Introduction: General Outlines of Assessment and Management of Osteoporosis – Postmenopausal Osteoporosis as an Example

Piet Geusens, Robert Lindsay, and Philip N. Sambrook

Summary

- Assessment and treatment of postmenopausal osteoporosis are well documented.
- Lifestyle adaptations, including diet (calcium and vitamin D supplements, protein intake) and fall prevention, are indicated in all postmenopausal women but are not sufficient for fracture prevention in postmenopausal women with osteoporosis.
- Case-finding can identify many patients at high risk for osteoporosis before the first fracture has occurred. Treatment can reduce the risk of the first fracture in adequately selected patients with osteoporosis.
- After a fracture has occurred, the recognition that osteoporosis is the underlying cause is an essential step towards treatment that can further lower the risk for new fractures.

The approach of osteoporosis in daily clinical practice is dependent on the awareness of doctors and patients on the clinical presentation and available treatment modalities for osteoporosis. It is the aim of this book to contribute to improve the awareness of busy practitioners in the assessment and treatment of osteoporosis.

The clinical expression of osteoporosis is the occurrence of fractures. Fractures result in pain, functional limitations, decreased quality of life, psychosocial isolation, and increased mortality. Fractures are associated with an increased risk of new fractures, even within a short time. This leads to a vicious circle of recurrent fractures and decreasing quality of life (Figure I.1).

The aim of treatment of osteoporosis is to prevent fractures. By preference, the occurrence of the first fracture should be prevented in patients at high risk for osteoporotic fractures. In patients with a prevalent fracture, treatment should be started soon after a fracture has occurred with agents that reduce the risk of new fractures within a short time. In women early after menopause, the aim is mainly to prevent vertebral fractures. Later after the menopause, the aim is to prevent vertebral, non-vertebral, and hip fractures.

From the clinical standpoint, several subgroups of individuals with osteoporosis that need specific approaches are encountered. The clinical approach is different between women and men (see Chapter 20), between patients with and without history of a fragility fracture (see Chapters 16–18), between primary and secondary osteoporosis (see Chapter 21), and between patients with mainly osteoporosis or mainly an increased risk for falls (see Chapters 12 and 26).
General Approaches for Assessment of Postmenopausal Osteoporosis

Clinical risk evaluation is the cornerstone of the first approach towards osteoporosis (Figure I.2). Case-finding allows selection of those patients who will have most advantage of further evaluation and treatment (see Chapters 4, 5, and 26). Recognition of risk factors for osteoporosis before the first fracture has occurred is often overlooked until the doctor or patient is aware of osteoporosis and takes the initiative to consider (or exclude) the risk for osteoporosis. Low awareness for osteoporosis is found even when patients already have a history of recent fragility fracture, many of which are not recognized by doctors and patients as being the result of osteoporosis.

In patients with a history of vertebral fracture, dual-energy X-ray-based absorptiometry (DXA) is not necessary before starting treatment. However, DXA can be useful for monitoring response to therapy and to enhance compliance. Two-thirds of vertebral fractures are asymptomatic, i.e. without a typical acute back pain episode. Therefore, when vertebral fractures are suspected clinically (e.g., in the presence of height loss, thoracic hyperkyphosis, or chronic back pain), a lateral X-ray of the spine is indicated in addition.

In patients without a history of vertebral fracture, the treatment options depend on the presence of osteoporosis as documented by DXA. In the absence of vertebral fracture, the clinical question then is which patients should be measured by DXA. Many clinical risk factors for osteoporosis are documented, some of which are readily

![Figure I.1 The vicious circles of osteoporosis, falls, fractures, pain, handicap, and psychosocial isolation.](image-url)
Vertebral fracture after minimal trauma

Suspected vertebral fracture

Major risk factors for fracture due to osteoporosis
- Postmenopausal female
- > 65 years
- Low body weight
- Prior low trauma fracture
- Family history of osteoporosis
- Low calcium intake
- Immobilisation
- Diseases and medications associated with rapid bone loss (for glucocorticoid therapy, see specific recommendations)
- Radiological osteopenia
- Height loss
- Low bone mass as assessed by techniques other than DXA

A BMD test is not necessary but can be useful for monitoring response to therapy and to enhance compliance

Confirm fracture on spine X-ray

Lifestyle + Calcium + Vitamin D
Bisphosphonates
Alendronate + + +
Risedronate + + +
SERM Raloxifene +
Nasal Calcitonin +
Intermittent rhPTH + +

BMD Test (DXA Hip +/- Spine)

T score below –2.5 SD from young, normal mean

T score –1.0 to –2.5 SD from young, normal mean

T score above –1 SD from young, normal mean

Differential Diagnosis

Treatment of osteoporosis to prevent (first or new) fracture

Prevention of fractures
Vertebral Non-vertebral Hip

Lifestyle Calcium + Vitamin D Bisphosphonates
Alendronate + + +
Risedronate + + +
SERM Raloxifene +
Nasal Calcitonin +
Intermittent rhPTH + +

