for bone quality. *Osteoporos Int*. 2003; 14: S105. Abstract SY21.
33. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med*. 2004;350:459-468.
34. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: TROPOS study. *J Clin Endocrinol Metab*. 2005;90:2816-2822.
35. American College of Rheumatology. Teriparatide (Forteo™) for the treatment of osteoporosis. [www.rheumatology.org/publications/hotline/0103tpd.asp](http://www.rheumatology.org/publications/hotline/0103tpd.asp) (January 2003).