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Review Article

Recent Trends in Management of Osteoporosis

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ABSTRACT

It is a condition seen in significantly large population in India (around 26 million). Recent studies in this field further increase the available information about formation of peak bone mass and mineralisation of bone. BMD happens to be the main non-invasive procedure to assess osteoporosis with DXA. Role of Biological markers proved to be important prognostic tool in treatment. The drugs used in osteoporosis have quite significant side effects. Hence are to be used judiciously and as per guidelines prescribed by American Association of Clinical Endocrinologists (AACE).

***Key words*:** Osteoporosis, Osteopenia, RANKL, BMD, Osteoblast, Osteoclast, T-score.

INTRODUCTION

It is a condition characterised by reduced bone mass & bone strength, which is commonly seen in old age & post menopausal women. It is also seen in individuals with nutritional deficiencies & endocrinal disorders. Its major complications are a) vertebral fractures, b) fracture of neck of femur, although the fracture secondary to osteoporosis, can occur at any site. More than 10 million people are suffering from Osteoporosis in U S & around 26 million people are suffering in India.

This is one of commonest condition seen in orthopaedic practice. Being a degenerative disorder it is practically seen in each & every individual sometime or the other.

Definition:

1. It is defined as the reduction in bone mass & bone strength leading to increased risk of fractures.
2. (WHO) It is the condition where the bone density falls 2.5 standard deviation (SD) below the mean for the healthy young individual of same gender. This is referred to as " T - score" which is less than -2.5. [1]

EPIDEMIOLOGY

- Around 10 million people in US suffer from this condition. Around 26 million people suffer from osteoporosis in India & the number is likely to increase to 35 million. [2,3]
- Review of 119 hips fractures, found that, in Indian population, 2 peaks

are seen in fragility fractures, i) at 30 -39 yrs. ii) at 50 -70 yrs of age. [2,3]

- 3 lakhs cases of fracture around hips occur every year.
- 5 % of the men & 14% of the women above the age of 50 have risk of Hip fractures .
- The mortality rate is around 5 – 20 % during 1st year of surgery.
- Incidence of DVT & Pulmonary embolism is 20 -50 %
- Approximately 7 lakhs people suffer from vertebral fractures.
- Multiple vertebral fractures cause a) height loss, b) kyphosis / kyphoscoliosis,
- c) altered biomechanics of spine resulting in pain discomfort.
- It is also associated with chronic ailments like Rheumatoid Arthritis, malabsorption, cigarette smoking, dementia, Parkinson's disease, multiple sclerosis.
- The prevalence rate in Indian population is around 29 – 35 % [2,3]

Causes:

Primary causes	Secondary causes
• Personal history of fractures in adulthood • Female sex • Advanced age • Caucasian race	• Low body weight • Cigarette smoking • Early menopause • Menorrhagia • Reduced calcium intake • Inadequate Physical exercises • Alcoholism.

Pathophysiology: [1]

During the growth phase, the linear growth takes place by apposition of new bone tissue – It is called bone modelling. It involves transformation of basic molecular unit (BMU → preosteoblasts →osteoclasts →osteoblast→new osteoid).

Numerous genes control skeletal growth, peak bone mass, bone density, & body size. Linkage study reveals genetic locus on chromosome 11 is associated with high bone mass.

Bone remodelling involves

i) Repair of micro-damage within skeleton, to maintain skeletal strength,
ii) To transfer calcium from skeleton to maintain serum calcium.

In remodelling there is increased osteoclast formation, secondary to chronic increased demand for calcium (hyperparathyroidism).

It is regulated by a) Hormones (systemically)—estrogen, androgen, Vit D, PTH.

b) locally by IGF(I & II), TGF—β, PTHrP(PTH related peptide), ILs, PG-E2, members of TNF family.

Cytokinines responsible for communication between Osteoblasts & osteoclasts are RANK (Receptor activator NF-kappa-β also called RANKL) which is member of TNF family.

Another factor which plays imp role here is osteoprotegerin (OPG).

Osteoblastosis→increased levels of OPG & reduced levels of RANKL

Osteoclastic action→increased levels RANKL & reduced levels of OPG.

In young adults, after the peak bone mass is achieved, the rate of bone resorption & new bone formation is almost same. Hence the net bone mass remains constant.

