

# Osteoporosis – Advances in Management

T. K. Biswas, S. Biswas, A. Biswas

## Introduction

Osteoporosis is a common condition that affects about 1 in 4 women and 1 in 8 men<sup>1</sup>. It is associated with an increased risk of fractures, vertebral fractures, are the most common and account for about 40% of all osteoporotic fractures. Fractures of the hip and wrist and other nonvertebral fractures are the next most common. Hip fractures are associated with 20% mortality one year after fracture. Unfortunately, most patients with osteoporosis, including those presenting with fragility fractures are not diagnosed, evaluated or treated.<sup>2</sup>

Osteoporosis is an important health care issue that needs to be addressed. Better diagnosis and management of osteoporosis will lower health care costs and reduce the morbidity and mortality associated with it. Patients at risk of osteoporosis should be evaluated for risk factors for fractures

**Table 1 : World Health Organization Criteria for Diagnosis of Osteoporosis**

T Score represents the number of standard deviation (SD) a patient is above or below the mean BMD of a young adult population.

T Score	Classifications
> - 1	Normal
- 2.5 to - 1	Osteopenia
< 2.5	Osteoporosis
< - 2.5 and fracture	Severe osteoporosis

with appropriate intervention, fractures can be significantly reduced<sup>3</sup>.

## Definition

WHO defines osteoporosis as a progressive systemic disease, characterized by low bone density and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fractures.<sup>4</sup>

Fragility fractures are fractures caused by trauma that would not cause a normal bone to fracture or by a fall from standing. Before fragility fractures occur, osteoporosis can be diagnosed on the basis of decreased bone mineral density (BMD)<sup>3</sup> (Table 1).

## Pathophysiology

In life the skeleton is highly active living tissue. Our bones are being forever eaten away by osteoclasts and rebuilt by osteoblasts and in this process of continuous remodeling that provides bone with its durability. About 10% of the adult skeleton is remodeled each year with the result that we can have a new skeleton about every ten years. During skeletal growth bone mass increases gradually reaching a peak by about 30 years of age. Thereafter skeletal mass steadily declines with age at rate in both sexes of about 1% per year.

**Table 2 : Causes of Secondary Osteoporosis**

Diseases	Diseases
• Multiple Myeloma	• Corticosteroid therapy
• Thyrotoxicosis	• Cancer Chemotherapy
• Cushing's Syndrome	• Anticonvulsants
• Hypogonadism in Male	• Heparin
• Inflammatory Bowel Disease	• Barbiturates
• Gonadotrophic Releasing Hormone	• Aluminium containing antacids
• Chronic Renal Failure	• Prolonged immobilization
• Osteogenesis Imperfecta	• Rheumatoid Arthritis
• Ankylosing Spondylitis	• Malnutrition

**Table 4 : Tests to Exclude Secondary Causes of Osteoporosis**

• Complete Blood Count
• Serum Calcium (Correct for albumin)
• Serum Phosphate
• Total alkaline Phosphatase
• Serum Creatinine
• Serum Protein Electrophoresis

Unfortunately, women experience an accelerated phase of bone loss following menopause, which lasts between 3 and 10 years. Subsequently, the rate of bone loss is similar in both sexes. Early menopause is associated with an increased risk of osteoporosis <sup>5</sup>.

## Classification

Osteoporosis may be Primary or Secondary. Primary osteoporosis is more common form and is due to age related loss of bones. Secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss.

Secondary osteoporosis has an equal sex distribution and can occur at any age. Causes of Osteoporosis is given in Table 2.

Most causes of male osteoporosis are due to disease or drug therapy. However, in 30% to 45% of affected individuals no cause can be identified.

