

OSTEOPOROSIS: KEY ISSUES IN MANAGEMENT

Amrish Mithal* and Nidhi Malhotra#

From the Senior Consultant in Endocrinology*, DNB student in Endocrinology#, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110 076, India.

Correspondence to: Dr. Amrish Mithal, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110 076, India.

Osteoporosis is a disease characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility. This increases the susceptibility to fracture. Osteoporosis is a major public health problem. Hip fractures are the most devastating consequence of osteoporosis. Osteoporosis is essentially an asymptomatic disease. Medical evaluation includes complete history and examination to identify risk factors, secondary causes of osteoporosis, and secondary complications of fractures. Low bone mass can only be diagnosed by measuring bone mineral density (BMD) by various techniques of which the gold standard is DEXA. Current management strategies include nonpharmacological measures like regular exercise, Calcium and vitamin D rich healthy diet, abstinence from smoking and prevention of falls. Pharmacological measures include Anticatabolic drugs like Bisphosphonates (Alendronate, Risedronate, Zoledronate). SERMs. Estrogen, Calcitonin, and anabolic drugs like Teriparatide, and Strontium. Correction of metabolic abnormalities by judicious use of calcium and vitamin D is desirable before initiating specific drug treatment. Ralixifene, Estrogen and Strontium are used in mild osteoporosis, Bisphosphonates are recommended in moderate to severe osteoporosis and Teriparatide use is indicated in severe osteoporosis with fractures. Calcitonin is used as adjuvant especially for its adjuvant effect.

Key words: Osteoporosis, Hip fracture, DEXA, Bisphosphonates, Teriparatide, Calcium, Vitamin D.

OSTEOPOROSIS is a disease characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility. This increases the susceptibility to fracture.

BACKGROUND

- (1) Osteoporosis is a major public health problem. There is rapid increase in aging population in India.
- (2) Normally, one out of two women suffer from osteoporosis beyond age 50 and one out of 4 have lifetime risk of fractures.
- (3) Hip fractures are the most devastating consequence of osteoporosis (20% mortality, another 25% require life time assistance). Recent data suggests that multiple vertebral fractures have major impact on the quality of life, although their overall impact is less than that of hip fractures.
- (4) Although solid data are not yet available, in India the risk may be even higher due to associated nutritional vitamin D and calcium deficiency.
- (5) Average osteoporotic fractures occur 10-20 years earlier in India. Earlier diagnosis and treatment can improve morbidity and mortality.

CLINICAL EVALUATION

Osteoporosis is essentially an asymptomatic disease. It

results in fractures which may occur on trivial activities like fall from standing height, lifting heavy objects, sudden jerks, coughing, sneezing etc. Vertebral fractures may present as severe back pain, loss of height, and spinal deformities like kyphosis, stooped posture etc. Hip fractures are the most serious consequence of osteoporosis; sometimes the patient falls as a result of the spontaneous hip fracture (as opposed to a fall causing the fracture).

Medical evaluation includes complete history and examination to identify risk factors, secondary causes of osteoporosis, and secondary complications of fractures. In addition, the patient's risk of falling should be assessed-poor vision, overall frail health, unsteady gait, instability, neurological disorders and the use of sedatives are important factors.

Certain laboratory tests are needed in all patients: complete blood count, serum calcium, phosphorus, alkaline phosphatase, liver and renal function tests. Additional laboratory evaluation includes serum PTH, TSH, 25 hydroxy vitamin D and serum protein electrophoresis (*Table 1*).

Diagnosis

Low bone mass can only be diagnosed by measuring bone mineral density (BMD) by various techniques, of

Table 1. Evaluation of osteoporosis.

To diagnose
 Bone mineral density measurements
 To rule out secondary causes of bone loss
Hematological disease and malignancy
 Complete blood count, ESR or CRP, Serum protein electrophoresis (>50 yrs of age)
Chronic Liver Disease
 Liver function tests
Metabolic bone disease
 Serum calcium, phosphorus, alkaline phosphatase, serum 25(OH), vitamin D, PTH
Endocrine disease
 24 hr urine free cortisol, serum estradiol, testosterone, FSH, PTH and TSH
Chronic renal disease and Malabsorption
 Serum creatinine, Endomyseal antibodies to exclude celiac sprue

which the gold standard is DEXA (Dual energy X-ray Absorptiometry). BMD assessment confirms diagnosis, detects disease in asymptomatic state, predicts chances of future fractures, and is also useful for monitoring response to therapy.

