

Osteoporosis in Elderly

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ABSTRACT

Osteoporosis is silent but progressive bone disease which makes bones weak resulting in increased tendency to fracture. Elderly person and postmenopausal women are most commonly affected by osteoporosis. FRAX index is introduced by WHO to predict 10 year fracture risk in osteoporotic patients which also helps in choosing different line of therapy. Current drug therapy includes bisphosphonates, calcitonin, estrogen or hormone therapy, selective estrogen receptor modulators, and teriparatide. Denosumab is novel drug introduced for treatment of postmenopausal osteoporosis.

Key words : postmenopausal, teriparatide, Denosumab.

Introduction -

Osteoporosis word is derived from Greek which means porous bone. In 1994, osteoporosis was defined by the WHO as “a generalized bone disease characterized by a decreased bone mass and a deterioration of bone microarchitecture resulting in an increased fracture risk”. It is a silent but serious disease of skeletal system as associated with physical, psychosocial, and economic consequences which has to bear by health care system. Its rising incidence globally has attracted scientists in last 2 decades to search for latest ways for early diagnosis and newer safe, more effective treatment modalities.

Osteoporosis is underestimated problem all over world although considered as preventable disease. Most of the time diagnosis is done when patient presents with fracture. Osteoporotic fractures (fragility fractures, low-trauma fractures) are those occurring from a fall from a standing height or less, without major trauma.¹

Primarily affected population by osteoporosis is the elderly individuals. Ageing is important and irreversible risk factor for development of osteoporosis.² Among elder individuals

postmenopausal lady and people above 70 years of age are the most common sufferers. The incidence of both postmenopausal osteoporosis (type 1)³ and senile osteoporosis (type 2) is predicted to be more in future due to improved longevity of people.

Bone health in old life depends on prenatal and postnatal factors. Dennison EM et al revealed that the health of the mother in pregnancy, infant's birth weight, and child's weight at age 1 year were predictive of adult bone mass in the seventh decade for men and women.⁴ Healthier babies who grows rapidly in infancy has more bone mass in adults aged 65-75 years. Peak bone mass is achieved by a woman by third decade of life,⁵ bone loss begins after that time which is further accelerates at menopause. Most of the women lose about 30% of their peak bone mass by age 80.

Early recognition and treatment of osteoporotic patients are crucial for the prevention of fractures. Various tools have been studied by different groups for the prediction of fractures. North American Menopause Society (NAMS) recommends measuring the total hip, femoral neck, and posterior anterior lumbar spine, using the lowest of the three BMD scores for diagnosis.⁶ FRAX is a fracture risk assessment tool introduced by World Health Organization (WHO) which includes various risk factors like personal history of fracture after age 40, history of hip fracture in a parent, cigarette smoking, excess alcohol consumption, glucocorticoid use, RA, or other secondary causes of osteoporosis. It

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calculates score which predicts 10 year fracture risk for the patient.

Indian clinicians have tried developing simple and cost effective tool for predicting fracture risk in Indian population. They used quantitative ultrasound and body mass index (BMI) of patient to calculate risk of fracture.⁷

Epidemiology -

Global : Osteoporosis is the most common metabolic bone disease worldwide and it is estimated to affect over 200 million people.⁸ Approximately 1 in 2 women and 1 in 5 men older than 50 years will eventually suffer osteoporotic fractures. Gullberg B and colleagues predicted that by 2050, the worldwide incidence of hip fracture is projected to increase by 240% in women and 310% in men particularly in developing countries is Asia.⁹ The percentage of primary osteoporosis in men is only 35-40%, they have a higher prevalence of secondary osteoporosis, with an estimated 45-60% of cases due to presence of hypogonadism, alcoholism, or excess glucocorticoid use.¹⁰ Overall, osteoporosis has a female-to-male ratio of 4:1.

India : On the basis of the 2001 census, approximately 163 million Indians > 50 years would be suffering from osteoporosis which is further expected to increase to 230 million by 2015.¹¹ Acharya S and colleagues has studied that Indian women attain menopause almost a decade earlier and osteoporotic fracture occur 10-20 years earlier than their Western counterparts.¹² Similarly Alekel DL revealed that osteoporotic fractures usually occur 10-20 years earlier in Indian/Pakistani men and women as compared with western Caucasian counterparts and farmer group have women have lower BMD than American, placing them at greater osteoporotic risk. The shorter hip axis of Indian/Pakistani versus American might also attenuate hip fracture risk in former group.¹³

Etiology -

Osteoporosis in elderly is a primary type of osteoporosis which is again subdivided into postmenopausal (type I) and age-associated or senile (type II) osteoporosis.

