



University of Jordan - Faculty of Medicine
(2013-19)



Endocrine System

☐ Anatomy/Embryology/Histology

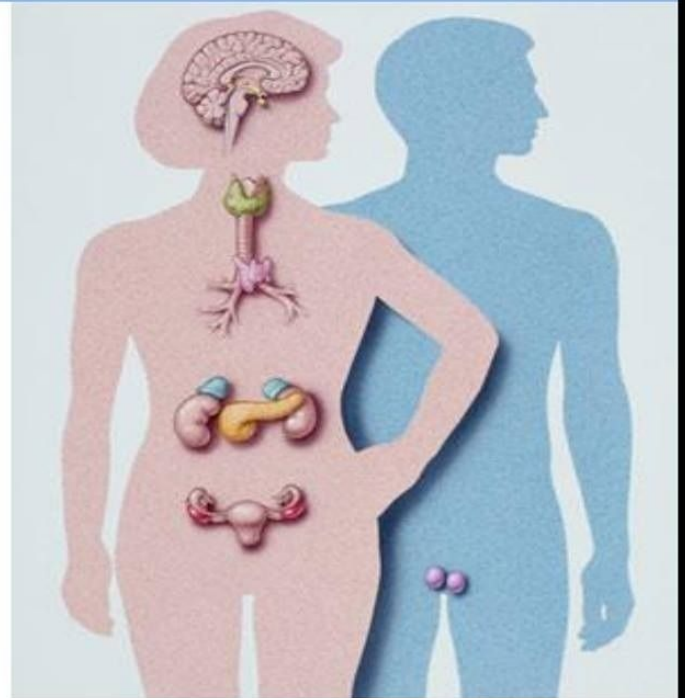
☐ Biochemistry

☐ Physiology

☒ Pharmacology

☐ Pathology

☐ PBL



☒ Slide ☐ Sheet ☐ Handout ☐ Other

slide #: 3

Date:

Dr's Name: munir gharaibeh

Price:

Designed by: Zakaria W. Shkoukani

Parathyroid Gland & Calcium Metabolism

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Calcium

Normal Ca^{++} blood level is around 9-10 mg/dl

Ca^{++} excess causes weakness

Ca^{++} causes tetany.



3 factors are involved in Ca^{++} blood level:

PTH

Vitamin D

Calcitonin

3 tissues are also involved:

Bone

Intestine

Kidneys

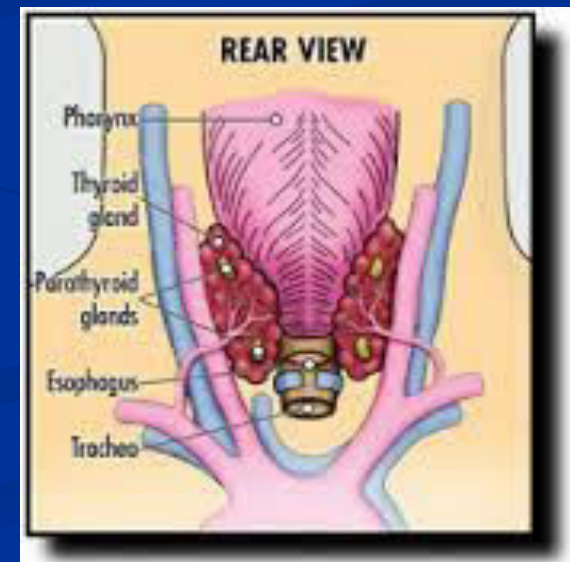
Parathyroid Hormone (PTH)

84 a.a peptide translated as a pre-prohormone

Regulation of synthesis & release is by blood level of Ca^{++} :