WHO criterion for diagnosis of osteoporosis is based on ‘T’ score (Table 2). T score depicts the bone density of a person when matched to young adult normal bone (which corresponds to peak density of a 30-year-old person). ‘Z’ score denotes the bone density of a person when matched to same age.

There are factors other than BMD that help in assessing the risk of Osteoporotic fractures (Table 3). Five to ten per cent of all menopausal women is fast losers of BMD and hence has a higher risk of fracture. Bone biochemical

markers can distinguish such fast losers from average losers e.g., bone specific alkaline phosphatase and osteocalcin (bone formation markers) and urinary N-telopeptide, C-telopeptide and PINP (bone resorption markers). These bone turnover markers are suppressed to 50% within 3 months of starting antiresorptive therapy. This allows earlier identification of non-responders. However, they can’t be used to diagnose osteoporosis or evaluate severity.

CURRENT MANAGEMENT STRATEGIES

Non-pharmacological approaches [1]:

- (i) *Exercise*: Regular physical exercise, especially weight bearing and muscle strengthening exercise, delays the physiologic decrease of BMD that occurs with ageing (Ernst, 1998). One beneficial effect of exercise in the elderly is likely to be the reduction in the risk of falling that result from improved muscle strength and coordination.
- (ii) *Diet*: The nutrients known with certainty to be important are calcium, vitamin D, and protein. Phosphorus, certain trace minerals (manganese, copper, and zinc), and vitamins C and K, while involved in bone health generally, are less certainly involved in osteoporosis. A well balanced diet providing 1.2 g of calcium and 800 IU of vitamin D should be recommended for women of all ages.
- (iii) *Fall prevention*: Most fractures other than vertebral fractures are associated with falls. With increasing age, falls become more frequent and the risk of injury from any single fall also increases. Therefore prevention of falls is likely to reduce the incidence of fractures in elderly women. Hip protectors should be recommended in those prone to falls.
- (iv) *Smoking cessation*: Smoking increases bone loss. It also reduces the beneficial effects of postmenopausal hormone replacement therapy.

Table 2: World Health Organisation criterion for the diagnosis of osteoporosis 1994.

Category	Definition by bone mineral density	T-score
Normal	A value for BMD that is not more than 1 SD Below the young adult mean value	≥1
Osteopenia	A value for BMD that lies between 1 and 2.5 SD Below the young adult mean value	-1 to -2.5
Osteoporosis	A value for BMD that is more than 2.5 SD Below the young adult mean value	≤-2.5
Established osteoporosis	A value for BMD more than 2.5 SD below the young adult mean value in the presence	≤-2.5 + presence of one

TABLE 3: Secondary causes of osteoporosis

1. Hyperthyroidism
2. Hyperparathyroidism
3. Cushing's syndrome
4. Acromegaly
5. Hypogonadism
6. Glucocorticoid therapy
7. Inflammatory disorders (arthritis, bowel disease, pulmonary disease)
8. Cancer (especially hematological conditions, multiple myeloma)
9. Congenital disorders (osteogenesis imperfecta, homocystinuria)
10. Neurologic disorders (including immobilization and treatment with antiepileptic drugs)
11. Transplantation.

Pharmacological approaches

According to the latest nomenclature, the anti Osteoporotic drugs have been classified into anti-catabolic and anabolic, depending on their effects on bone remodeling and with respect to the mechanisms of fracture reduction [2].

Anti-catabolic drugs: These drugs increase the bone strength by decreasing bone remodeling (less BMUs are formed) that leads to preservation of skeletal microarchitecture. They reduce the bone turnover largely by decreasing Activation frequency and recruitment of osteoclast precursors. The fracture reduction associated with anticatabolic drugs is largely caused by inhibition of high bone turnover, independent of its effect on preventing bone loss.

