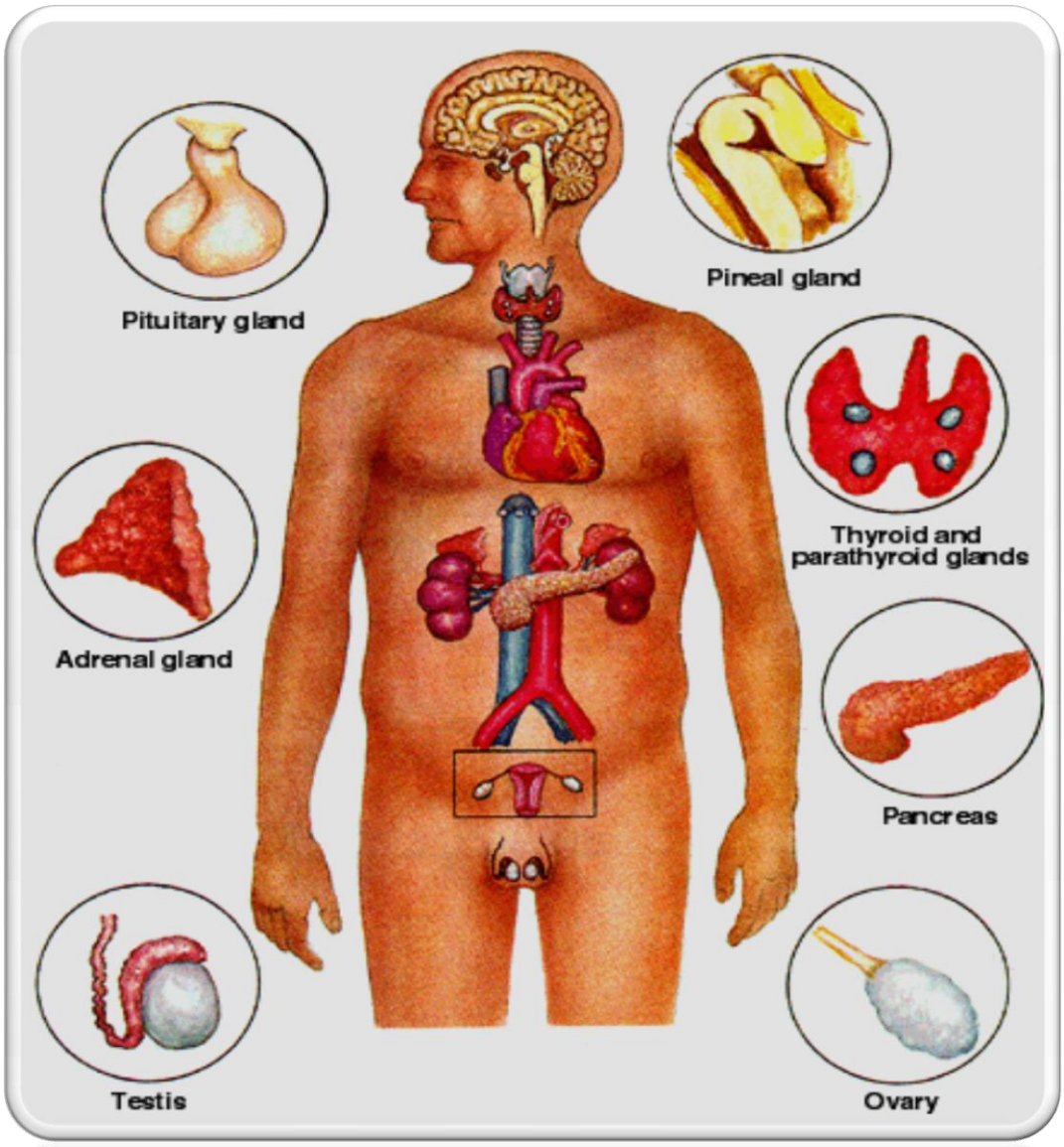
ENDOCRINE BLOCK

PHYSIOLOGY TEAM 431



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Distribution of Ca++ in Body

(in % of total body content)*important

- Total body content is 1300g:
  - Bone & Teeth→99%.
  - Intracellular fluid (ICF) (stored in the Endoplasmic Reticulum)→1%.
  - Extracellular fluid (ECF) →0.1%.

