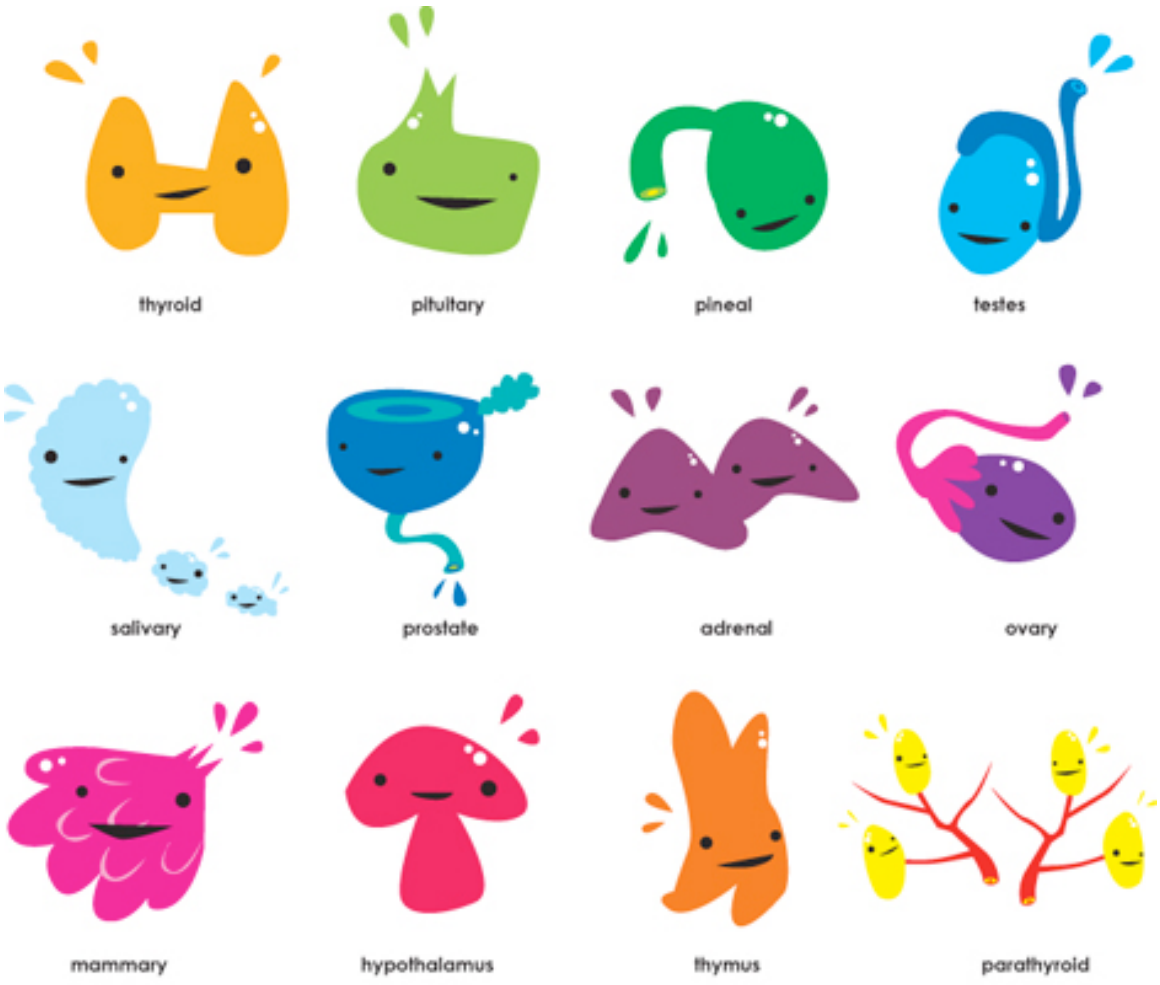
Lecture 8 & 9: Calcium Homeostasis & Parathyroid Disorders



Note: 1) This is a rearrangement of the slides + Few notes

2) Focus on every figure and graph. Do not ignore them!