Anabolic drugs: These drugs increase the bone strength by increasing bone mass substantially as a result of an overall increase in bone remodeling (more BMUs are formed) combined with a positive BMU balance (the magnitude of the formation phase is more than that of the resorption phase). This results from the combination of increased osteoblast function and an inhibition of apoptosis that extends osteoblast life span.

ANTICATABOLIC DRUGS

Calcium and vitamin D

Supplementary calcium and vitamin D are generally given with other anti catabolic agents as enhancers whose small, but significant, effects depend mainly on whether there is nutritional deficiency.

Mechanism of action: Whenever absorbed calcium intake

is insufficient to meet either the demands of growth or the drain of cutaneous and excretory losses, resorption will be stimulated by PTH (parathyroid hormone) and bone mass will be reduced.

Clinical data: Calcium and vitamin D supplementation reduces bone loss and fractures at all ages especially in elderly. They are, however, usually not used as the sole treatment of osteoporosis, but as essential adjuncts to treatment. The fact that vitamin D deficiency osteomalacia is very common in urban Indians [3], it is necessary to ensure adequate intake of Calcium and vitamin D before embarking on any pharmacological therapy for osteoporosis. Many experts now feel that at least 800 IU of vitamin D and 1.2 g of calcium are required daily by every individual.

BISPHOSPHONATES

Types of Bisphosphonates:

- (a) Nitrogen containing compounds Alendronate, Risedronate, Pamidronate, Zoledronate.
- (b) Non-nitrogen containing compounds: Etidronate, Clodronate, Tiludronate

Mechanism of action

They act by binding avidly to mineralized bone surfaces and reduce bone turnover, largely by decreasing activation frequency and the recruitment of osteoclast precursors, but they also reduce the amount of bone removed during the resorption phase of the BMU cycle by either decreasing osteoclast work capacity or by increasing apoptosis. They should be taken first thing in the morning with water, and 30 minutes before the first food, drink or oral medication to be taken that day. Patient should remain upright for at least 30 mins. Bisphosphonates currently in use are:

ALENDRONATE

Clinical Data: Alendronate (10 mg/day) after 3 years of treatment produces a vertebral fracture risk reduction of 47%, non- vertebral (osteoporotic) fracture risk reduction of 36% and hip fracture risk reduction of 51% (Fracture intervention trial) [4]. It also reduces bone turnover markers by 50-70%. Once weekly dosing improves patient compliance and also pharmacokinetics of the drug.

Although 10 years of alendronate treatment appears to be safe, the optimal duration of treatment has not been established [5].

Dose schedule

The recommended dose of alendronate for prevention of postmenopausal osteoporosis is 5 mg/day or 35 mg/week and for treatment is 10 mg/day or 70 mg/week. For

treatment of corticosteroid-induced osteoporosis, the indicated dose is 5 mg/day for men and estrogen replete women and 10mg/day for postmenopausal women.

RISEDRONATE

While first and second generation bisphosphonates are known to have gastrointestinal side effects, Risedronate is better tolerated.

It increases BMD by 3-6% and reduces bone turnover by 40-60%. Risedronate (5 mg/day) taken over a period of 3 years produces a vertebral fracture risk reduction of 41% and non-vertebral fractures risk reduction of 40% (VERT trial) [6].

Dose schedule

The approved dose is 5 mg/d or 35 mg/wk. It seems to have better GI tolerability as compared to Alendronate. According to a recent Gastroenterology study, both Alendronate and Risedronate have mucosal irritative and healing impairing effects in the stomach, yet the effect of Risedronate was much less pronounced compared to Alendronate [7].

PAMIDRONATE

It is approved by the FDA for treatment of hypercalcemia of malignancy and Paget's disease of bone.

Clinical data

It has been shown to increase BMD or prevent bone loss in patients with post menopausal osteoporosis and corticosteroid induced osteoporosis.

Dose schedule

It is given as an initial dose of 90 mg I/V with subsequent doses of 30 mg every 3rd month.

ZOLENDRONATE

It is the most potent bisphosphonate currently available. Intravenous administration of zoledronate is also considered a superior alternative to oral bisphosphonates in osteoporosis which are known to carry some limitations related to long term compliance, gastrointestinal intolerance and poor and variable absorption from gastrointestinal tract.