ECF= interstitial fluid + plasma

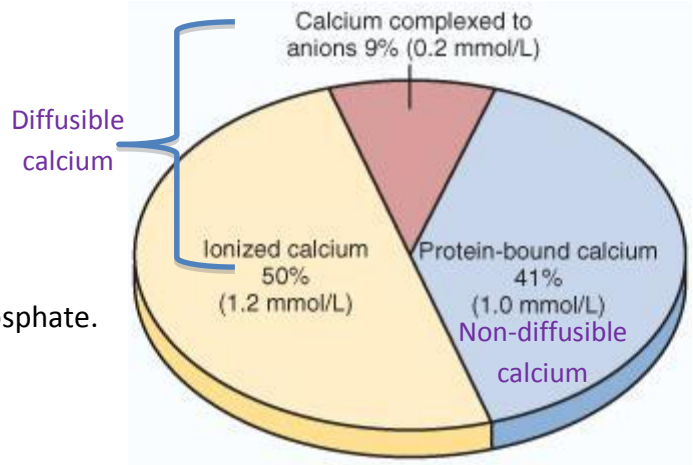
❖ Distribution of Ca++in ECF:

- Total plasma calcium= 9-10.5 mg/dl

It has 3 forms:

1- Non diffusible 41% :Protein-bound calcium
"will not diffuse through the capillary membrane"

2- Diffusible 59%:
   1- 50%: Ionized calcium "free"
   2- 9%: Calcium complexed to anion eg: citrate & phosphate.



Protein-bound calcium:

- Most of this calcium is bound to albumin & much smaller fraction is bound to globulin.
- Binding of calcium to albumin is pH-dependent
  Eg: Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level.
  •When ionized calcium falls below normal, permeability of neuronal cell-membranes to sodium increases → depolarization →hyperexcitability of the nervous system → patients become prone to develop tetanic muscle contractions & seizures .

Physiological importance of Calcium

- Calcium salts in bone provide structural integrity of the skeleton.
- Calcium ions in extracellular and cellular fluids is essentialto normal function for the biochemical processes:
  –Neuromuscular excitability
  –Hormonal secretion
  –Enzymatic regulation
  –Blood coagulation
  –Second messenger

High blood calcium→ CNS depressed
Low blood calcium→ CNS excited

Phosphate

- Phosphorous is an essential mineral necessary for ATP, cAMP second messenger systems, and other roles
- PO4plasma concentration is around 4 mg/dL.
- Most of it is ionized (diffusible) → around 50% of total
- The remainder (50%) and much less of it is un-ionized (non-diffusible) and protein-bound
- Calcium is tightly regulated with Phosphorous in the body.

Calcium metabolism

Source	Daily requirements	Absorption
•**Milk** •**dairy products** •**Fish**	•Infants & adults→12.5 -25 mmol/day •Pregnancy,lactation&after menopause→ 25-35 mmol/day	•**Duodenum:** active transport •**small intestine:**concentration gradient

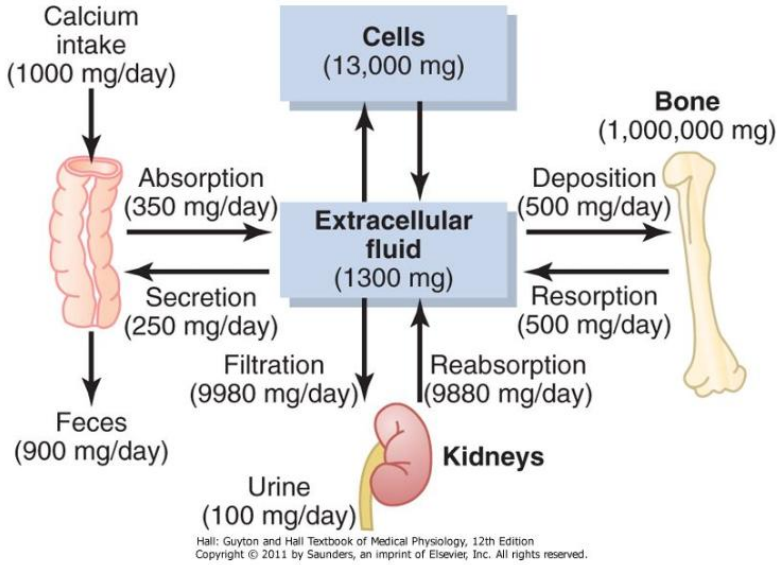


Figure 79-3 Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Regulation

- Total plasma calcium= 9-10.5 mg/dl

If Total plasma calcium> 10.5mg/dl →Renal stone and cardiac arrhythmias

If Total plasma calcium <9mg/dl→ Tetany

◆ Regulation of plasma calcium and phosphate concentrations:

- Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium.
- Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations.

