Review Article

Management of osteoporosis

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Osteoporosis is a major neglected public health problem associated with significant morbidity and mortality. Treatment in a patient with osteoporosis is targeted at reducing the future fracture risk, which is achieved through a combination of non-pharmacological and pharmacological interventions. Education on simple measures aimed at fall prevention, and adequate calcium and vitamin D supplementation should be ensured in all patients treated for osteoporosis. Medications approved for treatment of osteoporosis include antiresorptive agents (estrogen, calcitonin, selective estrogen receptor modulator raloxifene, bisphosphonates and denosumab) and anabolic agents (teriparatide and abaloparatide). A search for newer treatment targets has enabled development of two new effective drugs-odanacatib and romosozumab. However, these drugs have not been approved due to increased risk of stroke and cardiovascular events seen in the study participants. At present, combination therapy with anabolic and antiresorptive agents is not recommended due to lack of data on antifracture efficacy and cost-effectiveness. The sequential therapy should comprise of anabolic agent first, followed by an antiresorptive agent to maintain the bone mineral density (BMD) gains achieved with the initial treatment. BMD should be monitored periodically and increasing (or maintained) areal BMD without incident fractures indicates successful treatment.

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The treatment goal in a patient with osteoporosis is to reduce the risk of future fractures. This is accomplished through a combination of non-pharmacological and pharmacological interventions, which will be discussed in this chapter. There has been a great advance in the medical treatment of osteoporosis. While in 1980s, treatment options for postmenopausal osteoporosis (PMO) were limited to estrogen and calcitonin, in the current era, treatment armamentarium has expanded to include bisphosphonates, selective estrogen receptor modulator (raloxifene), monoclonal antibody to receptor activator of nuclear factor-κB (NF-κB) ligand (denosumab), parathyroid hormone analogue (teriparatide) and parathyroid hormone-related peptide analogue (abaloparatide). Insights from the rare sclerosing bone disorders and better molecular understanding of the bone cell biology has further enabled development of two new agents- cathepsin K inhibitor (odanacatib) and inhibitory monoclonal antibody to sclerostin (romosozumab).

Non-pharmacological Interventions :

It is important to emphasize following simple measures to reduce the fracture risk in each patient with osteoporosis[1].

(a) Fall prevention measures: Slippery floors, obstacles on the walking space and poorly lighted rooms may all increase the risk of falls and should be avoided. Patients should be instructed to use handrails while climbing stairs. Issues with vision, balance and proprioception may also increase the risk of falls and should be addressed appropriately.

(b) Weight bearing exercise should be encouraged, as much as possible, to improve muscle and bone mass. A sedentary lifestyle leads to low muscle mass, postural changes and deconditioning, increasing the risk of falls. In those with existing vertebral fracture, weight lifting and excessive strain on the spine while bending should be avoided.

(c) Avoid drugs that may increase the risk of falls (hypnotics, benzodiazepines, tricyclic antidepressants, alcohol) and predispose to osteoporosis (glucocorticoids, methotrexate, heparin, anticonvulsants). In patients with diabetes and/or hypertension, avoid hypoglycemia and/or hypotension to prevent falls.

(d) Ensure adequate calcium and vitamin D intake. Calcium and vitamin D deficiency may contribute to secondary hyperparathyroidism and the resultant bone loss in patients with osteoporosis. National Osteoporosis Foundation (NOF) recommends calcium intake (by diet and/or supplements) of 1000 mg/day for men aged 50-70 years and 1200 mg/day for women aged >50 years and men aged >70 years[2]. Calcium carbonate based calcium supplements are better absorbed when taken with food, while calcium

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citrate based supplements can be given regardless of the food timings.NOF also recommends vitamin D intake of 800-100 IU/day for adults >50 years of age[2].

Pharmacological Interventions :

Estrogen : In the era preceding the landmark Women's Health Initiative (WHI) study, estrogen used to be a popular therapy for prevention and treatment of PMO3.The Women's Health Initiative (WHI) study included >16000 postmenopausal women aged 50-79 years, who were randomised to conjugated equine estrogen (0.625 mg) plus medroxyprogesterone (2.5 mg) or placebo for a mean duration of 5.6 years. Though the risk of hip fracture and total fractures was significantly lower in the treatment arm, a concomitant increase in the risk of coronary heart disease, stroke and invasive breast cancer was seen[4,5]. The WHI results lead to a significant decline in the use of estrogen for PMO and currently it is used mainly as a short-term therapy to treat menopausal symptoms.