After 30-45 yrs, there occurs imbalance between new bone formation & bone resorption, the latter exceeding the new bone formation, thus resulting net bone loss.

Increased number of remodelling sites→increased number of Osteoclasts→ increased levels of RANKL→reduced skeletal mass & disruption of normal architechture of bone→formation of porous bone.

Mineralisation of bone: [4]

It includes biochemical process of incorporation of calcium phosphates into clusters of hydroxy-apatite crystals. This process is called Nucleation.

Amorphous & crystalline Ca phosphates are embedded in interstitial matrix with collagen, elastin, & PPS.

A layer of water, "hydration shell" is believed to be bound to the surface of crystals. It facilitates transfer of ions to & from the crystallised surface.

Urist's hypothesis of mineralisation

Phase I: Disruption of cross-linkages in protein & PPS by calcium ions & Formation of calcium complexes with anionic group.

Phase II: formation of soluble protein Ca-PO4 complexes. In this step the conc. of Serum PO4 should not exceed than normal otherwise the Ca-PO4 precipitates out of solutions.

Phase III: Crystallisation & nucleation takes place.

$Ca \rightarrow PO4$ = active Cal^{++} + active $HPO4^{-}$

Active Ca^{++} × Active $HPO4^{-}$ = K (solubility constant)

Steps of mineralisation:

1. Formation of calcifiable matrix.
2. Ionic uptake of phosphates.
3. Formation of ultramicroscopic spaces in tissues by efflux of proteins.
4. Formation of tripartite cal-phosphate complexes for nucleation.
5. Formation of nucleation centres
6. Crystal formation.

Glimcher's hypothesis:

Inorganic Cal-phophates (amorphous)→organise collagen & Ca-PO4 (amorphous+crystals)→more stable complexes by recrystallisation. This is called " nucleation".

Calcium metabolism

Inadequate Cal intake leads to sec. Hyperparathyroidism- increased no of remodelling sites.

Actions of PTH:

a) stimulates hydroxylation of Vit D (1-25-OH2—D)

b) increased gastro-intestinal absorption of Cal

c) reduces Cal loss from kidneys.

Recommended dose of Calcium is 1000 - 1200 mg / day.

Calcium less than 400mg / day is detrimental to skeleton.

Vit. D : Recommended dose of 25 (OH) D is more than 75 nmol / L or 30ng /ml./day.

Estrogen deficiency:

a) It activates bone remodelling sites,

b) Exaggerates imbalance between bone formation & resorption..

Chronic ailments like malabsorption syndrome & less physical activity & medication like Glucocorticoids, anticonvulsants & immunosuppressants promote bone resorption.

Investigations:

i) CBC
ii) Serum & 24 hr urinary Calcium
iii) KFT
iv) LFT
v) BMD
vi) Serum PTH
vii) Serum 25 (OH) D

Out of the above BMD is one non-invasive technique to assess the skeletal quantitatively.

Dual energy X-ray absorptiometry (DXA), Single energy-ray absorptiometry (SXA).

DXA is more accurate out of the two.

"T score": Individual reading compared to that of healthy young individual.

Upto 0 : healthy, -1 to -2.5 ---Osteopenia, less than -2.5---osteoporosis.

"Z score": Individual reading compared to that of the healthy individual of same age group.

Limitations of DXA:

- 2 dimensional technique, fails to assess the depth.
- False positive results are seen in osteophytes & spurs.

CT:

- 3 dimensional technique, better than DXA, Expensive, & risk of radiation
- Latest invention—high resolution CT scan (Xtreme CT)

USG:

- It calculates attenuation of signal as it passes through bone.
- No risk of radiation, Less accuracy than DXA

Biological Markers:

For bone formation:

i) Serum bone specific Alk. phosphatase
ii) Serum Osteocalcin.
iii) Serum propeptide of type I procollagen.

For bone resorption

i) Serum & urine crosslinked N-telopeptide.
ii) Serum & urine crosslinked C-telopeptide.
iii) Urine total & free Deoxy pyridinoline.

Biological markers are important to differentiate patient at high risk of fractures, rather than estimation of bone mass.

It has important role in monitoring the response of the patients to the treatment.

