

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,

Types of Osteoporosis

	Type I	Type II
Age (senile)	(post menopausal)	
Calcium Deficiency	NO	YES
Estrogen Deficiency	YES	NO
Functional State osteoblastic deficiency	Osteoclast Excess	
Bone Turnover	HIGH	LOW

Drug induced Osteoporosis

Many Drugs cause/worsen Osteoporosis. These include

- Heparin
- Glucocorticosteroids
- Cyclosporine
- Warfarin
- Phenobarbitone
- Phenytoin
- 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

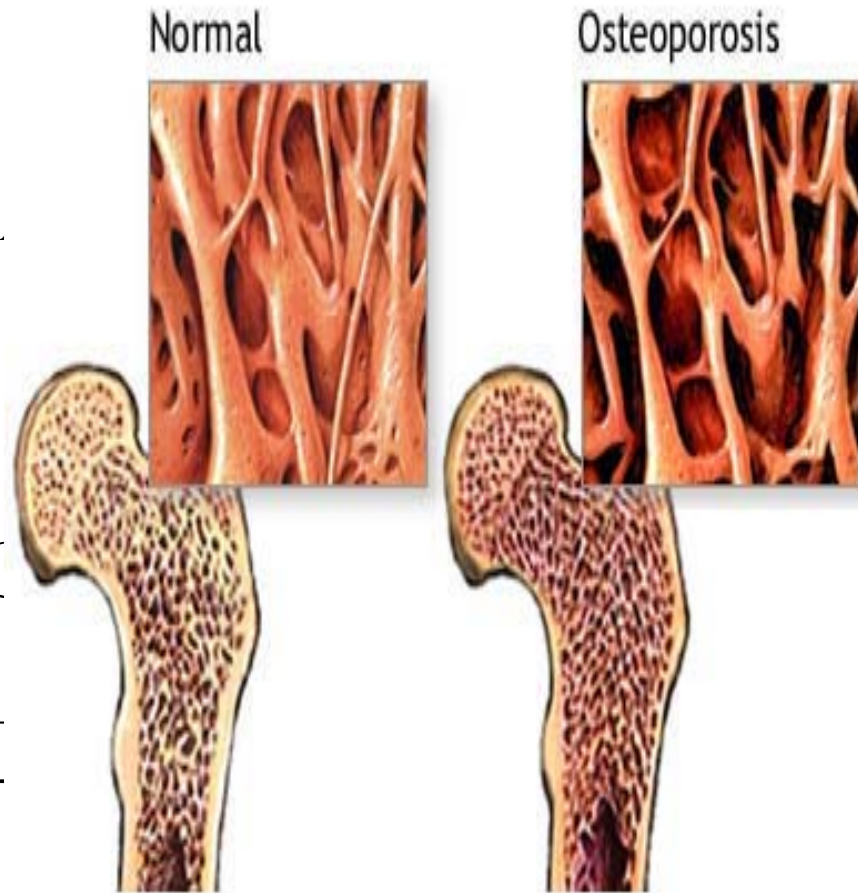
CLASSIFICATION OF DRUGS USED IN RX OF OSTEOPOROSIS

ANTIRESORPTIVE AGENTS

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

BONE FORMING AGENT

- FLUORIDE
- ANDROGEN
- PARATHYROID HORMONE



Hormones

- Testosterone
- Teriparatide
- Growth hormone

Nutritional supplements

- Calcium
- Vitamin D
- n-3 fatty acids
- CLA
- Phytoestrogens
- Alternative medicines

Antibodies and protein inhibitors

- Denosumab
- Odanacatib
- Inhibitors of wnt signaling pathway

Bisphosphonates and SERMs

- Alendronate
- Risendronate
- Ibandronate
- Etidronate
- Clodronate
- Raloxifene

Increase bone mass

Non pharmaceutical therapy

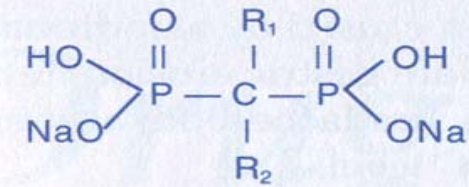
- ↑ Physical activity
- ↑ Muscle strength
- Fall prevention measures

Combination treatments

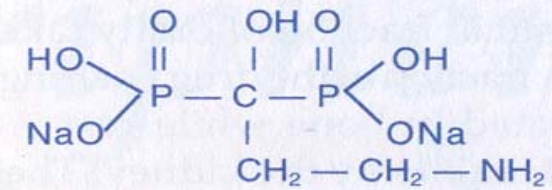
- Hormones and BP
- Hormones and nutritional supplements
- Hormones and physical activity

Bisphosphonates

⌘ 1st generation : Etidronate



Bisphosphonate



Pamidronate

⌘ 2nd generation : Alendronate
Pamidronate, (Ibandronate)

⌘ 3rd 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/oral oxifene & ↓ 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 $t_{1/2}$ 10.5 years. So treatment not required for more than 5 years
Excreted through Urine.