Calcitonin : Calcitonin (200 IU intranasal daily or 100 IU subcutaneous/intramuscular every other day) is Food and Drug Administration (FDA) approved therapy for treatment of PMO. However, due to modest anti-fracture efficacy compared to the other drugs and concerns regarding malignancy with long-term use, it has fallen out of favour in the current clinical practice[6,7].

Bisphosphonates : Bisphosphonates are the most commonly used drugs for prevention and treatment of PMO and glucocorticoid-induced osteoporosis. They are stable pyrophosphate analogs, which act through inhibition of the enzyme farnesyl pyrophosphate synthase. The enzyme is required for generation of isoprenoid lipids, which causes post-translational modification of guanine triphosphate (GTP)-binding proteins required for osteoclast viability and function[7]. While alendronate, risedronate and zoledronate have been shown to reduce the risk of both vertebral and hip fractures[8,9,10,11], the data for hip fracture reduction with ibandronate is lacking[12] (Table 1).

Hypocalcemia, vitamin D deficiency and renal dysfunction (glomerular filtration rate <30-35ml/minute) should be excluded before initiating treatment with bisphosphonates[13]. Oral bisphosphonates should be taken on empty stomach (reduced bioavailability with food) with a full glass of water and patients should be instructed not to lie down for 30-60 minutes after taking the medication (to prevent dyspepsia and esophagitis). Patients should also be warned about the possibility of developing fever and muscle aches within 24-48 hours after the intravenous zoledronate infusion (especially with the first dose). Rare side effects of bisphosphonate therapy include atypical femur fractures[14] (3-50 cases per 100,000 person-years) and osteonecrosis of jaw15 (1-10 cases per 100,000 person-years). It should be remembered that the benefit of treatment in a patient with high risk of fractures far outweighs the risk of these rare adverse effects[16] (approximately 80-5000 fragility fractures are prevented for 1 atypical fracture fracture associated with bisphosphonate treatment).

Selective Estrogen Receptor Modulators (SERMs) : SERMs have estrogen agonistic action at bone and antagonistic action at breast and uterus. Raloxifene is the prototypical SERM which is approved for prevention and treatment of PMO. It has been shown to reduce the risk of vertebral fractures, but the data for hip fractures is lacking[17] (Table 1). The adverse effects associated with raloxifene use include hot flashes and increased risk of venous thromboembolism. Bazedoxifene is another SERM, which in combination with conjugated estrogen has been shown to reduce hot flashes and has been approved by FDA for prevention of hot flashes and osteoporosis in postmenopausal women.

Denosumab : Denosumab is a fully human monoclonal antibody to receptor activator of NF-?B ligand (RANKL). RANKL along with macrophage colony-stimulating factor (M-CSF) is required for osteoclast development; denosumab, thus, works as an antiresorptive agent. In the FREEDOM trial18, denosumab was found to reduce the risk for both vertebral and hip fractures (Table 1). Like bisphosphonates, hypocalcemia and vitamin D deficiency should be excluded before starting treatment; however, renal dysfunction (of any severity) is not a contraindication to denosumab use. Rare adverse effects of denosumab include atypical femur fractures and osteonecrosis of jaw. Cost is often a limiting factor with denosumab therapy.

Teriparatide : Teriparatide (parathyroid hormone 1-34) is a parathyroid hormone (PTH) analogue which is FDA approved for the treatment of PMO. Its use as an agent to treat osteoporosis is based on the observation that, while continuous PTH exposure leads toincreased bone resorption, intermittent PTH exposure results in increased bone formation as well as bone resorption, with a net anabolic effect. The data on vertebral fracture reduction with teriparatide is impressive, however, hip fracture data is lacking[19] (Table 1). Due to the increased risk of osteosarcoma in rodents treated with high dose of teriparatide, a "black box" warning has been added by FDA and the treatment duration limited to 24 months. Contraindications to the use of teriparatide include hypercalcemia, hyperparathyroidism, Paget's disease of bone, history of bone irradiation, open epiphysis, unexplained elevation in alkaline phosphatase (ALP) of bone origin and severe renal dysfunction.The cost of therapy and compliance with daily injection are the factors commonly limiting use of teriparatide therapy.