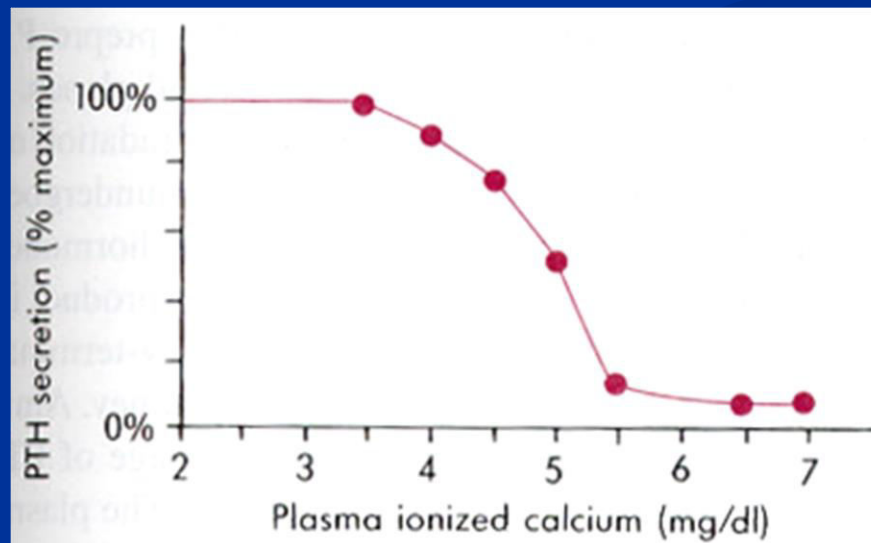
$\downarrow [\text{Ca}^{++}] \rightarrow \uparrow \text{PTH}$; $\uparrow [\text{Ca}^{++}] \rightarrow \downarrow \text{PTH}$

Little if any regulation by PO_4^-



Parathyroid Hormone (PTH)

- Maximum secretion of PTH occurs at plasma Ca^{++} below 3.5 mg/dl
- At Ca^{++} above 5.5 mg/dl, PTH secretion is maximally inhibited



Effects of PTH

■ On bone (1° target tissue):

↑ **R**esorption of Ca^{++} & PO_4^{--}
(cAMP) mediated effect

■ On intestine:

↑ **A**bsorption of Ca^{++} & PO_4^{--}

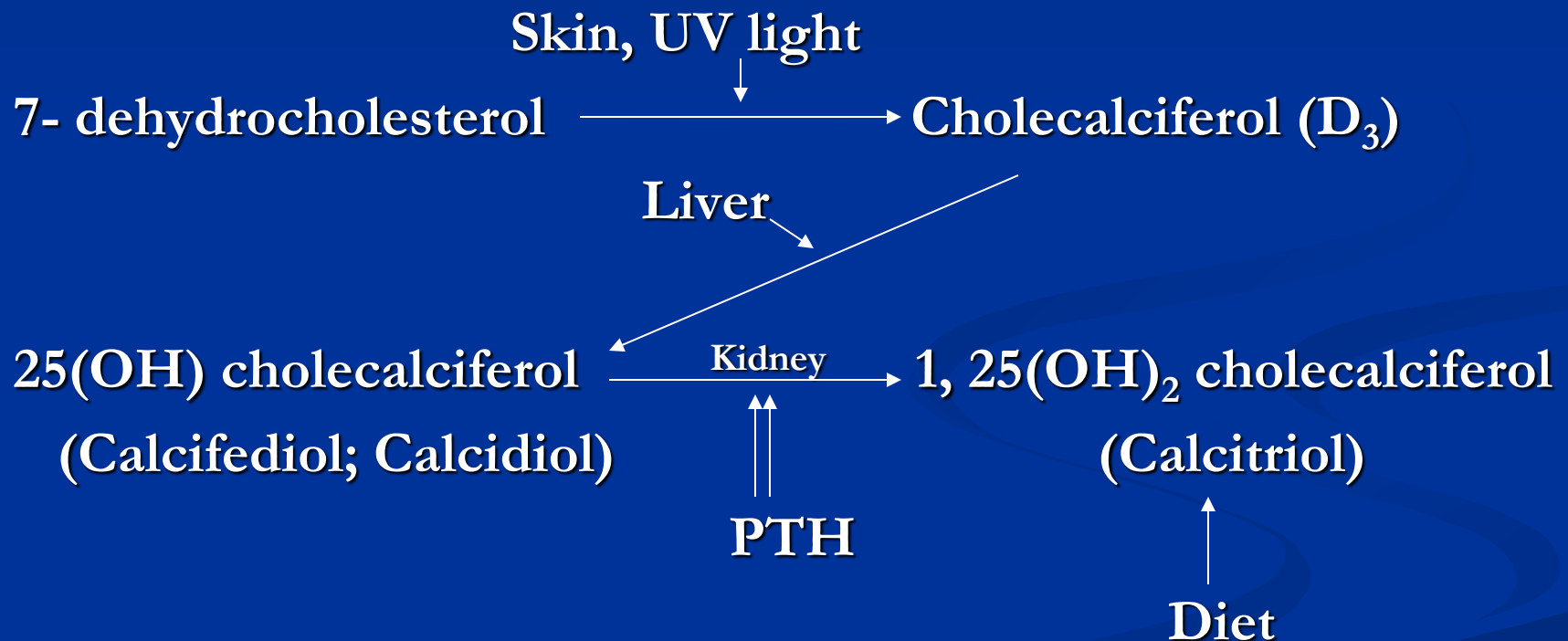
An indirect effect through ↑ Vit. D synthesis

■ On kidneys:

↑ **R**eabsorption of Ca^{++} , ↑↑↑ excretion of PO_4^{--}
(cAMP mediated effect)

Vitamin D

■ Synthesis:



Vitamin D

Normal daily requirement 400 IU/day.