notes are in purple

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CALCIUM HOMEOSTASIS

- **Roles of Body Calcium:**
  - ✦**Calcium salts in bone provide structural integrity of the skeleton**
  - ✦**Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes:**
    - **– Neuoromuscular excitability: Ca regulates Potassium permeability. E.g. ↓ plasma Ca >> >>hyper-excitability of muscles.**
    - **– Hormonal secretion: E.g. insulin secretion depends on Ca.**
    - **– Second messenger: in phospholipase C mechanism**
    - **– Blood coagulation**
    - **– Enzymatic regulation**
    - **– Milk production.**
    - **– Maintains normal permeability of cell membranes.**

- **Serum Calcium:**

Total Plasma Calcium = 9 - 11 mg/dl
= 2.4 mEq/L

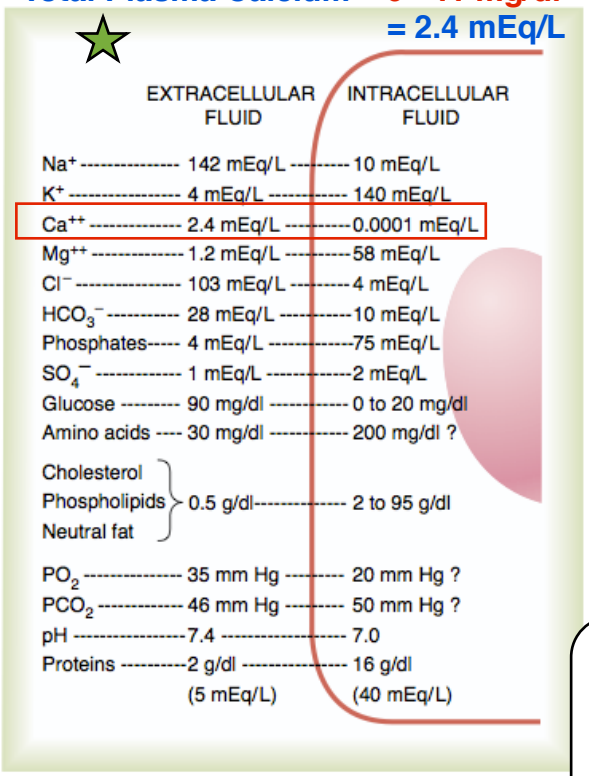
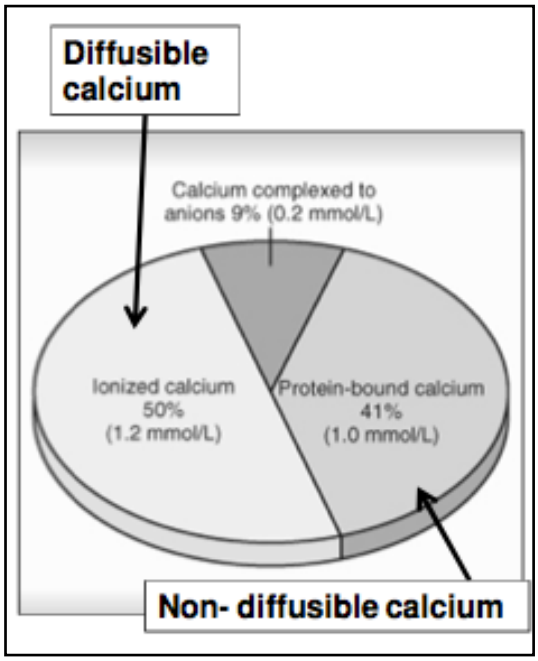


Figure 4–1

Chemical compositions of extracellular and intracellular fluids.



Extracellular **Ca** [Plasma **Ca**]: must be tightly regulated within a narrow range [9-11 mg/dl]

Intracellular **Ca**: is negligible because all **Ca** is stored in endoplasmic reticulum. **Ca** has a harmful effect on cells.