Table 1 — *FDA approved drugs for the treatment of postmenopausal osteoporosis*

Drug (Pivotal study)	Dose	VF (% Risk reduction)	HF (% Risk reduction)	NVF (% Risk reduction)	Reference
Alendronate (Fit)	70 mg/week p.o. 10 mg/day p.o.	48%	53%	36%	8
Risedronate (Vert and Hip)	35 mg/week p.o. 5 mg/day p.o.	41%	40%	39%	9,10
Ibandronate (Bone)	150 mg/month p.o. 2.5 mg/day p.o.	50%	N/A	No. Significant reduction only in subgroup analysis	11
Zoledronate (Horizon)	5 mg/year i.v.	70%	40%	25%	12
Raloxifene (More)	60 mg/day p.o	30%	N/A	No	17
Denosumab (Freedom)	60 mg/6 months s.c.	68%	40%	20%	18
Teriparatide (Neer et al)	20 ug/day s.c. for 2 years	65%	N/A	53%	19
Abaloparatide (Active)	80 ug/day s.c for 2 years	86%	N/A	43%	21

FDA-food and drug administration, VF-vertebral fracture, HF-hip fracture, NVF-nonvertebral fracture, p.o.-per oral, i.v.-intravenous, s.c.- subcutaneous, N/A-data not available.

Abaloparatide : Abaloparatide (parathyroid hormone-related peptide 1-34) is a parathyroid hormone-related peptide (PTHrP) analogue which is the latest addition to the list of FDA approved agents for the treatment of PMO. Although both teriparatide and abaloparatide act at PTH receptor type 1, teriparatide activates receptor towards R0configuration (resulting in persistent intracellular cyclic adenosine monophosphate (cAMP) release), while abaloparatide activates receptor towards RG configuration (resulting in more transient cAMP release)[7]. The net resultwith abaloparatideis stimulation of bone formation, with less concomitant bone resorption, increasing the anabolic effect and decreasing the risk of hypercalcemia, compared to teriparatide[20]. Abaloparatide has been shown to have increased bone mineral density (BMD) response at spine compared to teriparatide and a highly positive response at hip, where teriparatide has been shown to have only marginal effects. In the ACTIVE trial, incidence of hypercalcemia was found to be lower with abaloparatide (3.4%) than teriparatide (6.4%)[21].The risks, warnings and contraindications with abaloparatideare similar to teriparatide.

CathepsinK inhibitor : CathepsinK is an enzyme secreted by mature osteoclasts to degrade bone matrix proteins. Loss of function mutation in the gene encoding for cathepsinK results in a rare sclerosing bone disorder "pyknodysostosis", characterised by decreased osteoclast resorptive activity with preserved osteoblast function. In the LOFT trial[22], cathepsinK inhibitor odanacatib (50 mg/day) was compared with placebo in >16,000 women with PMO and was found to significantly reduce the risk of vertebral, nonvertebral and hip fractures. However, due to the increased risk of stroke (HR 1.16, 95% CI 1.10-1.71), Merck & Co, in 2016, decided to discontinue the development of this agent.

Sclerostin inhibitor : Sclerostin is an endogenous negative regulator of Wnt signaling pathway, which results in decreased osteoblast function and bone formation. Absence of functional sclerostin results in the clinical phenotype of two rare genetic disorders "sclerosteosis" and "van Buchem's disease", both characterised by increased bone mass. Romosozumab is a humanized monoclonal antibody to sclerostin, which has been shown to reduce the risk of vertebral fractures in women with PMO. In the phase 3 FRAME trial[23], romosozumab at a dose of 210 mg subcutaneous once/month was compared with placebo in >7000 women with PMO and was shown to significantly reduce the risk of vertebral fractures by 73% at 12 months. Adverse effects include injection site reaction, atypical femur fracture, osteonecrosis of jaw and increased risk of cardiovascular (CV) events. Owing to the increased risk of CV events, FDA in 2017, rejected the approval of romosozumab for PMO, till more safety data is available from other studies.