Clinical data

At 12 months zoledronic acid regimens were associated with decreases of 49 to 52% in serum CTx and decreases of 54 to 65% in serum NTx, increase in lumbar spine bone density by 4.3 to 5.1%, femoral neck bone density by 3.1 to 3.5%, with no significant difference among various zoledronic groups. Therefore, administration of zoledronate at intervals of 6 to 12 months or more is likely

to be much more acceptable to patients and could reduce the costs [8].

Dose schedule

Single annual dose of 4 mg is given as an intravenous infusion over 1-2 hrs.

In trials of treatment with zoledronic acid for bone metastasis, 9-15% of the patients developed renal deterioration [9].

IBANDRONATE

It recently got FDA approval for its use as a once monthly oral tablet.

Clinical data

Significant reduction in new vertebral fractures in both treatment arms (62% and 50% respectively, versus placebo), was observed after 3yrs in women with established postmenopausal osteoporosis [10]. Both treatment groups also produced a statistically significant relative risk reduction in clinical vertebral fractures (49% and 48% for daily and intermittent ibandronate, respectively). The incidence of non-vertebral fractures was found to be similar in both ibandronate and placebo groups.

Recently, oral intermittent ibandronate administered once a month was shown to be therapeutically equivalent to daily oral regimen thus demonstrating the feasibility of once monthly dosing in the management of postmenopausal osteoporosis [11].

Dose schedule

It is approved as a once daily oral tablet (2.5 mg/day) and also as a once monthly oral tablet in postmenopausal osteoporosis with recommended dosage of 150 mg on the same date each month. This drug requires a more prolonged 1 hr fast for adequate absorption as compared to other bisphosphonates. Ibandronate is also the first bisphosphonate with the potential for administration by IV injection over 10 to 20 secs without adversely affecting renal function [12].

ESTROGEN

Estrogen deficiency is associated with an increase in the secretion of cytokines IL-1, IL-6, TNF, M-CSF, RANK Ligand. Increased cytokine activity results in the recruitment and activation of more osteoclasts which leads to increased bone resorption. Estrogen treatment reverses this process within 4 weeks.

Clinical data

In the WHI trial HRT reduced the risk of hip and

vertebral fractures by 34% and of all other osteoporotic fractures by 24%. This reduction was nominally significant for all fractures. After 3 years of treatment, total hip BMD was increased by 3.7% in the HRT group compared with 0.14% in the placebo group [13].

Side effects

However, the overall results show that health risks outweigh these benefits of HRT. Women's Health Initiative study (WHI), and the Million Women study, have confirmed that the use of HRT does not reduce the risk of CHD and increases the risk of breast cancer, stroke and venous thromboembolic events. As a result of these findings, other antiresorptive agents are now the drugs of choice for the prevention and treatment of osteoporosis in postmenopausal women. Use of HRT is presently limited to postmenopausal women with severe hot flashes and vaginal and skin changes. HRT should be used for the shortest time possible, at as low a dose as possible in order to stop the menopausal symptoms (hot flashes) and only when benefits outweigh the risks.

Dose schedule

Estrogens are used orally at a dose of 0.3 mg/d for esterified estrogens, 0.625 mg/d for conjugated equine estrogens and 5 mcg/d for ethinyl estradiol. For transdermal estrogen the recommended dose is 50mcg estradiol per day. In women with an intact uterus, progestin is added to reduce the risk of uterine cancer.

SERMS (Selective estrogen receptor modulators)

This group includes drugs like Tamoxifen and Raloxifene that have tissue-specific effects in classical target tissue for estrogen action. Raloxifene like Tamoxifen has antiresorptive effects on bone, but, unlike Tamoxifen, it does not cause endometrial stimulation.

Clinical data

According to the MORE (Multiple Outcomes of Raloxifene Evaluation) trial, Raloxifene (60 mg/day) after 3 years of treatment, showed positive effects on bone mineral density at lumbar spine and femoral neck (2-3% increase). These increased over time and were independent of dose. The relative risk reduction of new vertebral fractures produced was 30% to 50%. Raloxifene does not, however, have a significant effect on nonvertebral fractures [14].

