Osteoporosis: Current Management Strategies

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ABSTRACT

Osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The disease affects millions of people and is a cause of significant morbidity and mortality. Recent advances in the understanding of bone biology have improved the therapeutic options for osteoporosis. Management strategies for osteoporosis include nonpharmacological and pharmacological measures. Nonpharmacological measures (diet, exercise, smoking cessation) are recommended for all patients regardless of BMD. Pharmacological interventions are expensive and should therefore be targeted to those at high risk of fractures. These drugs act on the bone remodeling cycle, where they either inhibit osteoclastic bone resorption (antiresorptives) or increase bone formation (anabolics). Bisphosphonates are the most potent antiresorptives available, of which, alendronate and risedronate are the most commonly used and form the first line of drugs for postmenopausal and corticosteroid-induced osteoporosis. Ibandronate, a recently introduced newer bisphosphonate, is another promising agent. Other antiresorptives in use are Calcitonin, Hormone Replacement Therapy (HRT) and Selective Estrogen Receptor Modulators (SERMS). These are commonly used in patients with mild to moderate degree of osteoporosis. The only anabolic agent in use is Parathyroid hormone, Teriparatide.[1-3] Its use is recommended in severe osteoporosis. There are other newer anabolic agents under evaluation of which Strontium and BMP-2 holds great promise. Currently studies are ongoing to assess role of combination therapies to enhance response. Regardless of mode of treatment adequate calcium and vitamin D intake is mandatory. Response to treatment is monitored by measuring bone turnover markers and bone mineral density. Despite all these measures the fracture risk is reduced only by 50-60%, thus still greater research is required in this field.

INTRODUCTION

Osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.[1] More recently, the NIH Consensus Development Panel defined osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.[2] Bone strength reflects the integration of two main features: bone density and quality.

Because BMD (bone mineral density) is a powerful predictor of bone strength and fractures an operational definition for osteoporosis was developed by a study group of the WHO, as a BMD that is more than 2.5 SD below peak bone mass (Table 1).

Bone Remodeling

The mechanical integrity of the skeleton is maintained by the process of bone remodeling which occurs throughout life. This process of regeneration, degradation and repair, allows damaged bone to be replaced by new bone. Remodelling can be subdivided into four phases:

Table 1 : 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 of one or more fragility fractures	≤ -2.5 + presence of one or more fractures

Resorption – Activated lining cells along with osteoblastic precursors secrete RANKL (receptor activator of nuclear factor kappa B) which along with M-CSF (macrophage colony stimulating factor), NFkB (nuclear factor kappa B) and c-fos promotes differentiation and activation of committed precursors to mature osteoclasts. These produce bone resorption.

Table 2: Risk Factors for Osteoporotic Fractures

Major risk factors	Minor risk factors
Age > 65 years	Rheumatoid Arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40 years	Chronic anticonvulsant therapy
Family history of osteoporotic fracture (especially maternal hip fracture)	Low dietary calcium intake
Systemic glucocorticoid therapy of > 3 months duration	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight < 57 kg
Osteopenia apparent on radiograph	Weight loss > 10% of weight at age 25 years
Hypogonadism	Long-term heparin therapy
Early menopause	(before age 45 years)

Reversal – Osteoclastic bone resorption is followed by apoptosis and removal of osteoclasts and recruitment and differentiation of osteoblasts.

Formation - The active, secreting osteoblasts then make layers of osteoid and slowly refil the cavity. This then gets mineralized, increasing the bone density.

Quiescence - The final osteoblasts turn either into lining cells which participate in calcium release from bone or osteocytes which senses mechanical stresses to the bone.

Whom to treat?

Universal public health measures (calcium/ vitamin D/ exercise) are recommended in all patients regardless of BMD, as they are efficacious, safe and cost-effective. Pharmacological interventions are expensive and should therefore be targeted to those at high risk of fractures (Table 2). It is recommended that a BMD measurement be taken for those patients who have at least one major or two minor risk factors.[3]

Treating the underlying cause

Specific treatment of secondary causes of osteoporosis, such as male hypogonadism and hyperthyroidism increases bone density, in some instances by 10%-20%. Serum 25-hydroxyvitamin D (25-OHD) and intact parathyroid hormone measurements may be useful in diagnosing vitamin D deficiency and secondary hyperparathyroidism in patients with limited sunlight exposure, previous gastric resection, malabsorption, or anticonvulsant treatment. If vitamin D deficiency is a major contributor to the low bone density, as has been seen in the Indian setting, very striking rises in bone density can be observed with calcium/ vitamin D supplementation.[4,5]

In individuals with unexplained osteoporosis and a history or investigations suggestive of malabsorption, tests for antiendomyseal antibodies should be performed to exclude coeliac disease.

MANAGEMENT STRATEGIES

Non-pharmacological approaches[6]

1. *Exercise*: Regular physical exercise, especially weight-bearing and muscle strengthening exercise, delays the physiologic decrease of BMD that occurs with ageing. 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 co-ordination.
2. *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 gm of calcium and 800 IU of vitamin D should be recommended for women of all ages.
3. *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.
4. *Smoking cessation*: Smoking increases bone loss. It also reduces the beneficial effects of postmenopausal hormone replacement therapy.

