Drug Therapy Of Osteoporosis

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Plan of discussion

- Osteoporosis definition
- Etiopathogenesis
- Classification of drugs
  - Antiresorptive drugs
  - Bone forming agents
- Summary
Definition
- Multifactorial disease in which there is diminution in the unity of trabecular and cortical bone mass, leading to increased frequency of fractures.

Common fractures are of vertebral bodies, ribs,
<table>
<thead>
<tr>
<th>Types of Osteoporosis</th>
<th>Type I</th>
<th>Type II</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>(post menopausal)</td>
<td>(senile)</td>
</tr>
<tr>
<td><strong>Calcium Deficiency</strong></td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Estrogen Deficiency</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Functional State</strong></td>
<td>Osteoclast Excess osteoblastic deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Bone Turnover</strong></td>
<td>HIGH</td>
<td>LOW</td>
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</table>
Drug induced Osteoporosis

Many Drugs cause/worsen Osteoporosis. These include

• Heparin
• Glucocorticosteroids
• Cyclosporine
• Warfarin
• Phenobarbitone
• Phenytion
• Carbamazepine
• Medroxyprogesterone
• Anticancer drugs
• Thyroxine
Diagnosis

Bone mass density - expressed as T score

Diagnosis -
• Non traumatic, Non pathological fracture spine or when T score lower than -2.5
• Normal score +1 to -1
CLASSIFICATION OF DRUGS USED IN RX OF OSTEOPOROSIS

**ANTIRESORPTIVE AGENT**

- BISPHOSPHONATES
- CALCIUM
- VIT D AND ITS AN.
- OESTROGEN
- SERM
- CALCITONIN
- THIAZIDE DIURETIC
- ANTIBODIES

**BONE FORMING AGENT**

- FLUORIDE
- ANDROGEN
- PARATHYROID HORMONE
Bisphosphonates

1\textsuperscript{st} generation: Etidronate

2\textsuperscript{nd} generation: Alendronate, Pamidronate, (Ibandronate)

3\textsuperscript{rd} generation: Risedronate, Zoledronate
Bisphosphonates

Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Mechanism of Action

At the cellular level, localization to sites of bone resorption, specifically under osteoclasts due to strong affinity for CaPO$_4$-2

They do not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity.
Alendronate

- 2nd gen. BP with efficacy equal to HRT/raloxifene & ↓ risk of fractures by 47-53%
- Absorption: oral BA- 64% for doses ranging from 5 to 70 mg
- Distribution and excretion:
  - Low plasma concentrations, wide distribution, Protein binding - 78%
  - Terminal t½ 10.5 years. So treatment not required for more than 5 years.
  - Excreted through Urine.
Dose: For prevention & Treatment of osteoporosis: 70 mg tablet once weekly or 10 mg tablet once daily

Taken on empty stomach in morning with full glass water patient not lie down or take food for at
Contraindications

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration
- Hypersensitivity to any component of this product
- Hypocalcemia
Bisphosphonates cont...

**Risedronate:**
- **Pharmacokinetics:** Rapid absorption orally - 1 hr
  - Oral bioavailability - 0.63 % & Excreted in urine
- **Oral Dosage:** 5mg per day OR 35 mg per week OR 75 mg on two consecutive days monthly
- **For men:** 35 mg per week

**Pamidronate:** More potent, given by only parenteral route: For patients with severe oesophageal distress it may be given as 3hr infusion 30 -90mg OD to once every 3 months.
Uses of Bisphosphonates

- **Osteoporosis**: post menopausal ♀ / age related / steroid induced osteoporosis in both men & women
- **Paget's disease**
- **Osteolytic bone metastasis**: Inj. Pamidronate
- **Hypercalcemia of malignancy**: Inj. Pamidronate & Etidronate
Oestrogen

Mechanism of action:

1. $^{17}$β estradiol acts on osteoblasts to decrease production of interleukin 6.
2. Upregulate the production of osteoprotegerin (OPG).
3. Enhance elaboration of OPG from osteoblasts which binds rankl and prevent activation of osteoclast precursors.
**Cond...**

- **Dosage:** 0.625 mg per day conjugated estrogen per day cyclic + progesterone norethisterone 2.5mg for last 10 days.

- **Hysterectomized women estrogen alone and with uterus both E+P**

- **HRT not recommended beyond 5 years use.**

- **BPN more effective than HRT**
Fig. 24.2: Hormonal regulation of bone remodeling unit

Bone remodeling involves the interaction of various hormones and cells. Osteoclasts, which are derived from osteoclast precursors, play a crucial role. Calcitriol, a potent vitamin D metabolite, stimulates osteoclast activity. PTH (parathyroid hormone) acts on osteoblasts to promote bone resorption. Calcitonin, produced by the thyroid gland, inhibits bone resorption. RANKL (receptor activator of nuclear factor kappa-B ligand) is involved in the activation of osteoclasts. OPG (osteo-protection factor) antagonizes the effects of RANKL. Calcium ions (Ca²⁺) are essential for bone remodeling, participating in the activation and differentiation of osteoblasts.
TIBOLONE

Converts to 3 Metabolites which exert estrogenic, progestational and weak androgenic action

Dose: 2.5 mg per day for 1 year

A/E: weight gain, facial hair
RALOXIFEN (S.E.R.M)