Role of combination and sequential therapy : There is no rationale in combining two antiresorptive agents together. Combination of anabolic agent (teriparatide) with antiresorptive agents (zoledronate, denosumab) has been studied in two separate clinical trials[24,25]. The combination therapy was found to be associated with greater BMD increase at the hip and spine than either drug alone; however, antifracture benefit of this strategy remains to be seen. Thus, combination therapy cannot be recommended currently, till more data on antifracture efficacy and cost-effectiveness becomes available.

When using teriparatide and bisphosphonate in a sequential therapy, teriparatide should preferably be used first followed by bisphosphonate. This is explained by the fact that most important anabolic effect of teriparatidetherapy is achieved during the initial few months of therapy and its use after bisphosphonate therapy has been associated with delayed and blunted anabolic effect, as shown by the response in bone formation markers and BMD[26].

Drug holiday : In the 5 year extension trial of alendronate (FLEX)27 and 3 year extension trial of zoledronate (HORIZON extension trial)28, patients were randomised to receive continued bisphosphonate therapy or placebo. In both the studies, there was small but significant decline in BMD at hip and spine in subjects who discontinued therapy at 3 or 5 years, however, even at the

end of follow-up, the BMD remained above pre-treatment level, suggestive of residual antiresorptiveeffect of these agents on the bone. The risk of clinical vertebral fractures and morphometric vertebral fractures was increased in the placebo group in alendronate and zoledronate extension trials respectively. Based on the results of these two studies, bisphosphonates drug holiday should only be tried in patients with low risk of fractures; patients at high risk of fractures (prevalent vertebral fractures, history of fragility fractures or low femoral neck BMD at attempted discontinuation (T score =-2.5)) should continue to receive treatment. During the drug holiday, patient should be followed closely (BMD at 6-12 months interval) and treatment re-initiation considered in case of significant decline in BMD, increase in bone turnover markers (BTMs) and development of new osteoporotic fractures. It is important to note that the residual effect has only been conclusively demonstrated with alendronate and zoledronate. While limited data with risedronate suggests rapid offset and lesser residual effect[29], the long term data with ibandronate is not available. The residual effect seen with the two bisphosphonates also contrasts with other agents (such as estrogen, raloxifene, denosumab and teriparatide), where BMD gains are rapidly lost after 1-2 years of the treatment discontinuation and BTMs quickly return to pre-treatment levels[30,31,32].

Indications for treatment : According to NOF2, postmenopausal women and men above the age of 50 years with following should be considered for treatment:

(a) Hip or vertebral (clinical or morphometric) fracture

(b) T score $\leq$-2.5 at the femoral neck, total hip or lumbar spine by dual-energy x-ray absorptiometry (DXA)

(c) Low bone mass (T score between -1 and -2.5 at the femoral neck, total hip or lumbar spine by DXA) and 10 year probability of hip fracture $\geq$ 3% or 10 year probability of major osteoporotic fracture $\geq$ 20% by fracture risk assessment tool (FRAX)

Monitoring osteoporosis treatment : Serial BMD measurements (done at interval of 1-2 years) are most commonly used to monitor osteoporosis treatment. However, whether the long term antifracture efficacy of the treatment is governed by increased (or maintained) BMDremains a subject of debate[33]. Serial BMD measurement should be done on the same DXA machine and areal BMD (gm/cm^2) change should be taken into account. A stable or increasing BMD (BMD increase more than the least significant count) without incident fractures suggests successful treatment. Adequate calcium and vitamin D supplementation should be ensured and biochemistry (serum total calcium, inorganic phosphorous, alkaline phosphatase, albumin, creatinine, PTH, 25(OH)D and 24 hour urine calcium/creatinine) should be repeated at 6-12 months interval.

Conclusion :

Management of osteoporosis involves both non-pharmacological and pharmacological interventions directed towards reduction of the future fracture risk. With better understanding of the bone biology, newer molecular targets are being explored, diversifying the available treatment options. Better awareness among the physiciansmay improve the wide treatment gap associated with this commonly neglected public health problem.

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