PHARMACOLOGICAL APPROACHES ANTIRESORPTIVE AGENTS

Calcium and Vitamin D

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. 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. Many experts now feel that at least 800 IU of vitamin D and 1.2 gms of calcium are required daily by every individual.

In a study of elderly women in institutional care who had inadequate intake of both calcium and vitamin D, calcium and vitamin D supplementation (tricalcium phosphate 1.2 gm plus vit D 800 IU) was found to reduce hip fractures by 43%, and non-vertebral fractures by 32% compared with placebo.[7]

The alpha-hydroxylated metabolite of vitamin D (alpha-calcidol) and calcitriol have been suggested to reduce fractures, but it is not completely clear if their effects are different from those of vitamin D itself.[8]

Bisphosphonates

Bisphosphonates are the best studied of all agents for prevention of bone loss.

Bisphosphonates are made up of two phosphonic acids joined to a carbon plus two side chains. They are the first line of drugs in postmenopausal and corticosteroid induced osteoporosis.

Types of Bisphosphonates

1. Nitrogen containing compounds –

Table 3: Evaluation of osteoporosis

1.	Bone mineral density measurements To rule out secondary causes of bone loss
2.	Serum calcium, phosphorus, creatinine. alkaline phosphatase, liver function tests
3.	Complete blood count
4.	Protein electrophoresis (>50 years of age)
5.	Serum 25(OH) vitamin D, PTH and TSH
6.	Serum testosterone and LH (in men)
7.	24 hr urine calcium and creatinine
8.	24 hr urine free cortisol
9.	Endomyseal antibodies to exclude celiac sprue

Pamidronate, Alendronate, Risedronate, Zoledronate.

2. Non-Nitrogen containing compounds
   Etidronate, Clodronate, Tiludronate

Alendronate and Risedronate are currently approved by FDA for use in osteoporosis.

Mode of action

They act by binding avidly to mineralized bone surfaces and reduce osteoclastic bone resorption. Nitrogen containing bisphosphonates inhibit mevalonic acid pathway resulting in decreased osteoclastic activity and reduced rate of remodeling. Non-nitrogen containing ones produce cytotoxic analogs of ATP, increasing osteoclast death. The net result is an increase in BMD and decrease in bone turnover markers.

As bisphosphonates persist in the skeleton for many months, their duration of action is prolonged beyond the period of administration.

Optimal effectiveness of bisphosphonates requires that patient engage in weight bearing exercise and have adequate calcium and vitamin D nutrition.

Administration

Bisphosphonates, when taken orally, are poorly absorbed. 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 30mins.

Side effects

Upper GI symptoms are most common. Rarely acute phase reactions in patients receiving I/V bisphosphonate may occur.

Commonly used bisphosphonates are:

a. ***ALENDRONATE :*** It was the first bisphosphonate approved by FDA for use in osteoporosis. The optimal dose appears to be 10 mg daily. The increase in BMD is greatest and occurs earliest at the spine, is less at the hip, and minimal at the forearm. Alendronate (10mg/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).[9] It also reduces bone turnover markers by 50-70%.

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 post-menopausal women.

b. ***RISEDRONATE:*** It increases BMD by 3-6% and reduces bone turnover by 40-60%. Risedronate (5mg/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).[10] According to the Hip Intervention Program (HIP) study the incidence of hip fracture was 2.8% in risedronate treated group and 3.9% in the placebo group.[11] It is approved by FDA for prevention and treatment of post-menopausal osteoporosis and for prevention and treatment of corticosteroid induced osteoporosis. The approved dose is 5 mg/d or 35 mg/wk. It has better GI tolerability as compared to alendronate.

c. ***PAMIDRONATE*:** It is approved by the FDA for the treatment of hypercalcemia of malignancy and Paget's disease of bone. It is administered intravenously and has been shown to increase BMD or prevent bone loss in patients with post-menopausal osteoporosis and corticosteroid-induced osteoporosis. It is given as an initial dose of 90 mg I/V with subsequent doses of 30 mg every 3rd month.

d. ***ZOLENDRONATE*:** It is the most potent bisphosphonate currently available. It is approved by FDA for treatment of hypercalcemia of malignancy and metastatic bone disease. In women with post-menopausal osteoporosis, a single I/V 4 mg dose of Zoledronate increased bone mass and resulted in sustained reduction in bone turnover that lasted at least 12 months.[12]

Zolendronate and Pamidronate are not approved in USA for use in osteoporosis because of lack of fracture efficacy data.

e. ***IBANDRONATE*:** This new bisphosphonate has recently been shown to be effective in osteoporosis, when used orally, either daily, in a dose of 2.5mg orally, or intermittently. Intermittent oral treatments (with a between dose interval of upto 3 months) are currently awaiting regulatory approval. Ibandronate has demonstrated efficacy in reducing the risk of vertebral and non-vertebral fractures.[13]

Estrogen

Mode of action

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.