- **Bone & CVS:** partial agonist
- **Endometrium & breast:** antagonist
- **Postmenopausal women:** prevents bone loss & ↑ BMD (0.9-3.4%)
- ↓ LDL cholesterol
- 65% reduction in risk of breast cancer
- No increased risk of endometrial cancer
- No relief of vasomotor symptoms

- **Orally absorbed but low BA**
- high first pass & t 1/2-28hrs & excreted in bile

**Side effects:** 3 fold increase in deep vein thrombosis & pulmonary embolism (same as oestrogen HRT)

**Dose:** 60 mg/day

**EFFECTIVE ALTERNATIVE TO HRT FOR PREVENTION AND RX OF OSTEOPOROSIS**
Parathyroid hormone [PTH(1-34), teriparatide]

It contains recombinant human parathyroid hormone (1-34), [rhPTH(1-34)], which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Mechanism of action:
stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity.
Dosage:

- 20 mcg once a day administered as a subcutaneous injection into the thigh or abdominal wall

Adverse effects

- Allergic events soon after injection
- Hypercalcemia
- Injection site and injection technique events including pain, swelling, erythema, localized bruising, pruritus and minor bleeding at the injection site

Contraindications:

- Pregnancy
- History of hypersensitivity
Calcitonin-salmon

- Nasal Spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin.

Mechanism of action

- Causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone.
Dosage and contraindications:

- Peak plasma concentrations of drug appear 35 minutes after nasal administration.
- $t\frac{1}{2}$ - 43 mins
- One spray (200 I.U.) per day administered intranasally, alternating nostrils daily.
- Contraindicated in pregnancy and allergy to calcitonin-salmon.
Calcium

- The rationale for using supplemental calcium to protect bone varies with time of life.
- Preteens and adolescents require adequate calcium for bone accretion.
- Higher intake during 3rd decade is related to final phase of bone acquisition.
- In the elderly supplemental calcium suppresses bone turnover, improves BMD, and decreases the incidents of fractures.
- Calcium supplementation causes reduction in cortical bone loss.
Preparations and dosages

- Calcium carbonate (commonly used)
- Calcium citrate (more efficiently absorbed)
- Calcium lactate, Calcium gluconate, Calcium phosphate
- Calcium hydroxyapatite

**Dosage:** 1000 mg /day.

Dosages > 2000 mg causes constipation.
Vitamin D

- It may improve intestinal calcium absorption, suppress bone remodeling and improve BMD in individuals with marginal or deficient Vit D status.
- **Dosage:** 400-800 IU /day.
- 600,000 units once in a month i.m

**Precautions**

- Calcitriol causes hypercalcemia and hypercalciuria which can be reduced by restricting the dietary calcium.
Androgens

- TESTOSTERONE REPLACEMENT THERAPY INCREASES BMD IN HYPOGONADAL MEN.
- ANDROGENS MAY IMPROVE BMD IN OSTEOPOROTIC WOMEN BUT THERAPY IS LIMITED BY VIRILIZING SIDE EFFECTS.
- NANDROLONE DECANOATE - 50 mg by injection every 3 weeks.
- ANDROGENIC PROGESTRIN (NORETHISTERONE ACETATE) - ACTS SYNERGISTICALLY WITH ESTROGEN TO INCREASE BMD IN OSTEOPOROTIC WOMEN.
Fluoride

- It increases the bone volume and trabecular BMD, by increasing the osteoblastic activity
- Sustained release fluoride is associated with lower blood fluoride levels, have shown favorable results on fracture incidence.
- Dosage: 30-60 mg/day
Thiazide diuretics

- Reduce urinary calcium excretion and constrain bone loss in patients with hypercalciuria.

Dosage

- Hydrochlorothiazide – 25 mg once or twice daily.


**Strontium ranelate**

- Suppress resorption + stimulate bone formation
- Reserved drug for more than 75 years age who cannot tolerate BPN
DENOSUMAB

- **Human monoclonal antibody against RANKL and block osteoclast formation**

- **60 mg/SC/ every 6 months increased BMD**

- **Option for post menopausal for osteoporosis when no...**
Fig. 24.2: Hormonal regulation of bone remodeling unit

- Osteoclast precursor
- RANK
- Calcitriol
- OPG
- RANKL
- Calcitonin
- PTH
- PTH receptor
- Calcitonin
- Calcitriol
- Osteoblast
- Osteoclast
- Osteoid
- Ca^{2+}

The diagram illustrates the hormonal regulation of bone remodeling, showing the interaction between different hormones and their receptors to control osteoclastic and osteoblastic activity.
Prevention

- Regular physical activity of reasonable intensity at all ages.
- Adequate dietary calcium intake for children and adolescents.
- Elderly – increased dietary calcium and/or Vit D supplements.
- Timely administration of Estrogen for women at menopause.
- Prevention or correction of hypogonadism
Summary

- Bisphosphonates are first line drugs for both menopausal and senile osteoporosis
- Hormone replacement therapy for menopausal osteoporosis but not more than five years
- Testosterone replacement therapy increases BMD in hypogonadal men
- Newer drugs include denosumab and strontium ranelate
- Calcium and vitamin D supplementations