**Table 3 : Risk Factors for Osteoporosis<sup>8</sup>**

• Genetic	• Excess alcohol intake
• Female Sex	• History of Amenorrhea
• Deficient diet	• Under weight
• Increasing age	• Systemic corticosteroids
• Sedentary occupation	• Long term Heparin Therapy
• Caucasian race	• Pregnancy
• Premature menopause	• Lack of Hormone Replacement Therapy
• Cigarette smoking	• Dilantin Sodium

**Table 5 : Drug Therapy of Osteoporosis:**

Antiresorptive Agents	Anabolic Agents (Stimulators of bone formation)
	PTH – Teriparatide
Calcium and Vit D	
Bisphosphonates	
• Etidronate	
• Alendronate	
• Risendronate	
• Ibandronate	
• Pamidronate	
SERM - Raloxifene	
Salmon calcitonin	
Hormone Replacement Therapy	

## Risk Factors for Osteoporosis

There are many risk factors for the development of osteoporosis and clinicians must evaluate all post-menopausal women and men over 50 years of age for the presence of risk factors for osteoporosis. The presence of any risk factor should alert the physician to the need for further assessment and intervention, pharmacological as well as non-pharmacologic to prevent fractures<sup>7</sup>. The risk factors are given in Table 3.

## Diagnosis

Clinical assessment includes a complete history and physical examination and appropriate laboratory tests<sup>9</sup> (Table 4). Diagnosis is confirmed by plain X-ray, MRI and DEXA Scan.

## Treatment

- Pharmacological

- Non-Pharmacological

### Drug therapy of Osteoporosis

Details are given in Table 5.

#### Therapeutic Foundation

Bone substance is made out of protein and mineral. Not surprisingly, therefore, the foundation of any preventive or therapeutic regimen is an adequate dietary intake of these bulk materials: high quality protein, calcium and phosphorus. The various anti-resorptive and anabolic agents available to date are not capable of stopping bone loss or producing bone gain if the patient is in negative nitrogen and mineral balance because of inadequate intake of these nutrients.<sup>10</sup>

- Optimal protein intake in the elderly are in the range of 1 gm / kg body weight.
- Calcium intake should be in the range of 1500 mg per day.
- Phosphorus intake should be at least at the level of RDA 700 mg / day and possibly more if the calcium intake come predominantly from carbohydrate or citrate based supplements.
- Vitamin D – recommended intake is 200 IU (5 mg) upto 50 years of age, 400 IU (10 mg) from 50 to 70 years, and 600 IU (15 mg) above the age seventy.

#### Pharmacotherapy

There are two broad classes of pharmacologic treatment agents now available: the antiresorptive and the anabolics.

Antiresorptives include the Bisphosphonates (etidronate, alendronate, risedronate, pamidronate and zolidronate), one selective estrogen receptor modulator (raloxifene), estrogen and calcitonin.

##### Bisphosphonates

They are compounds that specifically bind to the hydroxyapatite crystals on bone surfaces and inhibit osteoclast functions.<sup>11</sup>

##### Etidronate

The first bisphosphonate available for prevention

and treatment of osteoporosis. It is effective in decreasing vertebral fractures among post-menopausal women who were at high risk for such fractures. It has no beneficial effect on hip or nonvertebral fractures. It can impair bone mineralization in the same dose as it inhibits bone resorption, it must be given cyclically with drug free intervals every three months. If given continuously it can impair bone mineralization and allow osteomalacia to develop.

##### Alendronate

It has a rapid antifracture effect. Metaanalysis of trials evaluating alendronate have demonstrated impressive and consistent reductions in vertebral and nonvertebral fractures among women with post-menopausal osteoporosis.<sup>12</sup> Alendronates taken once weekly at a dose of 70 mg is convenient for patients.

##### Risedronate

It is an aminobisphosphate, has been shown to prevent vertebral and nonvertebral fractures effectively. Following 12 months therapy with risedronate, vertebral fractures were reduced by 61% to 65% in comparison with placebo in two trials (level 1 evidence).

Once weekly therapy with risedronate (35 mg) has comparable effects to one daily risedronate (5 mg) with respect to BMD changes in spine. Recently, it was shown that the residence of risedronate in the body is measured in months, whereas that of alendronate is measured in years. It is theoretically likely that a drug holiday of only a few months would allow teriparatide to reach maximum effect in patients who have been on risedronate but not on alendronate<sup>13</sup>.