Estrogen therapy / hormone therapy was initially considered to be an effective anti-resorptive HT agent for preventing post-menopausal bone loss. 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.[14]

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 post-menopausal women.[14]

Indications

Use of HRT is presently limited to postmenopausal women with severe hot flushes 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 flushes) and only when benefits outweigh the risks.

Dosing and administration

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 50 mcg estradiol per day. In women with an intact uterus, progestins are added to reduce the risk of uterine cancer.

SERMS (Selective estrogen receptor modulators)

These are estrogen-like compounds that bind with high affinity to the estrogen receptor (ER) and could have either estrogen agonist or antagonist activity.

Mode of action

Raloxifene is the first of the second generation SERMs and the only one to be available for the treatment of osteoporosis. It has agonist actions on the skeleton, and antagonistic action on the breast and endometrium. It therefore minimizes the undesirable effects of estrogens. 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.[15]

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.

Side effects

Thromboembolic disease (Relative risk similar or lower than that of HRT), flu syndrome, leg cramps and increase in hot flushes.

Dose

Raloxifene is taken as a once daily tablet (60 mg/day).

Calcitonin

Mode of action

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

Calcitonin 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.[16]

Dosing and administration: 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. It should be accompanied by optimal calcium and vitamin D. The unique feature of calcitonin in treatment of osteoporosis is its analgesic effect on bone pain of acute vertebral fracture.

Indications

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.

Side effects

Nasal calcitonin can produce rhinitis. Parenteral calcitonin may cause facial flushing, nausea and vomiting.

Bone-forming agents

Teriparatide rhPTH

It is the 1-34 amino acid fragment of parathyroid hormone.

Mode of action

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 produces increase in osteoblast number and function leading to bone formation.

Treatment with daily injections of h-PTH increases bone density at all skeletal sites, except the radius. Substantial effects are produced within 1 month of the start of therapy and no tachyphylaxis occurs. Teriparatide (20 mcg) has been shown to produce vertebral fracture risk reduction of 65% and non-vertebral fracture risk reduction of 53% in studies on postmenopausal women.[17] Similar risk reduction was observed among men also.

Indications

This anabolic agent is especially indicated in patients with severe osteoporosis at high risk of fractures and older patients with osteoporosis. Daily subcutaneous injections of h-PTH can be combined with calcitriol to promote calcium absorption and with estrogen/HRT co-therapy it produces increased trabecular bone thickening and connectivity. The benefits of PTH persist when antiresorptives are maintained. However, combination with alendronate may not work well and is not recommended.

Dosing and Administration

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 is limited to 24 months.

Side effects

There were few side effects attributable to the treatment at approved dose of 20 mcg/day s/c except for transient mild hypercalcemia and hyperuricemia.

Combination Therapies

Combining different osteoporotic treatments in order to improve efficacy in severe patients is an area of increasing interests. Bisphosphonates when combined with Raloxifene or estrogen or calcitonin have shown to produce a greater increase in BMD but combining two antiresorptives increases the cost and incidence of side effects. Ideal combination therapy should include antiresorptive agent and ananabolic agent. But alendronate when combined with PTH has been shown to attenuate the effects of PTH. Therefore to date, there is no combination licensed for the treatment of osteoporosis.

Future Emerging Therapies

Strontium Ranelate **-** It has recently completed phase III clinical trials. It acts by inducing uncoupling in bone remodeling, preventing the osteoclasts from resorbing the bone and also promoting osteoblasts to make new bone, as a result increasing DXA measured bone density.[18]

Osteoprotogerin (OPG) – This molecule binds to the RANKL on osteoblasts and prevents osteoclast activation. Greater and faster increase in BMD was observed with OPG-PTH cotreatment.

Nitrates

Growth hormone

rh PTH (1-84) **-** This is the intact molecule secreted by the parathyroid gland.

BMP - 2

Monitoring of Treatment

Approximately 10%-15% of patients fail to respond to treatment. Therefore, at least one repeat dual energy X-ray absorptiometry scan after 2 years is recommended to confirm treatment response. An alternative is to use bone turnover markers like type I collagen N-telopeptide (NTX), type I collagen C telopeptide (CTX), tartarate-resistant acid phosphatase (TRAP), which have a maximum suppression in the order of 50% within three months of starting therapy. This would allow earlier identification of non-responders. Bone turnover markers exhibit diurnal and day to day variation and are influenced by many other factors. In view of these difficulties, it is currently recommended that the use of bone turnover markers is confined to specialist centres and research studies**.**

CONCLUSION

The lack of direct head to head trials of treatments for osteoporosis, with reduction in fractures as an end-point, makes it difficult to determine the relative efficacy of the different treatments. 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, risedronate, or alendronate. If the goal is to reduce the risk of vertebral and non-vertebral fractures then a newer bisphosphonate like alendronate or risedronate would be preferable. For those with severe osteoporosis at high risk of fracture teriparatide would be a good option.

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