- On intestine (1° target tissue):

↑ absorption of Ca^{++} & PO_4^{--}

- On bone:

↑ bone resorption

- On kidney:

↑ reabsorption of Ca^{++} & PO_4^{--}

Calcitonin

32 a.a peptide.

Synthesized and released from parafollicular cells of the thyroid gland.

■ Regulation of synthesis & release:

$\uparrow [\text{Ca}^{++}] \rightarrow \uparrow \text{calcitonin};$

$\downarrow [\text{Ca}^{++}] \rightarrow \downarrow \text{calcitonin}$

■ Effects:

On bone: \downarrow bone resorption ($\downarrow \text{Ca}^{++}$ & PO_4^{--} movement)

On kidneys: $\uparrow \text{Ca}^{++}$ & PO_4^{--} excretion

? On intestine: $\downarrow \text{Ca}^{++}$ & PO_4^{--} absorption

Calcitonin

- May be more important in regulating bone remodeling than in Ca^{++} homeostasis.

Evidence: Chronic excess of calcitonin does not produce hypocalcemia and removal of parafollicular cells does not cause hypercalcemia.

- Regulation by PTH and Vitamin D_3 dominates Ca^{++} homeostasis.

Summary

	<u>PTH</u>	<u>Vit. D</u>	<u>Calcitonin</u>
[Ca ⁺⁺]	↑	↑	↓
[PO ₄ ⁻⁻]	↓	↑	↓

Causes of Hyposecretion (hypoparathyroidism)

- Thyroidectomy (most common cause)
- Idiopathic
- ↓ sensitivity of target tissues to PTH (pseudohypoparathyroidism)

Symptoms of hypoparathyroidism: Are those of hypocalcemia:

Parasthesia, tingling lips, fingers, and toes,
carpopedal spasm, muscle cramps, tetanic
contractions, convulsions (seizures)

Bronchospasm

Depression, anxiety, abdominal pain

Cataract

Lab. Tests of hypoparathyroidism

- ↓ blood $[Ca^{++}]$
- ↑ blood $[PO_4^{--}]$
- ↓ urinary [cAMP]
- ↓ urinary [PTH]
- ↓ urinary $[Ca^{++}]$
- ↓ urinary $[PO_4^{--}]$

Treatment of hypoparathyroidism

- **Vitamin D**

Calcifediol, Calcitriol, Ergocalciferol, α -Calcidol, Dihydrotachysterol...

Drugs of choice for chronic cases

- **Ca⁺⁺ supplement**

Ca⁺⁺ rich diet

Ca⁺⁺ salts (chloride, **gluconate, carbonate...**)

Drugs of choice in acute cases

- **Teriparatide** (synthetic rPTH)

Recently approved in the management of osteoporosis

Hyperparathyroidism

- 1° hyperparathyroidism (adenomas)
- 2° hyperparathyroidism:
any cause of hypocalcemia e.g. malabsorption syndrome, renal disease...
- 3° hyperparathyroidism

Results from hyperplasia of the parathyroid glands and a loss of response to serum calcium levels.

Most often seen in patients with chronic renal failure

Symptoms of hyperparathyroidism

Are those of hypercalcemia:

Generalized weakness and fatigue
depression, bone pain, muscle pain
(myalgias), decreased appetite, feelings of
nausea and vomiting, constipation, polyuria,
polydipsia, cognitive impairment, kidney
stones and osteoporosis.