Total diffusible	**60%**	**1.34**
Ionized (Ca^{2+}) it's only the free calcium that participate in biological processes	**50%**	**1.18**
Complexed to HCO_3^-, citrate, etc [Calcium bound to anions]	**10%**	**0.16**
Total nondiffusible (protein-bound)	**40%**	**1.16**
Bound to albumin	**80%**	**0.92**
Bound to globulin	**20%**	**0.24**
Total plasma calcium	**100%**	**2.50**

- **Calcium Metabolism:**

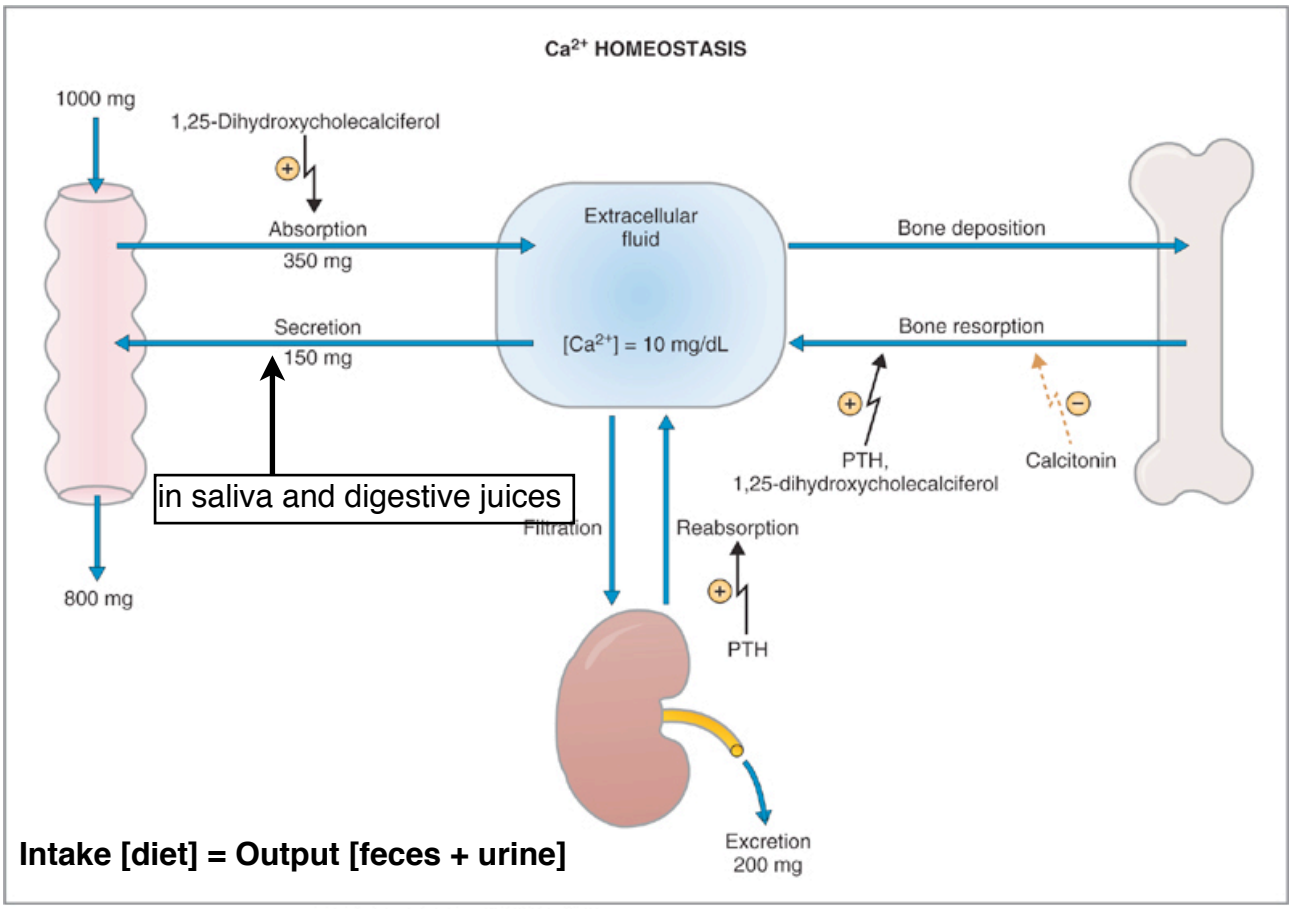
✦**Dietary Calcium**

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

•milk

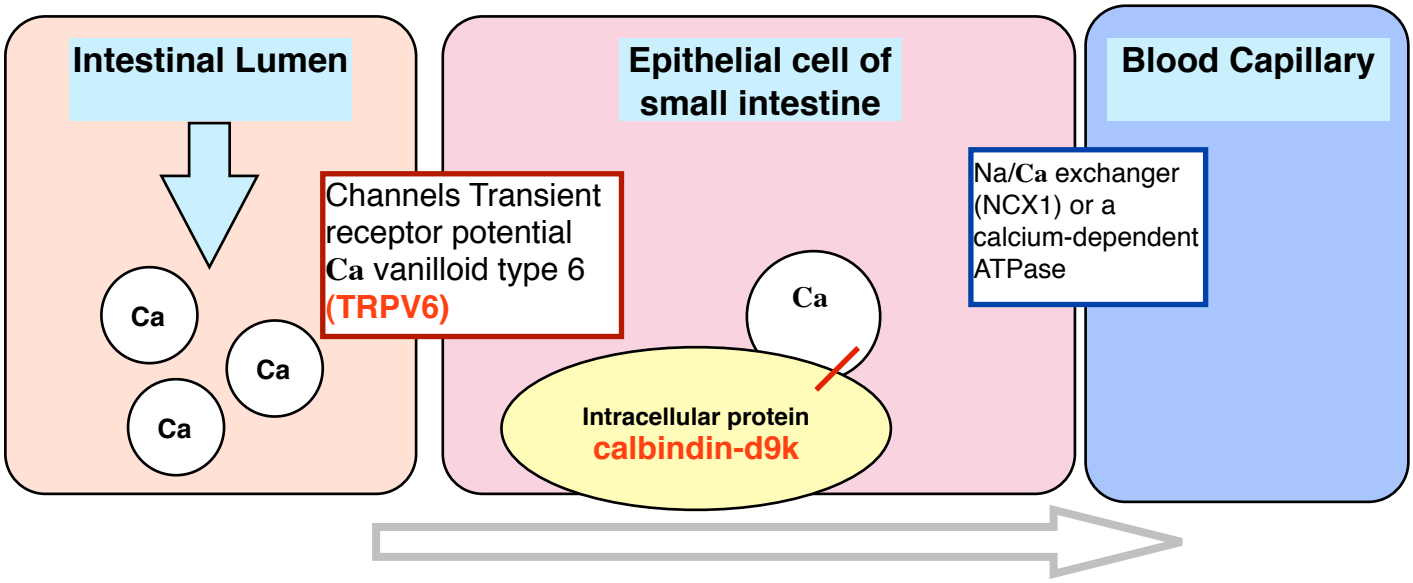
•dairy products

Uptake of calcium by active transport predominates in the duodenum and jejunum; in the ileum, simple diffusion predominates