◆ Hormonal Regulation of Calcium

- 3 principal hormones regulate serum Ca++ level:
- 2 of them **increase** it:

1- **Vitamin D3**
2-**Parathyroid hormone** > **Increase** Ca++ level

2- **Calcitonin**→ **decrease** Ca++ level

Vitamin D
1,25Dihydroxycholecalciferol

Vitamin D3 increases Ca^{++} level by :

1- ↑Ca^{++} absorption from the intestine

2- ↑Ca^{++} resorption from the bone (by increasing osteoclastic number & activity)

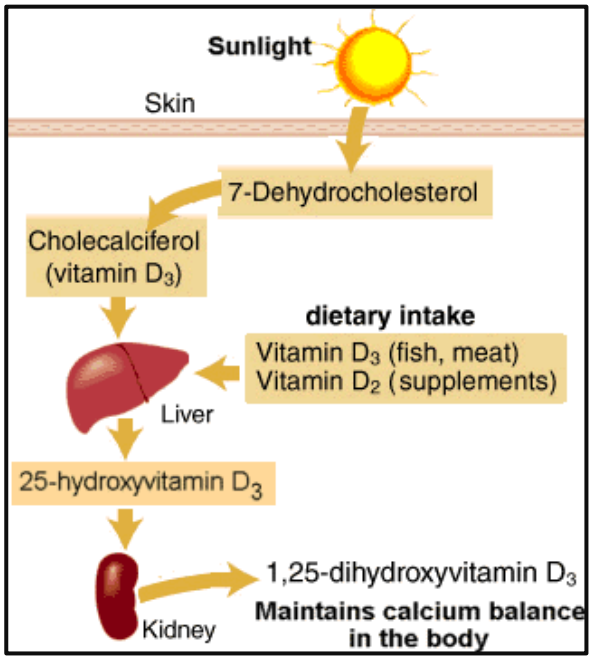
3- ↑Ca^{++} reabsorption by the kidney

Humans acquire vitamin D from two sources →

(1) Ingestion in diet (food)

(2) Skin : Vitamin D is produced in the skin by ultraviolet light.

* PTH stimulates Vit D synthesis



Mechanism of activation the vit.D

- Keratinocytesin the skin synthesize:7-dehydrocholesterol.
- 7-dehydrocholesterol is photo converted (by UV light in skin) to Cholecalciferol (previtaminD3) ,
- This form of Vitamin D is inactive, it requires two hydroxylation reactions→ the first one occurs in the liver and the second one in the kidney
- PTH stimulates Vit D synthesis

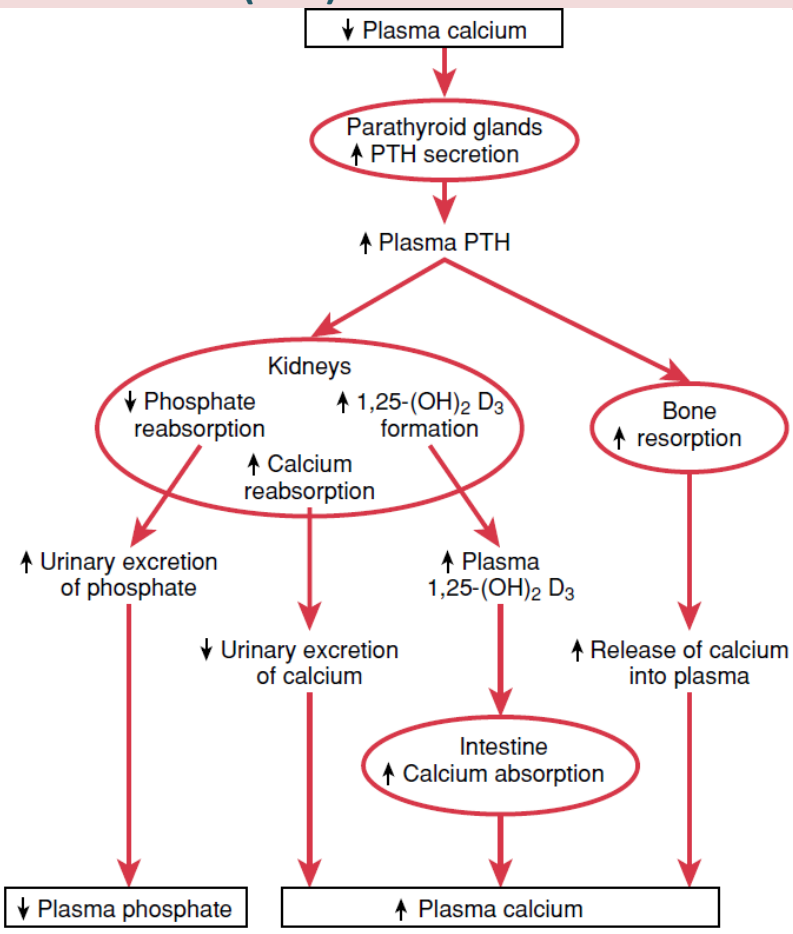
(Keratinocytes: is the predominant cell type in the epidermis, the outermost layer of the skin)

Parathyroid hormone (PTH)

Polypeptide hormone secreted by Parathyroid Glands.