Lab. Tests of hyperparathyroidism

- ↑ blood $[Ca^{++}]$
- ↓ blood $[PO_4^{--}]$
- ↑ urinary [cAMP]
- ↑ urinary [PTH]
- ↑ urinary $[Ca^{++}]$
- ↑ urinary $[PO_4^{--}]$

Bone x-ray → bone decalcification

Treatment of hyperparathyroidism

- Low Ca^{++} diet
- Na^+ phosphate
- Steroids e.g. Prednisolone... \downarrow Ca^{++} absorption
- Calcitonin
- Surgery (best Rx)
- **Cinacalcet (calcimimetic)**, oral tabs used to treat patients with chronic kidney disease who are on dialysis & also used to treat patients with 1° & 2° hyperparathyroidism & cancer of parathyroid gland

Treatment of hyperparathyroidism

- Diuretics, e.g. Furosemide (\uparrow Ca^{++} excretion)
- Plicamycin
- Biophosphonates:
Etidronate,
Pamidronate...
 \uparrow bone formation and \downarrow bone resorption

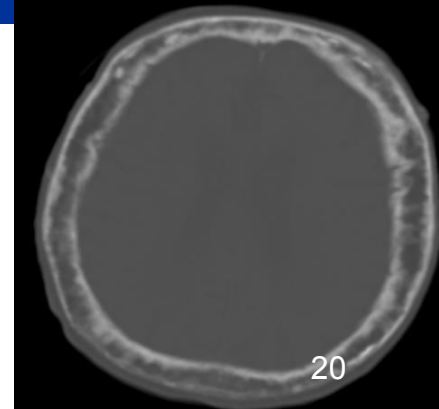
Paget's Disease

Rare bone disorder characterized by demineralization of bone, disorganized bone formation, ↑ bone resorption, fractures, spinal cord injuries, deafness...

■ R_x:

- Salmon calcitonin (drug of choice), S.C, I.M
- Biophosphanates, orally

Etidronate, alendronate, residronate, pamidronate...



Osteoporosis

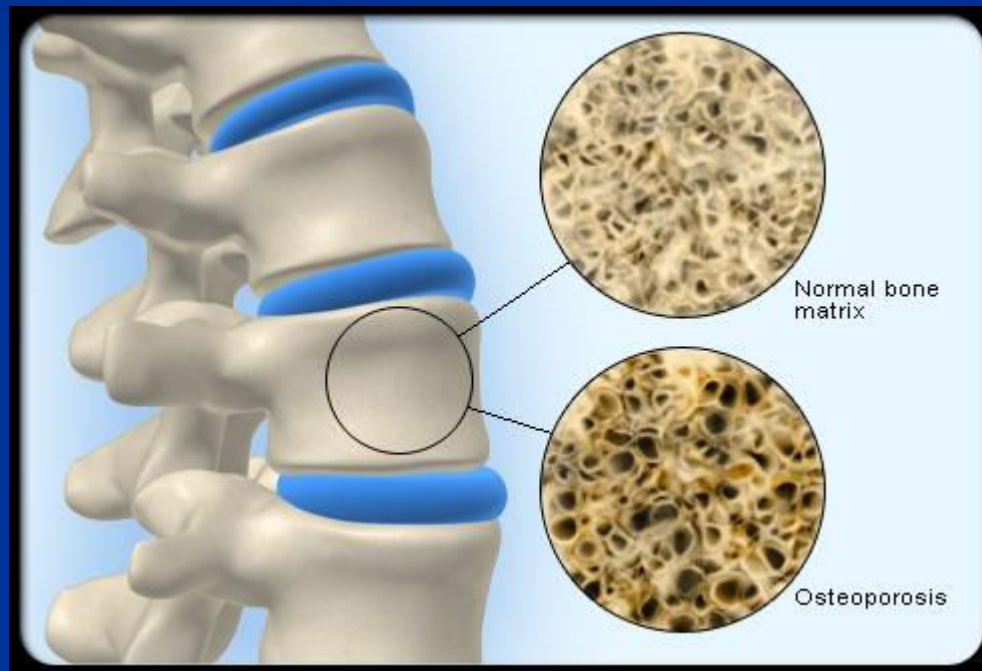
■ Definitions:

- **Osteoblasts:** fibroblasts, essential for bone formation and mineralization of bone matrix
- **Osteoclasts:** cells that break down bone and are responsible for bone resorption
- **Bone matrix:** the intercellular substance of bone formed by osteoblasts, consisting of collagenous fibers, ground substance, and inorganic salts
- **Bone resorption:** a process by which osteoclasts break down bone and release minerals resulting in transfer of Ca^{++} from bone to blood

Osteoporosis

- **Bone turnover or Bone remodeling:** removal of old bone and its replacement by new bone. Bone is constantly remodeled throughout adult life, and in general, the processes of bone resorption and formation are "coupled" so that there is no net change in bone mass.