Lifestyle + Calcium + Vitamin D
Consider prevention of bone loss in the presence of major or many risk factors for osteoporosis:
- HRT
- SERM Raloxifene
- Bisphosphonates
- Alendronate
- Risedronate

Repeat BMD after 1–3 years if major or many risk factors for osteoporosis

Lifestyle + Calcium + Vitamin D
Reassure

Repeat BMD after 2–5 years in the presence of major or many risk factors for osteoporosis

Figure I.2 Assesment and treatment of osteoporosis in postmenopausal women.
recognizable. Some risk factors are common but non-specific; others are rare but very specific. Several questionnaires focusing on the clinical recognition of risk factors for osteoporosis have been studied (see Chapter 26). The purpose of these indices is not to diagnose osteoporosis or low bone mineral density (BMD) but rather to identify women who are more likely to have low BMD for the purpose of identifying individuals who could then undergo BMD measurement for a definitive assessment. They are based on a combination of risk factors that are selected on the basis of the available evidence of their relationship to osteoporosis and fracture risk (age, weight, history of fracture, race, estrogen intake, rheumatoid arthritis). In addition, there is a long list of diseases and medications that are associated with osteoporosis, and differential diagnosis of secondary causes for osteoporosis should be considered (see Chapters 4, 5, and 20).

Risk factors differ between fractures. Fall-related risk factors are more frequent for hip fractures. These include neuromuscular dysfunction, cognitive dysfunction, impaired vision, and disturbed balance and gait. However, when choosing bone-directed therapy such as bisphosphonates, patients should not be selected exclusively on the basis of fall-related risk factors. Indeed, in the absence of a prevalent vertebral fracture, risedronate was shown to be effective in reducing the risk for hip fracture only in patients with proven low bone mass, and not in patients selected on the basis of mainly fall-related risk factors without proven low bone density.

General Approaches for Treatment of Postmenopausal Osteoporosis

(See Figures I.1 and I.3.)

Lifestyle recommendations include avoiding risk factors such as smoking and alcohol, ensuring adequate calcium and vitamin D intake, and advocating physical activity and exercise. In one study, calcium and vitamin D supplements reduced the risk of hip fractures and non-vertebral fractures in elderly institutionalized women, most of whom were deficient in calcium and vitamin D.

In frail, elderly women aged 80 years and older, fall-prevention strategies have had variable effects on the incidence of falls, but none of the studied approaches has been shown to prevent fall-related fractures. Hip protectors decreased the incidence of hip fracture in elderly people who were wearing the hip protector at the time of the fall. However, studies were complicated by a high rate of refusal to wear the hip protector, low compliance, and a high dropout rate.

In patients with osteoporosis (prevalent vertebral fracture and/or low bone mass), lifestyle recommendations are insufficient for maximal fracture prevention. Indeed, fracture prevention with the bisphosphonates (alendronate and risedronate), raloxifene, and calcitonin has been shown in addition to calcium and vitamin D supplements.

Inhibitors of Bone Resorption

In spite of epidemiologic evidence of a protective effect of hormone replacement therapy (HRT) on the incidence of fractures, no anti-fracture effect in the spine has been shown in a randomized, controlled trial using HRT in patients with osteoporosis.

Furthermore, the role of long term HRT in the management of osteoporosis remains controversial following the results of the Women’s Health Initiative study of
combined HRT. This study was stopped prematurely in May 2002 because the treatment was causing more harm than benefit. The WHI cohort experienced lower hip fracture rates (10 per 10,000 person years in the oestrogen and progestin group vs 15 per 10,000 person years in the placebo group). However in the WHI study, a 26% relative increase (38 vs 20 per 10,000 person years) in the invasive breast cancer rate was observed with combined HRT compared to placebo as well as increased risk of cardiovascular and cerebrovascular events. Use of combined HRT for osteoporosis requires a careful discussion with women about its benefits and risks by their treating doctors.

Raloxifene is a selective estrogen receptor modulator (SERM), a non-hormonal substance that has a spectrum of effects when binding to the estrogen receptor, with agonist effects on bone and antagonist effects on the breast. Raloxifene has been shown to reduce the incidence of vertebral fractures in postmenopausal women with low bone density in the spine or hip with or without a prevalent vertebral fracture. No effect has been shown on non-vertebral fractures.