Postmenopausal osteoporosis (PMO) is seen in women aged 50-65 years and is characterized by a phase of accelerated bone loss mainly from trabecular bones. PMO is associated with decreased levels of estrogen and is associated with fractures of the distal forearm and vertebral bodies.¹⁴ Process of increased bone turnover leading to more bone loss begins in early peri-menopausal period. Associated Vitamin D deficiency and poor calcium in diet results in poor bone health and more frequent osteoporotic bones.

Age-associated or senile osteoporosis (type II osteoporosis) is seen in women and men older than 70 years. This variety is a result of generalised aging process and is also aggravated by insufficient calcium and vitamin D intake. It is more gradual in onset and affects both cortical and trabecular bone. Wrist, vertebral, and hip fractures are the common sites of fracture of this type.

Elderly people who are at increased risk of developing osteoporosis are those with family history of osteoporosis, previous fractures, sedentary lifestyle, thin and short built, smokers, alcoholics, diet deficient in calcium and /or vitamin D, excess protein, sodium in diet.¹⁵ In addition, those who are on medicines like steroid or certain anti epileptic drugs¹⁶ and those who are suffering from metabolic diseases like inflammatory arthritis, hyperparathyroidism, and hyperthyroidism are at increased risk of developing osteoporosis.

Pathophysiology of Osteoporosis in Elderly -

Accelerated Bone Remodeling : Basic pathogenesis in osteoporosis is an imbalance between bone resorption and bone formation. Coupling is a phenomenon in bone where bone remodeling occurs at discrete sites within the skeleton and proceeds in an orderly fashion, and bone resorption is always followed by bone formation. Compressive strength of the bone is directly related to amount of calcium in bones and hence calcium deficient skeleton is more prone for osteoporosis development. In adults, approximately 25% of trabecular bone is resorbed and replaced each year, compared with only 3% of cortical bone. Osteoclasts are responsible for bone resorption, whereas osteoblasts

are responsible for bone formation.

Any process that increases the rate of bone remodeling (eg, after menopause), results in net bone loss over time.¹⁷ Hence, in postmenopausal period there is an increased risk for fracture as newly formed bone is less densely mineralized and the resorption sites are temporarily unfilled. In addition the isomerization and maturation of collagen is found to be impaired in postmenopausal period.

RANK / Osteoprotegerin (OPG) System : The final process of bone remodeling occurs though the receptor activator of nuclear factor-kappa B ligand (RANKL)/receptor activator of nuclear factor-kappa B (RANK)/osteoprotegerin (OPG) system. RANK expressed by osteoclasts and its precursors which promote osteoclast differentiation. Osteoprotegerin is a soluble decoy receptor that inhibits RANK-RANKL by binding and sequestering RANKL. Estrogen deficiency like in postmenopausal period leads to increased expression of RANKL and decreased release of OPG; increased RANKL results in higher numbers of preosteoclasts as well as increased activity, vigor, and lifespan of mature osteoclasts which accelerates bone resorption. The estrogen deficiency at menopause leads to an imbalance in the RANKL-osteoprotegerin system which accelerates osteoclast formation and hence bone resorption.¹⁸ Denosumab is a fully human monoclonal antibody that inhibit RANKL has been approved for treatment of PMO.

Osteoporosis and Immune System : Recently articles have been published where osteoporosis is considered as immunological disease at least in some cases.¹⁹ This point is well supported by occurrence of localised osteoporosis in areas of local inflammation or generalised osteoporosis in systemic inflammatory disorders.²⁰ Apart from this cytokines like IL-6, TNF-a, and IL-1 are all stimulators of osteoclast activity which supports the hypothesis that senile osteoporosis may be related to systemic low grade inflammation.²¹ Estrogen deficiency results in an upregulation of cytokines such as IL-6 which increase bone turnover.²²

Clinical Features -

Osteoporosis is generally remains undetected till fracture occurs. Clinical features resulting from osteoporotic fractures include morbidity (pain, decreased quality of life (QoL), physical impairment), increased risk for new fractures (even within the short term) and increased mortality as shown in **Table I**.

As highlighted in table1, osteoporotic hip fractures are the most serious in terms of disability, mortality, and use of medical care. Clinical signs of hip fracture include severe, acute functional restriction resulting in immobilisation with a shortened leg in external rotation. 50% of the patients who were mobile and suffered hip fracture need aid to walk in future life.