During growth, osteoblast activity is more than that of osteoclasts (bone formation), but in diseases such as osteoporosis, bone resorption is greater than bone formation, leading to a net decrease in bone mass



Osteoporosis

A reduction in bone mass per unit volume leading to fractures particularly the spine, distal radius and proximal femur

Often known as “ the silent thief ” because bone loss occurs without symptoms

■ Etiology:

- Hormone deficiencies

Estrogen deficiency in ♀'s; androgen deficiency in ♂'s

Causes of Osteoporosis

Postmenopausal osteoporosis is the most common form of osteoporosis

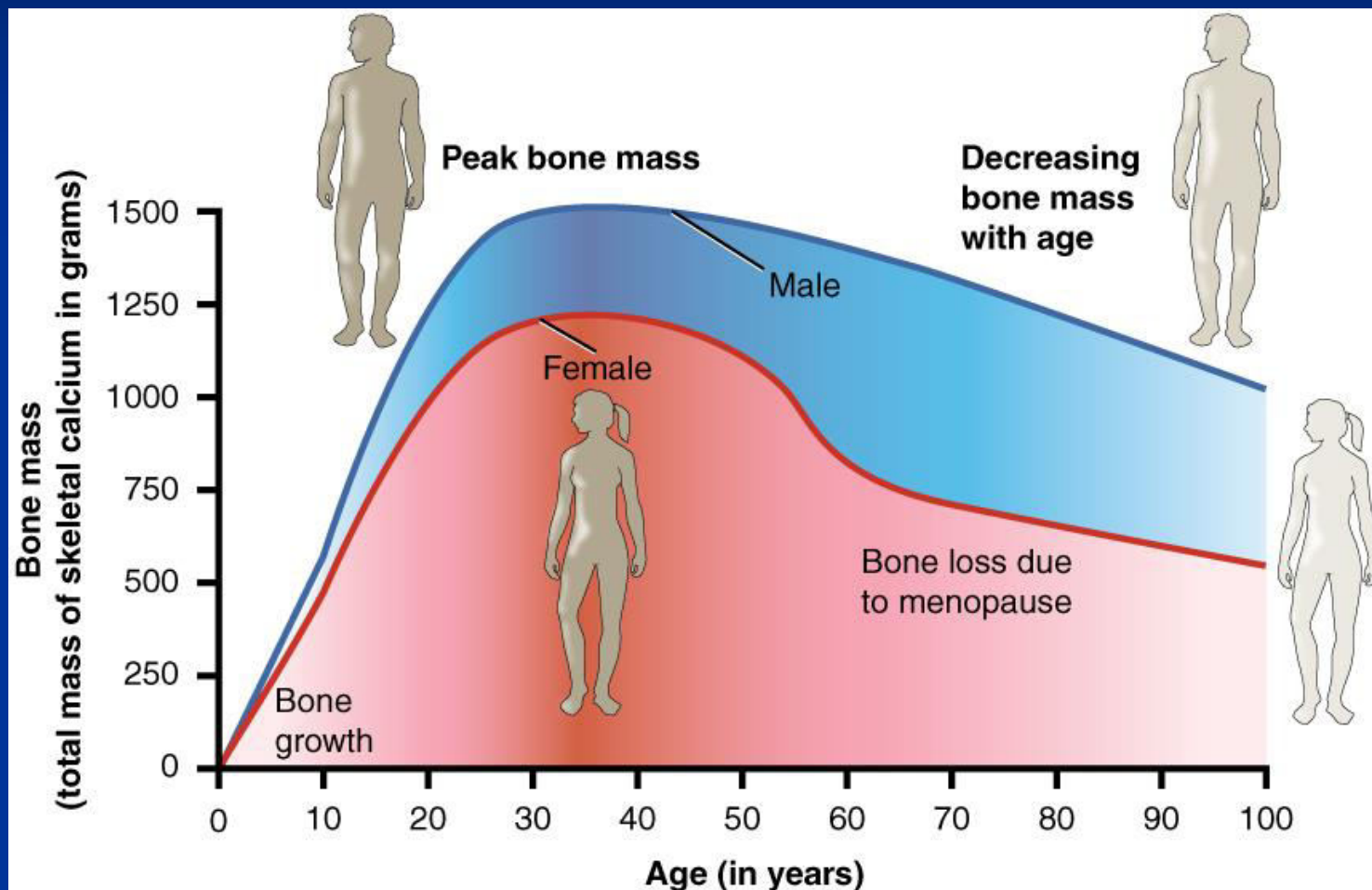
The greatest amount of bone density is lost during the first 5 years after the onset of menopause, so it is important to start therapy early.