A major side effect of bisphosphonate is esophageal or gastrointestinal intolerance.

##### Selective Estrogen Receptor Modulators (SERMs)

##### Raloxifene

It is a valuable treatment for both preventing and treating post-menopausal osteoporosis<sup>14</sup>. Raloxifene reduces incidence of new vertebral fractures by

55% after 3 years therapy (60 mg / day) (level 1 evidence)<sup>15</sup>.

Raloxifene has additional benefits. It reduces total and low density lipoprotein cholesterol, fibrinogen, lipoprotein A and homocysteine, but no effect on triglycerides and HDL levels. In the MORE trial cardiac events were reduced by 40% in women at increased risk of cardiovascular disease. Impressive reductions in risk of breast cancer have been documented with 84% reduction on estrogen receptor positive breast cancers in comparison with placebo. Thromboembolic disease, however, increases with raloxifene therapy. Raloxifene can be used in combination with aminobisphosphonates for patients at risk of hip fractures.

### Calcitonin

Synthetic salmon calcitonin given as intranasal spray or by injection has an antiresorptive effect that is 40-50 times as great as human calcitonin. It is associated with a modest increase in spine BMD and a reduction in vertebral risk<sup>16</sup> and is approved for the treatment of post-menopausal osteoporosis to women who are at least five years post menopausal. The Prevent Recurrence of Osteoporotic Fractures (PROOF), study evaluated calcitonin nasal spray in varying doses. Risk of vertebral fracture was significantly reduced with 200 IU / day dose<sup>17</sup>, but not with the 100 IU / day or 400 IU / day doses.

Calcitonin can be used in combination with other antiresorptive agents. It appears to have an analgesic effect that may be clinically useful in the treatment of acute painful vertebral fractures.

### Hormone Replacement Therapy (HRT)

HRT has been shown in the recent Women Health Initiative trial to reduce risk of fractures in post-menopausal women. Patients received 0.625 mg of conjugated equine estrogen with 2.5 mg of medroxyprogesterone acetate or placebo daily. At 5.2 years, relative risk of clinical, vertebral and hip fractures were reduced by 34% (level 1 evidence). In comparison with placebo, however, HRT was associated with a 29% increased incidence of cardiac events, a 41% increased risk of stroke,

a doubling of thromboembolic events and 26% increased risk of breast cancer. Benefits included a reduction in osteoporotic fractures and a 37% reduction in colorectal cancer. The overall risks associated with HRT outweigh the benefits with 5 years or more of treatment.<sup>18</sup> HRT is at present recommended primarily for menopausal and vasomotor symptoms.

### Strontium Ranelate

Strontium ranelate is one of the promising therapies in the developmental stages. It is an oral therapy composed of 2 atoms of stable nonradioactive strontium coupled with ranelic acid. Strontium ranelate is a compound that is likely to have both antiresorptive and anabolic properties. It is associated with large increase in BMD in part due to the incorporation of strontium with an atomic weight that is heavier than calcium, into bone. It decreases the risk of vertebral fractures and nonvertebral fractures.<sup>19</sup>

### Teriparatide: an analog of PTH

The N-terminal fragment of PTH known as teriparatide has been evaluated in doses of 20 and 40 mg in an RCT.<sup>20</sup> In this 21 month study, PTH reduced risk of vertebral fracture by 65% and 69% using 20 mg / day and 40 mg / day and risk of nonvertebral fracture by 53% and 54% using the 20 mg / day and 40 mg / day doses respectively in comparison with placebo (level 1 evidence). Side effects included nausea and headache. Persistent hypercalcemia in about 3% of patients required dose modification. The recommended dose for teriparatide is 20 mg / day. It also increases men's BMD. Parathyroid hormone(1 – 34) therapy has been approved by the FDA, USA. Studies of PTH in combination with antiresorptive therapy indicate that these combinations are safe and effective for clinical use<sup>21</sup>.