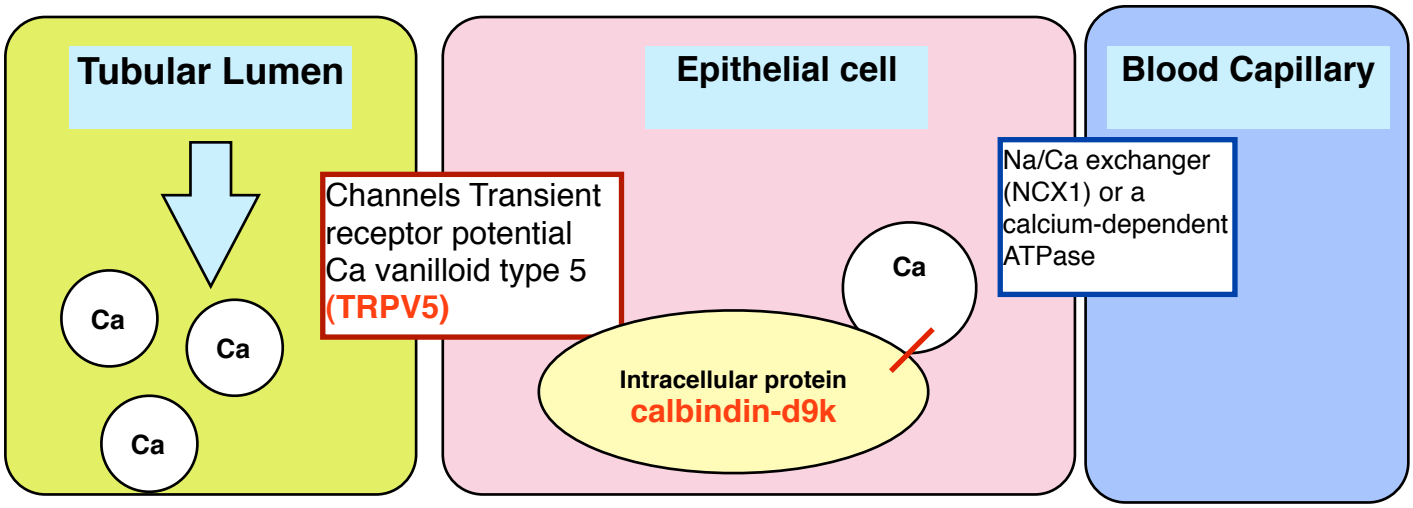
Intake [diet] = Output [feces + urine]

✦Calcium Absorption in Intestine:



Ca passes from the intestinal lumen to the epithelial cells passively through TRVP6
In the intestinal epithelium Ca binds to an intracellular protein called calbindin-d9k which protects the cell from Calcium harmful effects
It then passes actively to the blood capillary through Ca-ATPase Active transporor NCX1 countertransport

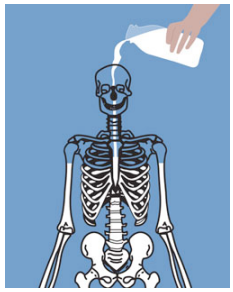
✦Calcium Reabsorption in Nephrone:



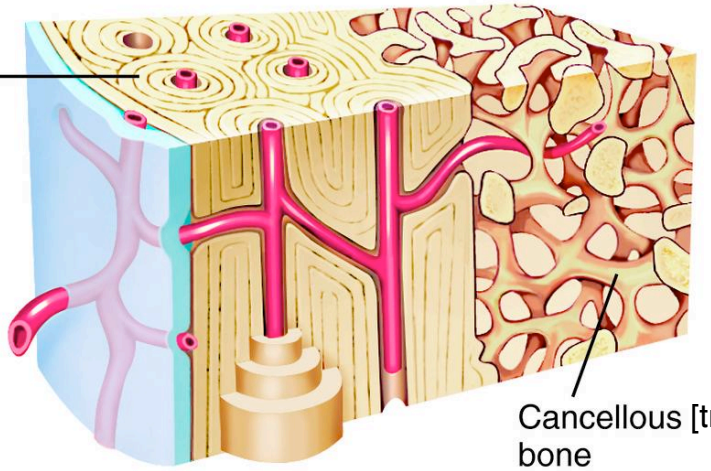
Ca passes from the intestinal lumen to the epithelial cells passively through TRVP5
In the intestinal epithelium Ca binds to an intracellular protein called calbindin-d9k which protects the cell from Calcium harmful effects
It then passes actively to the blood capillary through Ca-ATPase Active transporor NCX1 countertransport

-60% of Ca in glomerular filtrate is reabsorbed in the proximal tubules
-30% loops of Henle,
-10% in the late distal tubules and early collecting ducts

Only the **10% of DCT & CT** is under hormonal regulation and depends on Ca conc. in blood



- **Physiology of Bone Calcium:**
  - ✦**two types of bone:**



- Composed of osteons and supplied by central artery in Haversian canal

- Found peripherally [near periosteum]