Thyrotoxicosis

Hyperparathyroidism

Alcohol consumption

Smoking



Causes of Osteoporosis

Low Ca^{++} intake:

Dietary

Malabsorption syndrome

Drug-induced osteoporosis:

Glucocorticoids (Cushing's syndrome)

GnRH agonists

Anticonvulsants

Heparin...

Osteoporosis Risk Factors

- Female, menopause (early menopause → high incidence)
- Family history of osteoporosis
- Limited physical activity
- Low Ca^{++} diet
- Low Vit. D diet or limited exposure to sunlight

Osteoporosis Risk Factors

Caffeine consumption

Smoking

Alcohol intake

Chronic use of glucocorticoids or
anticonvulsants

Diagnosis of Osteoporosis

- Symptoms and signs:

No symptoms in early stage

Fractures of vertebrae, hips, or wrist

Low back pain

Neck pain...

- lab. Tests:

X-ray, bone mineral density (BMD; densitometry),
blood biochemistry, bone biopsy if necessary...



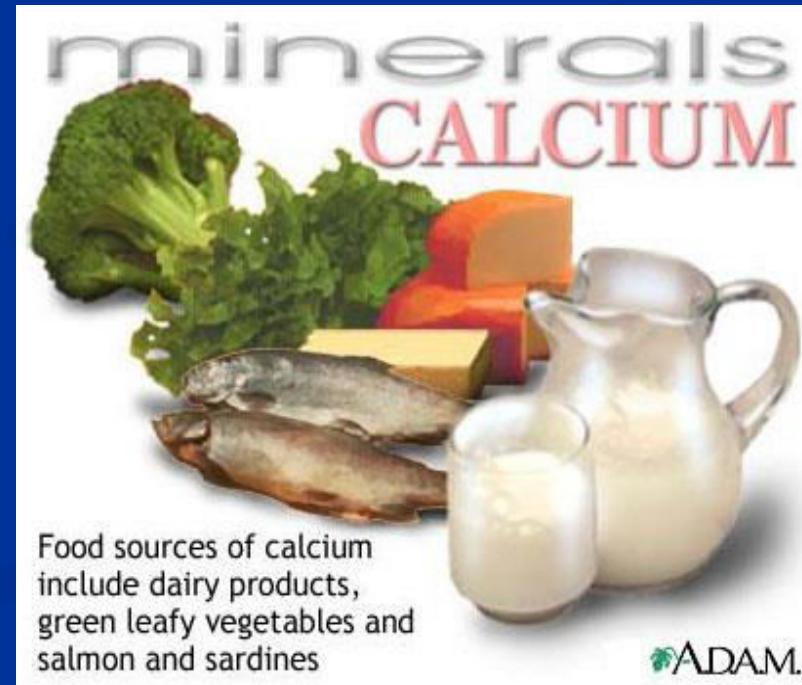
Treatment of Osteoporosis

Good outcome if started early.

Late osteoporosis or patients with fracture 2° to osteoporosis resist R_x but therapy could limit further fractures

Effective drugs:

- Estrogen + progesterone (to ↓ incidence of uterine cancer)
- Androgen therapy



Treatment of Osteoporosis

- Selective estrogen receptor modulators (SERM) e.g. **Raloxifene** (has estrogenic effects on bone & anti-estrogenic actions on the uterus and breast)
- **Vit. D + Ca⁺⁺**
- **Biophosphonates**
Etidronate, Alendronate...
- **Calcitonin** (intranasal)
- **Small doses of fluoride** (slow release sodium fluoride)
- **Synthetic rPTH** (Teriparatide), recently approved by FDA in the management of osteoporosis

Treatment of Osteoporosis

- **Denosumab:**

Given SC, every 6 months.

An inhibitor to Receptor activator of nuclear factor kappa-B ligand (RANKL).

Recently approved for use in postmenopausal osteoporosis, drug-induced bone loss and in bone metastasis

RANKL is a protein present on osteoblasts which activates osteoclasts.

Many side effects:

Hypocalcemia, serious infections of skin, bladder, heart(endocarditis), high blood cholesterol levels, pain in jaws and back...

Postmenopausal Osteoporosis R_x or prophylaxis

- **Estrogen + alendronate + Ca⁺⁺& vit. D + intranasal calcitonin**
- **Raloxifene + alendronate + Ca⁺⁺& vit. D + calcitonin**
- **Estrogen + progesterone**
- **Raloxifene + alendronate**
- **Teriparatide (rPTH) (S.C)**
- **Denosumab**