Apart from the skeletal effects Raloxifene induces a dose dependent decrease of serum total and LDL cholesterol and may reduce the risk of cardiovascular events especially in women with increased cardiovascular risk at baseline.

Dose schedule

Raloxifene is taken as a once daily tablet (60 mg/day). Side effects include thromboembolic disease (Relative risk similar or lower than that of HRT), flu syndrome, leg cramps and increase in hot flashes.

CALCITONIN

It is a polypeptide hormone that exerts its hypocalcemic effects directly by inhibiting osteoclast resorption.

Clinical data

Calcitonin, a weak anti catabolic drug, has been shown to increase the lumbar spine BMD in late post menopausal women by an average of 1-2%. According to the PROOF study there was a 33% reduction in the risk of new vertebral fractures in 200 IU calcitonin treated group. Calcitonin has no effect on non vertebral fractures [15].

Treatment of calcitonin should be considered for older women with osteoporosis on multiple medications on those who fail to respond / tolerate other treatments and in acute vertebral fractures because of its analgesic effect.

Dose schedule

It is currently available as a parenteral and nasal spray formulation. Administration of salmon calcitonin should be as 200 IU daily in alternating nostrils or 100 IU parenterally. Nasal calcitonin can produce rhinitis and parenteral calcitonin may cause facial flushing, nausea and vomiting.

ANABOLIC DRUGS

TERIPARATIDE rhPTH (1-34)

It is the 1-34 amino acid fragment of the native 84 amino acid parathyroid hormone molecule. PTH is an anabolic osteotropic agent.

PTH exerts its action on bone through PTH1 receptor. It can produce both bone resorption and bone formation. Continuous exposure to high dose PTH increases osteoclast differentiation and action leading to bone resorption. In contrast daily injections of low dose PTH (intermittent exposure) produces increase in osteoblast number and function leading to bone formation.

Clinical data

Randomized controlled trials have demonstrated the efficacy of human parathyroid hormone, (hPTH (1-34), in improving bone mass and reducing the risk of fractures in postmenopausal osteoporosis. In an international fracture prevention trial, compared with placebo, teriparatide significantly reduced the risk of vertebral fractures by 65-69% and nonvertebral fragility fractures by 53-54%

[16]. In addition to postmenopausal osteoporosis, Teriparatide is also a potentially useful therapeutic agent for osteoporosis in men. Orwall, *et al.* reported increase in spinal bone mineral density by 5.9% (20 mcg) and 9.0% (40 mcg), femoral neck bone density by 1.5% (20 mcg) and 2.9% (40 mcg) and whole body bone mineral content by 0.6% (20 mcg) and 0.9% (40 mcg) above baseline after 11 months of teriparatide therapy (once daily).

Patients are usually considered for Teriparatide [rhPTH(1-34)] treatment either because they remain severely osteoporotic or because they have failed antiresorptive therapy. Prior use of antiresorptives has shown to produce variable effects on PTH action. Ettinger *et al.* reported that prior treatment with Raloxifene allows for the Teriparatide induced BMD increases. In contrast, prior treatment with Alendronate prevents increases in BMD, particularly in first 6 months [17]. According to a study by Cosman *et al.* PTH when added to HRT, in women with osteoporosis, produced significant increase in bone mass and density, this elevation persisted for 1 year after discontinuation of PTH while women continued HRT [18].

Dose schedule

Teriparatide is administered at a dose of 20 mcg/day as a subcutaneous injection. Because of the occurrence of osteosarcoma in rats treated with very high doses of teriparatide, the duration of treatment recommended is 18 months.

STRONTIUM RANELATE

It has recently completed phase III clinical trials. It acts by inducing uncoupling in bone remodeling, increases bone formation by increasing the replication of pre-osteoblasts into osteoblasts, decreases bone resorption by reducing the differentiation of pre-osteoclasts into osteoclasts and the bone resorbing activity of osteoclasts, as a result increasing DXA measured bone density [19].