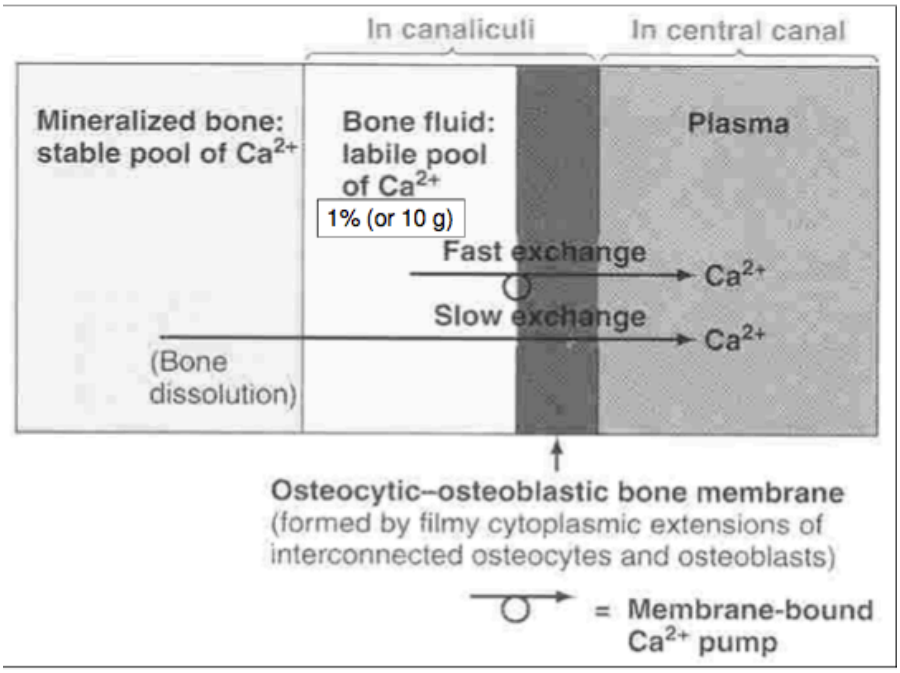
ECF is bathing the cells and supply is by diffusion

✦ **bone is composed of:**

1) **Organic Matrix 30%** responsible of tensile strength
   - **Collagen Fibers**
   - **Ground Substance**
     - **ECF**
     - **Proteoglycans**

2) **Bone cells (2% of matrix):** **Osteocytes** [Source of Fast Pool of Ca] **Osteoblasts** [bone forming cells] **& osteoclasts** [bone resorping cells]

3) **Bone Salts 70%** responsible of contractile [compressive] strength
   - **Salts of Ca & PO4 • Amorphous form • Crystalline Form (Hydroxyapatite)**



remember Ca pump is associated with fast exchange

Bone fluid is the Ca ready for exchange to correct any abnormality rapidly.
In chronic abnormalities bone fluid is depleted and mineralized bone will be affected

Any hormone has an effect on bones its receptor will be on osteocytes or osteoblasts because they're in contact with plasma.

B. Brief overview of bone physiology (*Fig. 1*)

1. Osteocyte: A major source of endogenous Ca^{2+} (via demineralization) and primary site of Ca^{2+} deposition (via mineralization)

2. Osteoblast: The mediator of bone mineralization

   - Synthesis of collagen by osteoblast with formation of extracellular matrix
   - Precipitation in this matrix of $Ca_{10}(PO_4)_6(OH)_2$ — hydroxyapatite

3. Osteoclast: Mediator of bone demineralization

   - Release of acid phosphatase and hyaluronic acid
   - Decrease in pH causes solubilization of hydroxyapatite with release of Ca^{2+} and PO_4^{3-}

REGULATION OF PLASMA Ca AND P04 CONCENTRATIONS

- **Non-hormonal Mechanisms:** can rapidly buffer small changes in plasma concentrations of free Calcium: First Line of Defense
  ➡ Mainly buffer system is through Ca-binding proteins and anions: in hypocalcemia Ca dissociate from anions & proteins to increase free Ca, and vice versa.