CON

D.....

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 orally 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
- ⌘ Hypercalcaemia of malignancy :
Inj . Pamidronate & Etidronate

Oestrogen

Mechanism of action:

- ⌘ 17β estradiol acts on osteoblast to decrease production of interleukin 6
- ⌘ Upregulate the production of osteoprotegerin (OPG).
- ⌘ 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 10days .
- ⌘ Hysterectomized women estrogen alone and with uterus both E+P
- ⌘ HRT not recommended beyond 5years use.
- ⌘ BPN more effective than HRT

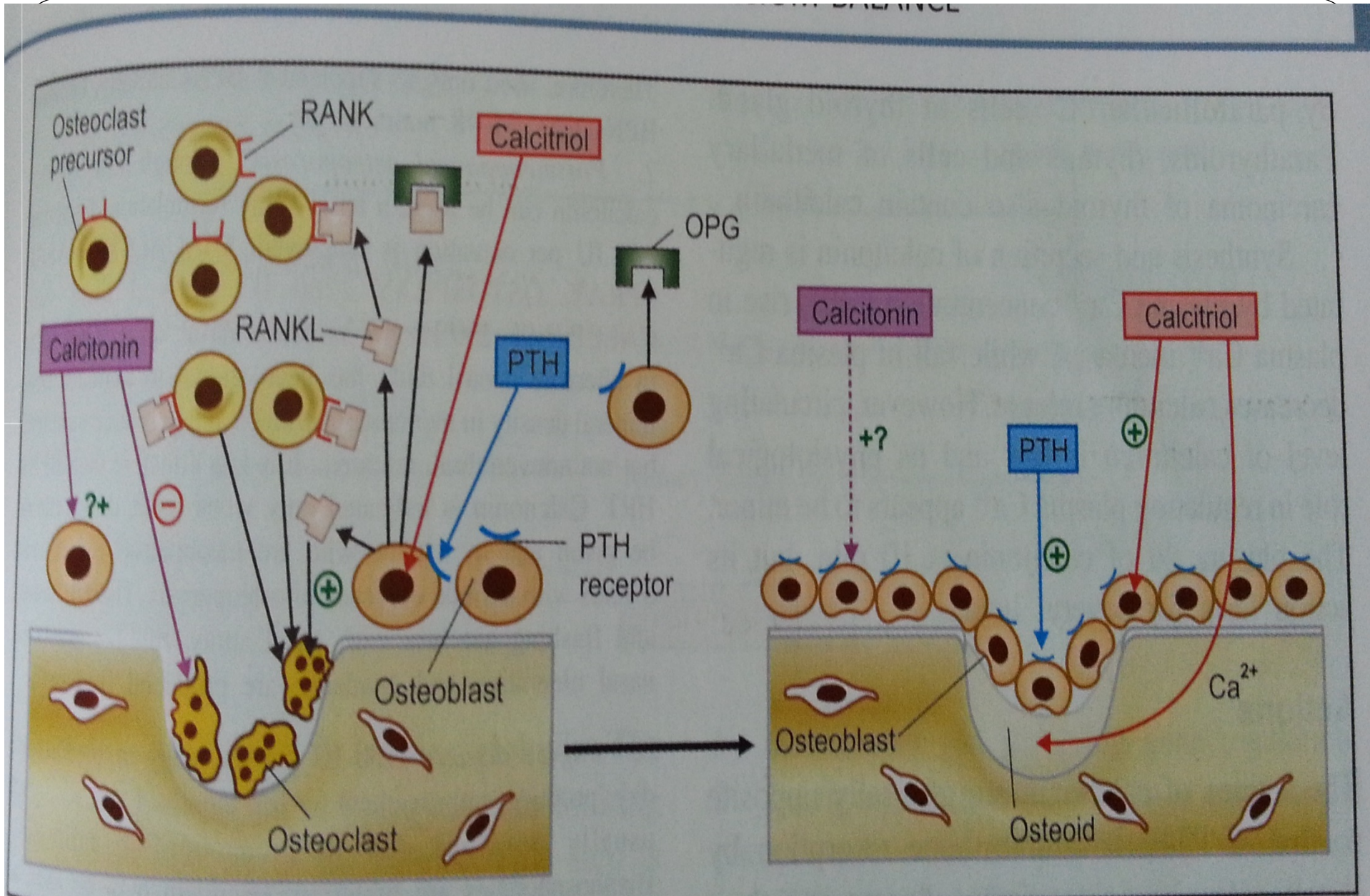


Fig. 24.2: Hormonal regulation of bone remodeling unit

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 : 60mg/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 pl asma concentrations of drug appear 35 minutes after nasal administration.
- $t_{1/2}$ - 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 > 2000mg 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 - 50mg by injection every 3 weeks .
- Androgenic progestin (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
- 60mg/SC/ every 6months increased BMD
- Option for post menopausal for osteoporosis when no