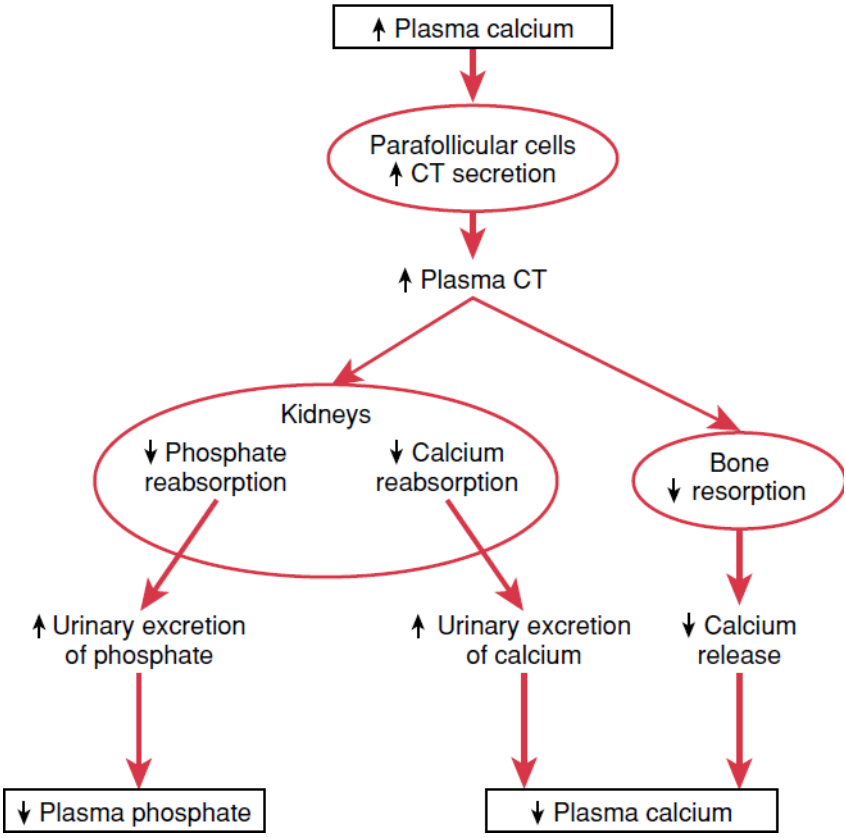
- Acts on: Bone, Kidney&Intestine to increase calcium level.

Effect of Ca level on PTH:



Calcitonin

- Polypeptide hormone secreted by Parafollicular (C) cells of Thyroid Gland.
- **Decrease** blood Ca++level very rapidly within minutes:
  - High plasma Ca^{++} → increased Calcitonin secretion:



  - **On bone:** inhibits osteoclasts activity & formation → inhibition of bone resorption → (1) increases bone formation(deposition)
    (2) Decreases blood Ca^{++} level.
    - Thus calcitonin plays a central role in bone re-modelling.

  - **On kidney:**
    - ↓Ca++ reabsorption
    - ↑Ca++ excretion (in addition to phosphate)

Abnormalities

Rickets (in children)

- Cause: lack of vitamin D in children leading to calcium/phosphate deficiency in ECF.
- Most affected areas:
  -Metaphyses of long bones subjected to stress →
  - Wrists - Knees - Ankles
- Features: -Low plasma calcium and phosphate
  -Weak bones
  -Bowed legs(Due to the effect of weight bearing on the legs)
  -Tetany
  -Delayed dentition(delayed teething)
  -Swelling of wrists and ankles
  -Short stature.

Osteomalacia-"Adult Rickets".

An adult disease characterized by a gradual softening and bending of the bones due to Serious deficiencies of both vitaminD and calcium occasionally occur as a result of steatorrhea (failure to absorb fat "vitD is a fat soluble").