Treatment of osteoporosis:

1. Management of underlying diseases & risk factors. Ex. Smoking, alcohol abuse.
2. Nutritional replenishments
   Calcium total intake 1000-1300 mg / day
   25(OH) D Vit D more than 75 nmol / L, or 30 ng / L
   Salt, Animal protein, Caffine, Vit K have beneficial effects
3. Exercise: Moderate exercise increases bone mass by 1-2 %
4. Pharmacologic therapies
   a) Estrogens,
   b) SERM i.e. Selective estrogen receptor modulators
   c) Bisphosphonates
   d) Calcitonin
   e) Parathormone PTH.

Drugs approved by American Association of Clinical Endocrinologists (AACE). [5]

Sr No.	Drug	Dose
1	Estrogens	Multiple regimen
2	Calcitonin	200 I U by nasal spray.
3	Denosumab**	60mg s/c per day.
4	Ralofifen	60 mg PO /day
5	Ibandronate	2.5 mg / day
		150 mg / month
		3 mg / IV /3 months
6	Allendronate	10 mg / day
		70 mg / days
7	Risedronate	5mg / PO /day
		35 mg / week
		150 mg /month
8	Zolendronic Acid	5 mg / IV /year.
9	Teriparatide	20 µg /s/c daily

** Denosumab is fully human monoclonal antibody against RANKL. It reduces RANKL in bone microenvironment.

Recommendations of AACE [5]

Maintain adequate intake of calcium and vit-D---R(1-2)

Limit the level of alcohol and caffine. Avoid smoking and perform moderate physical exercises R(3-6)

Adequate protein intake and use of hip protectors and physiotherapy R(7-11)

Pharmacological management R(22-27)

1st line therapy	allendronate, risdronate, Zolandronic acid, Denusumab
2nd line therapy	Raloxifene
3rd line therapy	Calcitonin

Use of Teriparatide in patients with very high risk of fracture or failure of Bisphosphonate treatment

Monitoring of DXA every one to two years R(28)

Criteria for successful management R(32-34)

i) BMD stable or increased
ii) No evidence of fracture
iii) Bone resorptive markers at normal level or below
iv) Incidence of single fracture does not indicate failure of treatment but demands alternative treatment

Treatments with Bisphosphonates to be continued for four to five years in moderate cases R(35)

Cases to be referred to clinical Endocrinologist R(37-40)

i) Evidence of fracture without major trauma in patients with normal BMD
ii) Evidence of recurrent fractures / increasing bone loss in spite of treatment
iii) Unexpectedly severe osteoporosis
iv) Osteoporosis with complications ex:- Renal failure, hyperparathyroidism.

Sr No.	Drug	Side effects
1.	Estrogens	High risk of My. Infarction, Stroke, DVT, Breast cancer
2.	SERM	High risk of uterine cancer with Tamoxifen.
3.	Bisphosphonates	Oesophagitis & stricture, Osteonecrosis of Jaw (ONJ), high incidence of Atypical Fractures after cessation of treatment. [6]
4.	Teriparatide	Muscle pain, weakness, dizziness, nausea. Induced osteosarcomas in rodents when used in high doses.

CONCLUSIONS

This is a problem faced by significantly large population, which requires critical evaluation & adequate expertise. Although quite a lot research is going in this field with many new drugs, these drugs are not free from side effects. Hence it is absolutely essential for treating physician to assess the drug for its beneficial effects & potential hazards. The table below mentions the drug & its potential side effects.

Recent study on animal model has shown that systemic administration of anti Sclerostin Antibodies (Scl-Ab) [7] leads to better implant fixation in osteoporotic bone. It leads to increased bone implant contact, peri-implant trabecular bone thickness, accounting for better implant fixation. Human clinical trials were conducted wherein Scl-Ab was administered in dose of 1-3mg/kg once a month. It has shown to increase bone formation& BMD. These trials are in initial stages. But this modality may prove to be the useful strategy in total joint replacement in future.

The safe modality of treatment still remains to be replenishment of nutritional supplements such as Calcium Vit D supplements, with moderate exercise work-up. Bisphosphonates & SERM's are to be used judiciously only in severe cases & with guarded care. Prior information of the potential side effects of the drugs, must be given to patients. Aggressive treatment has to be restricted to few cases who have high risk for secondary fractures. And in such cases it is preferred to have prior opinion from clinical endocrinologist before commencing the treatment.

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