Wrist fractures usually occur after a fall. Persisting hand pain (29-44% of patients), weakness (36-40%) and algodystrophy are the most commonly reported complications.

Osteoporotic vertebral fractures are mostly asymptomatic. Vertebral deformities are almost three times more common than in hip fracture. Pain due to vertebral fracture may be gradual or sudden and it may be mild to severe. Pain worsens with movement, coughing or sneezing, is often not relieved by rest. Pain may radiate along dermatomal distribution and may be accompanied by spasms of the paraspinal muscles.

Diagnosis -

Apart from specific blood tests and radiographs to diagnose secondary causes of osteoporosis and drug adverse effect monitoring measurement of bone mineral density (BMD) is gold standard in diagnosing osteoporosis.

Bone strength (and, hence, fracture risk) is dependent on many qualities of bone, of which BMD is the most commonly measured.²³ Other qualities of bone like degree of mineralization, hydroxyapatite crystal size, collagen structure, heterogeneity of bone microstructure, connectivity of trabeculae, and microdamage are difficult or impossible to measure in clinical practice at this

time hence BMD measurement is the “Gold standard” for the assessment of osteoporosis.

World health organization (WHO) has defined osteoporosis based on BMD scores as given in *table 2*.²⁴

BMD is currently measured by standard Dual-energy x-ray absorptiometry (DXA).²⁵ DXA provides the patient’s T-score, which is the BMD value compared with that of control subjects who are at their peak BMD.

BMD should be advised to women ≥ 65 years and men ≥ 70 years, postmenopausal women and men > 50 -69 years depend on their risk factor profile, post menopausal women and men > 50 years who has had an adult age fracture to diagnose and determine degree of osteoporosis.

Additional Bone Densitometry Technologies :

- **Quantitative CT-based Absorptiometry Computed Tomography (QCT) :** measures volumetric integral, trabecular and cortical bone density at the spine and hip and can be used to determine bone strength. Peripheral QCT (pQCT) measures the same at the forearm or tibia. In postmenopausal women, QCT measurement of spine trabecular BMD can predict vertebral fractures whereas pQCT of the forearm at the ultra-distal radius predicts hip, but not vertebral fractures.
- **Peripheral Dual-Energy X-Ray Absorptiometry (pDXA) :** measures areal bone density of the forearm, finger or heel. Measurement by validated pDXA devices can be used to assess vertebral and overall fracture risk in postmenopausal women.
- **Quantitative Ultrasound Densitometry (QUS) :** does not measure BMD directly, but rather speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the heel, tibia, patella and other peripheral skeletal sites.
- **Trabecular Bone Score (TBS)** is a recently FDA-approved technique which is available on some densitometers. It may measure the microarchitectural structure of bone tissue and

may improve the ability to predict the risk of fracture.

Vertebral Imaging should be performed -

- In all women age 70 and older and all men age 80 and older if BMD T-score is < -1.0 at the spine, total hip or femoral neck.
- In women age 65 to 69 and men age 70 to 79 if BMD T-score is < -1.5 at the spine, total hip or femoral neck.
- In postmenopausal women and men age 50 and older with specific risk factors : Low trauma fracture during adulthood (age 50+)
- Historical height loss of 1.5 inches or more (4 cm)

Bone Markers -

Markers of bone turnover have been extensively used in clinical research. They reflect the dynamic process of bone metabolism. Potential uses of bone markers include early prediction of changes in BMD during treatment, monitoring of drug efficacy and selection of patients for treatment (**Table 3**). They have little or no use in the diagnosis of osteoporosis or prediction of BMD, although some studies have suggested that they may have a role in monitoring compliance.

Treatment -

The primary clinical goal of osteoporosis management is to reduce fracture risk. So the targets for medicine would be to slow down or stop bone loss, or increase bone mass and/or bone strength, and minimizing factors that contribute to falls.

Prevention of osteoporotic fractures starts with lifestyle modification.

Non Pharmacological Measures -

Exercise : Risk factors, such as muscle weakness and impaired balance can be modified by Weight-bearing and muscle-strengthening exercise. Strength and balance training for the old people living in the community can reduce the risk of falls by 15 to 50%.²⁶ Weight-bearing exercise includes walking, jogging, stair climbing, dancing and tennis. Muscle-strengthening exercise includes weight

training and other resistive exercises, such as yoga, Pilates and boot camp programs.