### Non Pharmacological Measures for prevention and treatment

- Diet – Should be adequate in protein, total calories, calcium and vitamin D.
- High Impact Physical Activity :

- Jogging – Significantly increases bone density in men and women
- Stair climbing – increases bone density in women
- Regular Exercises – helps to increase strength and reduce the risk of falling
- Weight Training – helpful to increase muscle strength as well as bone density
- Balance Exercises - reduce falls.
- Adequate Spinal Support – avoid braces or corsets, rigid and excessive immobilization
- Use of hip Protectors
- Vertebroplasty and Kyphoplasty
- Cessation of smoking
- Stop or reduce Alcohol intake

## References

1. Khan SA. Bone densitometry: Applications and limitation. *J Obstet Gynaecal Can* 2002; 24 (6): 476 – 84.
2. Hajcsar EE, Hawker G, Bogosh ER. Investigations and treatment of Osteoporosis in patients with fragility fractures. *Can Med Assoc. J.* 2000; 163: 819 – 22.
3. Khan A. *Canadian Family Physician*, 2003; 49: 441 – 47.
4. NIA Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy *JAMA* 2001; 285: 786 – 95.
5. Stevens R, Cutis S. Managing Osteoporosis. *The Practitioner* 2003, 247: 525 -529.
6. Anderson FH. Osteoporosis in men. *Int J Clin Pract* 1998; 52: 176 – 80.
7. Dey AB, Handa R. Consensus statement of the Expert Group Meeting Convened by the Osteoporosis Society of India, New Delhi 2003: 9 - 10.
8. Forbes CD, Jackson WF; Color Atlas and Text of Clinical Medicine. 3<sup>rd</sup> ed El 2003. Mosley Edinborough.
9. Brown JP, Jose RG. Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada. *Can Med Assoc. J* 2002, 167 (Supp 10) S1 – 34.
10. Heaney RP. Advances in Osteoporosis *Clinical Medicine and Research* 2003; 2: 93 – 99.
11. Fleisch H. Bisphosphonatis in Osteoporosis. *Br J Clin Pract* 1994; 48: 323 – 26.
12. Karpf D, Shapiro D, Seeman E, Ensurd KE, Johnston CC Jr. Adminal S ef al. Prevention of non vertebral fractures by alendronate. A meta analysis. Alendronate Osteoporosis Treatment Study Group *JAMA* 1997; 277: 1156 – 64.
13. Barzel US. Osteoporosis In: *Conn's Current Therapy* 2006: 746 - 50.
14. Mitlak RH, Cohen FJ. Selective Oestrogen Receptor Modulators, a look ahead. *Drugs* 1999; 57: 653 – 63.
15. Lufkin EG, Wong M, Deal C. The role of selective estrogen receptor modulators in the preventions and treatment of osteoporosis. *Rheu Dis Clin North Am* 2001; 27: 163 – 85.
16. Cranney A, Tugwell P, Zytaruk N et al *Endocr Rev.* 2002; 23: 540 – 51.
17. Chestnut CH III, Silverman SI, Andraino K, Genant HK, Gimona A, Haris S ef al. A randomized trial of nasal spray salmon calcitonin in post menopausal women with established osteoporosis. Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med* 2000; 109: 267 – 76.
18. Writing Group for the Women's Health Initiative investigations. Risks and benefits of estrogen and progesterone in healthy post menopausal women – principal results from the women's health initiative randomized control trial *JAMA* 2002; 288: 321 - 33.
19. Reginster JY, Seeman E, De Vernejoul MC et al. *J Clin Endocrinal Metab* 2005; 90: 2816 – 22.
20. Neer RM, Arnand C, Zanchetta R, Prince R, Gaich GA, Reginster JY ef al. Effect of parathyroid hormone (1 – 34) on fractures and bone mineral density in postmenopausal women with osteoporosis *N Engl J Med* 2001; 344: 1434 – 41.
21. Rittmaster RS, Bolgnese M, Ettinger MP, Hanley Da, Hodsman AB, Kendier Dl ef al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate *J Clin Endocrinol Metab* 2000; 85: 2129 – 34.