Disorders of parathyroid hormone secretion

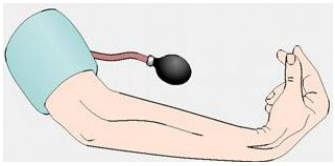
Hypoparathyroidism

- **Causes:**
  - Abnormal parathyroid gland → Reduced or absent synthesis of PTH.
  - Inadvertent (by mistake) removal of parathyroid gland during thyroid surgery.
    (This may lead to Tetany(increased excitability & hypersensitivity of nerves and muscles)) .
  - Autoimmune.
- **Signs & symptoms**(due to hypocalcaemia):

-Positive Chvostek's (facial muscle twitch) sign
-Positive Trousseau's (carpal spasm) sign
-Delayed cardiac repolarization with prolongation of the QT interval
-Paresthesia
-Tetany: Tetany can be overt"ظاهر"or latent"خفي"by using these 2 tests u can check if there is a latent tetany or not:

- Chvostek's sign:
  Tapping the facial nerve as it emerge from the parotid gland in front of theear →causes contraction of facial muscles.
- Trousseau's sign:
  Arresting (stopping) blood flow to the forearm for few minutes (e.g., by sphygmomanometer) →causes flexion at the wrist, thumb and metacarpophalangeal joints.






Hyperparathyroidism (Excess PTH)

- Primary: excess PTH secretion due to an abnormality of the parathyroid gland .Eg: Adenoma (tumor) of parathyroid gland
- Secondary(compensatory): excessive secretion of parathyroid hormone (PTH) in response to hypocalcaemia (low blood calcium levels).
  - Causes of Secondary hyperparathyroidism:
    - Low calcium diet
    - Pregnancy
    - Lactation
    - Rickets
    - Osteomalacia
    - Chronic renal failure→↓1,25(OH) –D3 synthesis
- Manifestations:
  - Hypercalcemia↑Ca2+
  - Hypophosphemia↓PO-4
  - Kidney: Hypercalciuria, Polyuria, polydipsia and renal stones.
  - Demineralization of bone → multiple bone cysts (osteitis fibrosa cystic)
  - Rickets or Osteomalacia.
  - GIT: Nausea, vomiting, indigestion, constipation, peptic ulcer, pancreatitis.
  - Musculoskeletal: Proximal muscle weakness.
  - Precipitation of calcium in soft tissues occur when Ca2+ > 17mg/dl.
  - CNS: Depression, memory loss, psychosis and coma.

Summary

- Total Ca++ in blood is 10mg/dl(9-11 mg/dl)
  1. Free ionized " active " (5 mg/dl)
  2. Non free, unionized " bounded "
     i. Protein-bound ca (40%) mainly bound to albumin
     ii. Complexed salt (10%) mainly bound to citrate & phosphate
- Binding of calcium to albumin is PH dependent
  High PH (alkalosis)→decreases ionized calcium level

- Hypocalcaemia→increase neuromuscular excitability →Tetany
- Hypercalcaemia→decrease neuromuscular excitability →cardiac arrhythmias

- Po4 plasma concentration is around 4mg/dl

- Hormonal regulation of calcium depend on 3 hormones
  1. Vitamin D3 & PTH(increase Ca)
  2. Calcitonin(decrease Ca)

- Vitamin D sources : 1. Food 2. Skin
- Actions of PTH on kidney: inhibition of phosphate reabsorption and stimulation of Ca++ reabsorption.
- PTH stimulates vitamin D synthesis
- 1.25-(OH)2- cholecalciferol is the active form of vit D
- Vitamin D deficiency lead to :
  1. Rickets(inchildren)
  2. Osteomalacia(in adults)

For more details http://advan.physiology.org/content/275/6/S206.full.pdf
(REGULATION OF CALCIUM AND PHOSPHATE Homeostasis, Linda)

Question

1. Which one of the following is a normal level of plasma calcium ?
    A. 6 mg/dl
    B. 8 mg/dl
    C. 10 mg/dl
    D. 12 mg/dl

2. Which of the following is an effect of Parathyroid hormone (PTH)?
    A. It decreases Calcium metabolization from bone
    B. It increases renal excretion of Calcium
    C. It decreases absorption of Calcium from intestine
    D. It increases renal excretion of phosphate

3. Which of the following hormones decreases plasma Calcium ?
    A. Vitamin D
    B. PTH
    C. Calcitonin
    D. Thyroxine

4. Which of the following occur in case of decreased plasma Ca++ conc. [hypocalcaemia]?
    A. Decrease excitability of nerve and muscle cell membranes
    B. Cardiac arrhythmia
    C. Increase excitability of nerve and muscle cell membranes
    D. constipation

5. In which of the following conditions positive chvostek sign occurs?
    A. Cretinism
    B. Pituitary dwarfism
    C. Hypocalcaemia
    D. DM

Answers : C , D , C , C , C