Falls Risk Assessment and Prevention : Around 30% of people 65 years and over and living in the community and over 50% living in residential care facilities fall each year.²⁷ Most falls are associated with identifiable risk factors, e.g. unsteady gait, visual impairment, medications, and addressing these factors can significantly reduce falls.

Some studies have promoted use of **hip protectors** in osteoporotic patients if they have has good compliance.

Cessation of Tobacco Use and Avoidance of Excessive Alcohol Intake should be promoted as they carries significant weakening of bone tissue.

Pharmacological Management -

Apart from calcium and Vitamin D supplement other group of medicines for treatment of osteoporosis is given in **Table 4**.

Calcium and Vitamin D Intake : Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D with osteoporosis medicines can reduce the risk of fracture.²⁸ Calcium requirement in elderly population is 1200mg per day and vitamin D should be given 800-2000 IU daily depend on presence or absence of osteoporosis, multiple fractures and conditions affecting Vitamin D absorption.

Bisphosphonates : Bisphosphonates are antiresorptive medicines which act by inhibiting osteoclasts. Currently they are the first line medicine being prescribed for osteoporosis management in elderly. **Table 4** highlighted FDA approved bisphosphonates their doses and side effects. “Drug holiday” is discontinuation of particular medicine to reduce side effects of therapy and has been tried with bisphosphonates. But this should be done by taking into consideration the severity of osteoporosis and risk of discontinuation in given patient.

Raloxifen : is an oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast. It is used in the prevention of osteoporosis in

postmenopausal women. Dosing and side effect profile is mentioned in **Table 4**.

Calcitonin : Calcitonin is a synthetic hormone recommended for the treatment of osteoporosis in postmenopausal women who are at least five years postmenopausal. Calcitonin slows bone loss and increases bone density in the spine. It reduces the risk of spine fractures but not in non-spine fractures.

Strontium Ranelate : Strontium is a trace element found in seawater and soil which play a role in the formation of new bone while slowing the breakdown of old bone, and thus may influence bone density. It has not gained popularity in management of osteoporosis as associated with side effects, requires monitoring and should not be combined with many osteoporotic medicines like bisphosphonates. It is not approved by FDA for management of osteoporosis.

Estrogen Therapy (ET) and Hormone Therapy (HT) -

Estrogen therapy (ET) and estrogen with progesterone hormone therapy (HT) are approved for the prevention of osteoporosis in postmenopausal women. ET and HT reduce bone loss, increase bone density in both the spine and hip, and reduce the risk of hip, spine and other fractures in postmenopausal women. ET and HT also relieve menopausal symptoms. Side effect profile has limited its wider use in managing osteoporosis.

Teriparatide PTH and its analog, teriparatide [recombinant human PTH (134)], represent a new class of anabolic therapies for the treatment of severe osteoporosis, having the potential to improve skeletal microarchitecture. At present, teriparatide therapy is approved for 2-yr duration.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappaB ligand (RANKL), an osteoclast differentiating factor. It inhibits osteoclast formation, decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of fracture. It is associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis and is associated with greater and

sustained increases in BMD.²⁹ currently it is not available in India.

Drugs Undergoing Research -

Romozumab : Sclerostin is a protein which inhibits bone formation. Romozumab is an antibody undergoing trials to block the function of Sclerostin. It may prove promising anabolic agent in osteoporosis treatment.

Ronacaleret : Calcium-sensing receptor is located in the parathyroid gland and the kidney that regulates release of PTH. Calcium-sensing receptor antagonists, named calcilytics like Ronacaleret releases PTH pulse following each dose. Hence they are being developed for the treatment of osteoporosis. Opposite to PTH, that needs to be injected daily, these agents can be administered orally.³⁰

Picolinic Acid : A product derived of the essential amino acid tryptophan. It has been found beneficial for management of osteoporosis in animal experiments.

2014 National Osteoporosis Foundation (NOF) Guidelines for Management of Osteoporosis in Elderly³¹ -

Pharmacologic Treatment Recommendations :
After appropriate evaluation -

- Initiate pharmacologic treatment in those with hip or vertebral (clinical or asymptomatic) fractures.
- Initiate therapy in those with T-scores < -2.5 at the femoral neck, total hip or lumbar spine by dual-energy x-ray absorptiometry (DXA).
- Initiate treatment in postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip or lumbar spine by DXA and a 10-year hip fracture probability > 3 percent or a 10-year major osteoporosis-related fracture probability > 20 percent based on the U.S.-adapted WHO absolute fracture risk model.
- Current FDA-approved pharmacologic options for osteoporosis are bisphosphonates (alendronate, ibandronate, risedronate and

zoledronic acid), calcitonin, estrogen agonist / antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens / bazedoxifene), parathyroid hormone 1-34 (teriparatide) and RANK ligand inhibitor (denosumab).

