Calcium

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

Ca++ excess cause 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:
↓ [Ca^{++}] → ↑ PTH; ↑ [Ca^{++}] → ↓ 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):**
  - ↑ resorption of Ca^{++} & PO_{4}^{--} (cAMP mediated effect)

- **On intestine:**
  - ↑ absorption of Ca^{++} & PO_{4}^{--}
  - An indirect effect through ↑ vitamin D synthesis

- **On kidneys:**
  - ↑ reabsorption of Ca^{++}, ↑↑↑ excretion of PO_{4}^{--} (cAMP mediated effect)
Vitamin D

**Synthesis of vitamin D**

1. **Skin, UV light**
   - 7-dehydrocholesterol $\rightarrow$ Cholecalciferol ($D_3$)

2. **Liver**
   - Cholecalciferol ($D_3$) $\rightarrow$ 25(OH)cholecalciferol (Calcifediol; Calcidiol)

3. **Kidney**
   - 25(OH)cholecalciferol $\rightarrow$ 1, 25(OH)$_2$cholecalciferol (Calcitriol)

4. **PTH**
   - 1, 25(OH)$_2$cholecalciferol $\leftrightarrow$ 25(OH)cholecalciferol

5. **Diet**
   - 25(OH)cholecalciferol $\rightarrow$ 1, 25(OH)$_2$cholecalciferol

- **Cholecalciferol (D$_3$)**
- **Calcifediol; Calcidiol**
- **Calcitriol**
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:
  \[ \text{\uparrow} [\text{Ca}^{++}] \rightarrow \text{\uparrow} \text{calcitonin}; \text{\downarrow} [\text{Ca}^{++}] \rightarrow \text{\downarrow} \text{calcitonin} \]

- Effects:
  
  **On bone:** \( \text{\downarrow} \text{bone resorption} \) (\( \downarrow \text{Ca}^{++} \& \text{PO}_4^{--} \) movement)

  **On kidneys:** \( \uparrow \text{Ca}^{++} \& \text{PO}_4^{--} \) excretion

  ? **On intestine:** \( \downarrow \text{Ca}^{++} \& \text{PO}_4^{--} \) 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.

- PTH and Vitamin D\(_3\) regulation dominates Ca\(^{++}\) homeostasis.
## Summary

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<th>PTH</th>
<th>Vit. D</th>
<th>Calcitonin</th>
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<tbody>
<tr>
<td>[Ca^{++}]</td>
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<td>↑</td>
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<td>[PO_4^{--}]</td>
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Disorders affecting the parathyroids:

**Hyposecretion (hypoparathyroidism):**

**Causes:**
- 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}^{2-}]
- ↓ urinary [cAMP]
- ↓ urinary [PTH]
- ↓ urinary [Ca^{++}]
- ↓ urinary [PO_{4}^{2-}]
Treatment of hypoparathyroidism

- **Vitamin D**
  Calcifediol, Calcitriol, Ergocalciferol, α-Calcidol, Dihydrotachysterol...

**Drug of choice for chronic cases**
- **Ca**

**Drug of choice in acute cases**
- **Teriparatide (synthetic rPTH)** - recently approved in the management of osteoporosis
Hyperparathyroidism

- 1º hyperparathyroidism (adenomas)
- 2º hyperparathyroidism
  2º to any cause of hypocalcemia
    e.g. malabsorption syndrome, renal disease...
- 3º 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$_4^{-2}$]
- ↑ urinary [cAMP]
- ↑ urinary [PTH]
- ↑ urinary [Ca$^{++}$]
- ↑ urinary [PO$_4^{-2}$]

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\(^{\circ}\) & 2\(^{\circ}\) hyperparathyroidism & cancer of parathyroid gland
Treatment of hyperparathyroidism

- Diuretics, e.g. Furosemide (↑ Ca++ excretion)
- Plicamycin
- Biophosphonates
  Etidronate,
  Pamidronate…
  ↑ bone formation and ↓ bone resorption
Paget’s disease

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

- $\mathbf{R_x}$:
  - Salmon calcitonin (drug of choice), S.C, I.M
  - Biophosphonates, 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\textsuperscript{++} 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 2º to osteoporosis resist Rx, but therapy could limit further fractures.

Effective drugs:

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

Food sources of calcium include dairy products, green leafy vegetables and salmon and sardines.
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 and activates activity of osteoclasts, osteoporosis

Many side effects:
Hypocalcemia, serious infections of skin, bladder, heart(endocarditis), high blood cholesterol levels, pain in jaws and back...
Postmenopausal osteoporosis Rx or prophylaxis

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