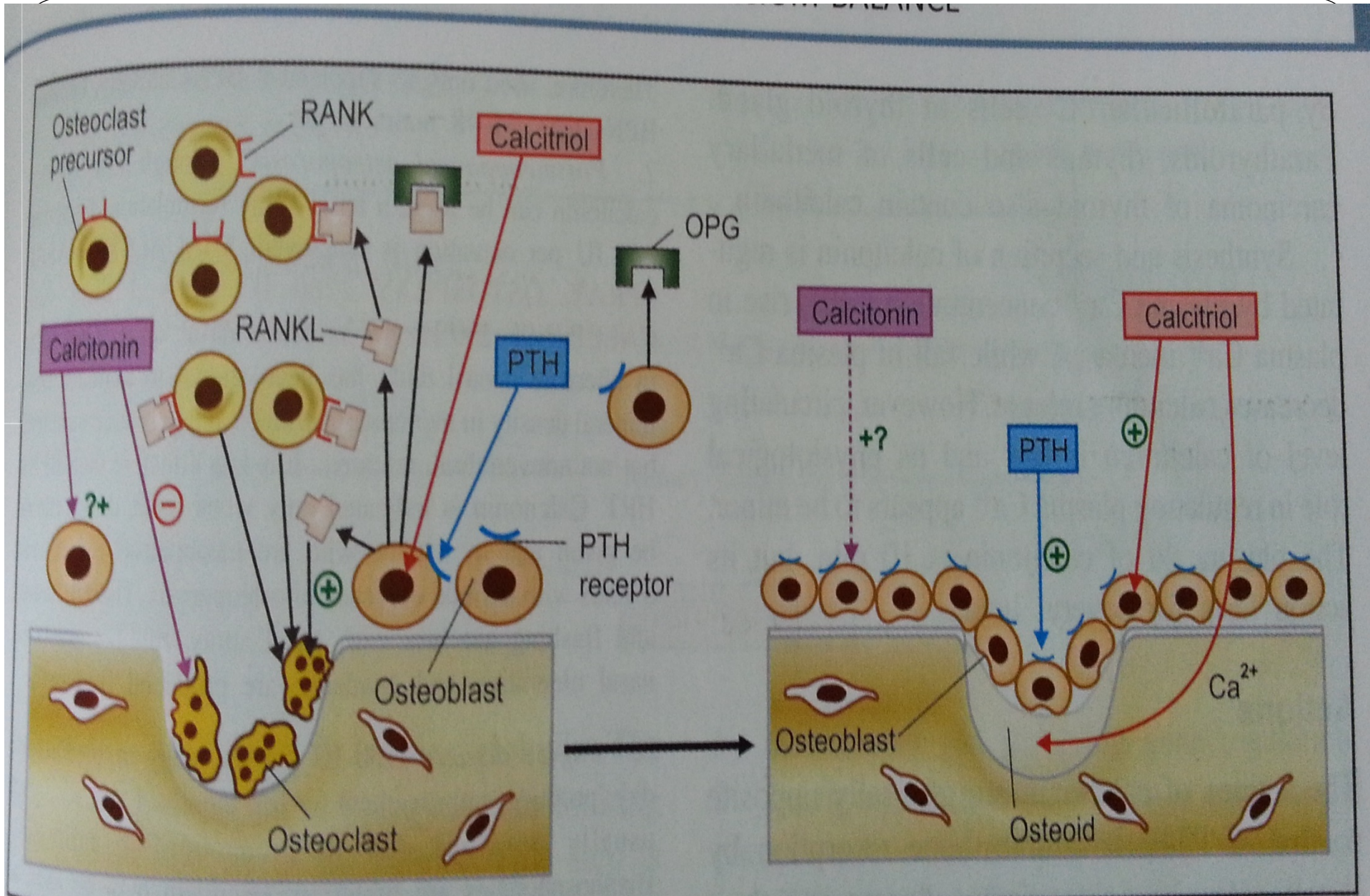


Fig. 24.2: Hormonal regulation of bone remodeling unit

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