- No pharmacologic therapy should be considered indefinite in duration. After the initial treatment period, which depends on the pharmacologic agent, a comprehensive risk assessment should be performed. There is no uniform recommendation that applies to all patients and duration decisions need to be individualized.
- In adults age 50 and older, after a fracture, institute appropriate risk assessment and treatment measures for osteoporosis as indicated. An alternative in many centers is a fracture liaison service (FLS) program where patients with recent fractures may be referred for care coordination and transition management.

Prevention -

Patient education is paramount in the treatment of osteoporosis. Many patients are unaware increased morbidity and mortality and consult clinician only when weak bone get fracture. Prevention and early treatment are important for complete osteoporosis management.

Patients should be educated about the risk factors for osteoporosis, with a special emphasis on family history and the effects of menopause. All postmenopausal women older than 65 years should be offered bone densitometry, as well as at risk younger women and men. Society at large also should be educated about the benefits of exercise with regard to osteoporosis.

In conclusion, rising incidence of osteoporosis and related complications should warrant meticulous screening of elderly individuals with increase risk. Current availability of effective medications and disciplined guidelines may result in global fracture risk reduction in future.

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Table 1 : Clinical features of osteoporotic fractures in elderly

	Hip	Vertebral	Wrist
Pain	Pain +, acute	Pain +, both acute & chronic	Pain +, both acute & chronic
Reduced function	+++	+	+
Psychosocial Impact	++	+	-
Compromised Quality of life	+++	++	+
Increased fracture risk	+	+	+
Excess mortality	++	+	-

Table 2 : WHO criteria for diagnosing osteoporosis using BMD

Definition	Bone Mass Density Measurement	T-Score
Normal	BMD within 1 SD of the mean bone density for young adult women	T-score ≥ -1
Low bone mass (osteopenia)	BMD 1-2.5 SD below the mean for young-adult women	T-score between -1 and -2.5
Osteoporosis	BMD ≥ 2.5 SD below the normal mean for young-adult women	T-score ≤ -2.5
Severe or "established" osteoporosis	BMD ≥ 2.5 SD below the normal mean for young-adult women in a patient who has already experienced ≥ 1 fractures	T-score ≤ -2.5 (with fragility Fracture [s])

Table 3 : Types of bone markers

Bone formation markers	Bone resorption markers
● Bone specific alkaline phosphatase	● N- telopeptide of collagen crosslinks
● Osteocalcin	● C- telopeptide of collagen crosslinks
● Carboxy-terminal propeptide of type 1 collagen	● Cross linked C- telopeptide of type 1 collagen
● Amino-terminal propeptide of type 1 collagen	● Free and total deoxypyridinolines

TABLE 4 : FDA approved Drugs for treatment of osteoporosis

Drug	Dose	Route	Adverse effects
Bisphosphonates			
Alendronate	10 mg daily or 70 mg Weekly	oral	Dyspepsia, abdominal pain, musculoskeletal pain
Ibandronate	Oral-150 mg monthly or IV 3 mg every 3 monthly	Oral and IV	Dyspepsia, abdominal Pain, musculoskeletal pain, back pain , headache
Risedronate	35 mg weekly or 5 mg daily	Oral	Rash, Dyspepsia, abdominal pain, diarrhoea, Arthralgia
Zoledronic acid	5 mg once a year	IV	Acute injection reaction, fever, fatigue, hypotension, nausea, vomiting, abdominal pain
Calcitonin			
Calcitonin	200 IU in one nostril daily every alternate day	intranasal	Rhinitis, dizziness, nasal irritation, nasal dryness
Selective estrogen receptor modulator			
Raloxifen	60 mg once daily	Oral	VTE, joint pain, leg cramps, flu syndrome, peripheral edema, hot flushes
Parathyroid hormone analogue			
Teriparatide	20 mcg once daily	sc	Transient hypocalcaemia, joint pain, body pain, nausea
Monoclonal antibody			
Denosumab	60 mg every 6 months	SC	Dermatitis, mild bone or muscle pain, UTIs