Calcitonin is a synthetic analog of a naturally occurring hormone that inhibits osteoclasts by binding to the calcitonin receptor. Nasal calcitonin (200 U/day) reduced the risk of vertebral fractures in postmenopausal women with osteoporosis, but a higher dose (400 U/day) had no effect (“PROOF” study). No effect was demonstrated on non-vertebral fractures with 200 IU daily.
The effect of bisphosphonates in the prevention of fractures has been documented extensively, with consistent results. In osteoporosis, bisphosphonate therapy decreased bone resorption to premenopausal levels and increased bone density. In a post-hoc analysis, etidronate therapy reduced vertebral fracture risk in a subgroup of women with low bone density and prevalent vertebral fractures. However, no effect was found on non-vertebral fractures in a recent meta-analysis.

Alendronate has been studied extensively in osteoporosis. In postmenopausal women with osteoporosis (one or more prevalent vertebral fractures and/or low bone density in the femoral neck), alendronate reduced significantly the risk for morphometric and clinical vertebral fractures, any clinical fracture, and fractures of the wrist and hip. The anti-fracture effect of alendronate was significant within one year for clinical vertebral and nonvertebral fractures. Quality of life was preserved by treatment with alendronate. Equivalence of changes in bone density, markers of bone turnover, and upper-gastrointestinal tolerance has been shown with alendronate doses of 10 mg daily, 35 mg twice weekly, and 70 mg once weekly.

Risedronate has also been studied extensively in osteoporosis. In postmenopausal women with osteoporosis (one or more prevalent vertebral fractures and/or low bone density in the femoral neck), risedronate reduced the risk for vertebral fractures, non-vertebral fractures, and hip fracture. Clinical vertebral fractures were prevented after the first six months of treatment. Equivalence of changes in bone density has been shown with risedronate doses between 5 mg daily and 35 mg weekly.

**Anabolic Agents**

The effects of fluoride on vertebral fractures are inconsistent. This may relate to dosing, the nature of blinding of the evaluation of spinal radiographs, or the nature of the control group.

Once-daily injections of recombinant human parathyroid hormone (rhPTH) (1–34) reduced the risk for vertebral and non-vertebral fractures in postmenopausal women with prior vertebral fractures.

**Speed and Duration of Anti-fracture Effect of Drug Therapy**

Bisphosphonates (alendronate, risedronate), raloxifene, and intermittent recombinant human parathyroid hormone (rhPTH) have an immediate effect on fracture reduction of vertebral fractures within six to 12 months. In order also to reduce non-vertebral fractures, long-term treatment is required. The optimal duration of drug therapy is not known. A persistent anti-fracture effect has been shown for the duration of the study for alendronate (5 years), risedronate (5 years), raloxifene (4 years), and rhPTH (21 months). Longer-term data on anti-fracture effects are not available. Further continuation or temporary interruption of drug treatment after this period depends on clinical judgment in the absence of prospective studies on this problem. From a clinical point of view, treatment could be continued if osteoporosis is still present at the end of three to five years’ follow-up. Treatment could be interrupted if BMD is increased to the level of normal at the end of three to five years of treatment (T score >−2.5) and restarted if bone loss occurs again or new fractures occur. However, further studies are necessary before definitive guidelines on longer-term treatment are possible.
Guidelines for Testing and Treatment of Postmenopausal Osteoporosis

Several guidelines on treatment of osteoporosis are available on the web and in the literature. Although there is heterogeneity in the recommendations, several common advices are found. Clinical case finding is advocated in all guidelines, but further research is suggested to evaluate the most effective case finding strategies. DXA is considered the golden standard for diagnosis of osteoporosis. The use of the T-score is considered different for diagnostic proposes and for treatment decisions. Other bone measurement techniques are proposed as risk evaluation or as alternatives when DXA is not available. Bone markers are currently not considered for evaluation in clinical practice. Some guidelines suggest assessment of the risk of fracture in an individual to be expressed as absolute rather than relative risk and be related to a relevant time interval, for example 10 years. This approach is likely to be increasingly used in the future to determine interventional, as opposed to diagnostic, thresholds. Further improvement of fracture prediction could be achieved by the addition of risk factors for fracture which are independent of bone mineral density, for example previous fragility fracture, maternal history of hip fracture and risk factors for falling.

Treatment options include general measures on life style and fall prevention, calcium and vitamin D supplements, raloxifene and bisphosphonates. Most consistent recommendations are found for raloxifene in reducing the risk of vertebral fractures and for alendronate and risedronate in reducing the risk of vertebral and non-vertebral fractures, including hip fractures and rhPTH is considered as a promising therapy for severe osteoporosis.

References

www.guidelines.gov; search “osteoporosis” (includes a review of guideline reports)
www.CBO.NL (in Dutch)
Osteoporosis in Clinical Practice
A Practical Guide for Diagnosis and Treatment
Geusens, P.; Sambrook, P.N.; Lindsay, R. (Eds.)
2004, XXIX, 224 p. 83 illus., Softcover