Clinical data

Strontium Ranelate has shown to produce continuous increase in BMD at 3 years by 14.4% at lumbar spine, by 8.3% at femoral neck and by 9.8% at total hip and bone strength is directly related to bone mineral density. The vertebral antifracture efficacy of Strontium Ranelate was demonstrated with reductions in the relative risk of new vertebral fractures by 49% after one year and by 41% after three years in postmenopausal women with osteoporosis and at least one vertebral fracture receiving daily oral Strontium (2 g/d) [20]. Non vertebral fracture efficacy in postmenopausal women with osteoporosis is demonstrated by relative risk reduction of 16% for all non vertebral

fractures and 36% for hip fractures in group at high risk [21].

Dose schedule

Daily oral dose of 2 mg/day. Strontium is well tolerated in upper gastrointestinal region. However, it has been known to be one of the causal agents for osteomalacia in patients with end stage renal failure on dialysis [22].

Treatment guidelines can be divided into 3 groups

- (i) Asymptomatic patients who need screening for osteoporosis.
- (ii) Patients with definite Osteoporosis.
- (iii) Patients with fracture due to osteoporosis

(i) Asymptomatic patients who need screening for osteoporosis.

- All postmenopausal women (65 yrs should routinely undergo a bone density test to assess baseline status. BMD measurements in Postmenopausal women < 65 yrs should be obtained if there is presence of risk factors for osteoporosis.
- BMD is not recommended routinely in premenopausal women, but start prevention with calcium/vitamin D if inadequate oral intake/ poor sunlight exposure. One can consider BMD assessment if multiple risk factors/ secondary causes are present.
- In case of males assess risk factors and secondary causes. BMD should be done if there is history of fragility fracture or secondary causes.

(ii) Guidelines for patients with established osteoporosis

- Do complete evaluation with history / physical exam and routine tests mentioned in medical evaluation above to establish the cause of osteoporosis.
- Do bone density every year to follow the treatment till stable then do every 2 yrs.
- Consider bone markers (N-telopeptide and osteocalcin) if needed to assess early changes during follow-up. These are particularly useful in steroid induced osteoporosis.
- If metabolic parameters do not indicate significant vitamin D deficiency, start treatment with specific medication. In general bisphosphonates like alendronate / risedronate are the most powerful agents. Risedronate may produce less GI intolerance. Although unproven in terms of fracture reduction, parenteral bisphosphonates like pamidronate and zolendronate are also options as they produce substantial increases in BMD.

- Raloxifene is a SERM, which provides multiple benefits to women of postmenopausal age. Although slightly less powerful than bisphosphonates, specially with regard to hip fracture reduction, it is a safe and convenient option for many patients.
- Limited role of HRT in light of recent studies. May be used if menopausal symptoms predominate.
- Consider combination therapy if no improvement after one year.

(iii) Guidelines for a patient with fracture due to osteoporosis

- Assess the site of fracture with X-ray.
- Assess bone density but do not include the fracture site (will give spuriously high results).
- Assess the severity of pain.
- Consider narcotics/ muscle relaxants if severe pain.
- Consider calcitonin nasal spray 200 IU daily for 2-3 months for analgesic effect. Higher doses can be used for initial analgesic effect.
- Start usual osteoporosis treatment in combination with calcitonin. Teriparatide is the drug of choice.
- After 2-3 months start physical exercise program.

CONCLUSION

As more anti-osteoporosis molecules become widely available in India, it is imperative for physicians to select appropriate therapy for their patients. The caveat in treating osteoporosis in India is the high prevalence of vitamin D/ calcium undernutrition. One should check the patient's calcium and vitamin D axis, by estimating serum calcium, phosphorus, alkaline phosphatase levels, and, ideally, by estimating serum PTH and 25(OH) vitamin D levels too. Correction of abnormalities in these levels by judicious use of calcium and vitamin D is desirable before initiating specific drug treatment. Failure to correct these abnormalities may not only result in poor response to drug therapy, but may actually have deleterious effects.

When deciding the treatment, aspects like individual values, absolute risk of fracture, extraskeletal effects, and costs need to be considered. If the goal is to decrease risk of vertebral fractures then the choices would include raloxifene, calcitonin, strontium in mild cases and risedronate, or alendronate in moderate to severe cases. If the goal is to reduce the risk of vertebral and non vertebral fractures then bisphosphonates like alendronate or risedronate or ibandronate would be preferable. For those with severe osteoporosis with pre existing fracture, teriparatide would be a good option.

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