- **Hormonal Mechanisms:** provide high-capacity, long-term regulation of plasma Calcium and Phosphate concentrations Second Line of Defense

- **HORMONES REGULATING Ca:**
  -Three Hormones
  (1) Vitamin D
  (2) Parathyroid Hormone PTH
  (3) Calcitonin

1st: Vitamin D

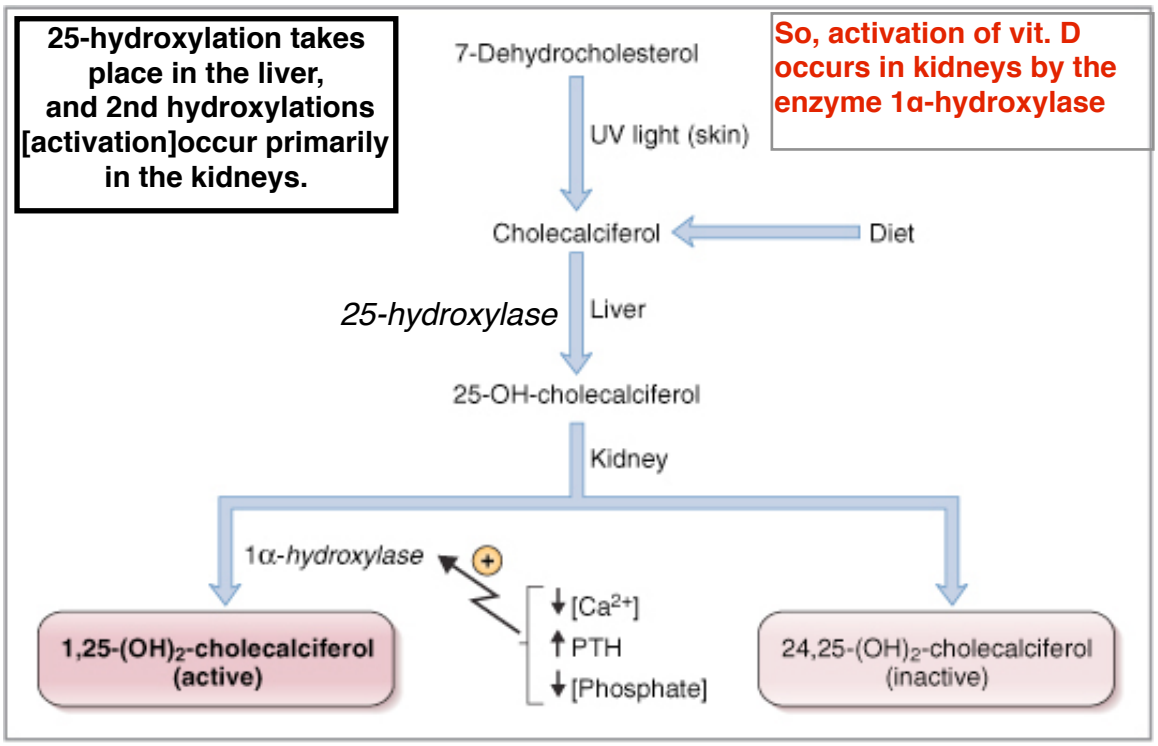
- **Source:** synthesized in the skin by sunlight (UV)
- **Chemistry:** considered a steroid hormone
- **MolecularWeight:** 384.6
- **Half Life:** of active vit. D is 2-3 weeks
- **Blood Levels:** 50–80 ng/ml (125–200 nmol/L)

From biochemistry lecture

•Formation and hydroxylation of vit D3.

25-hydroxylation takes place in the liver, and 2nd hydroxylations [activation]occur primarily in the kidneys.

So, activation of vit. D occurs in kidneys by the enzyme 1α-hydroxylase



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•Actions of vit D3.

normally it's a GI hormone, when pathologically increased it dissolves the bones)

1) On Calcium:

↑ **Absorption from Bone**

↓ **Renal Excretion** [↑reabsorption]

↑ **Absorption from GIT [main action]**

Net effect >> ↑ plasma Ca

2) On Phosphate:

↑ **Absorption from Bone**

↓ **Renal Excretion** [↑reabsorption]

↑ **Absorption from GIT**

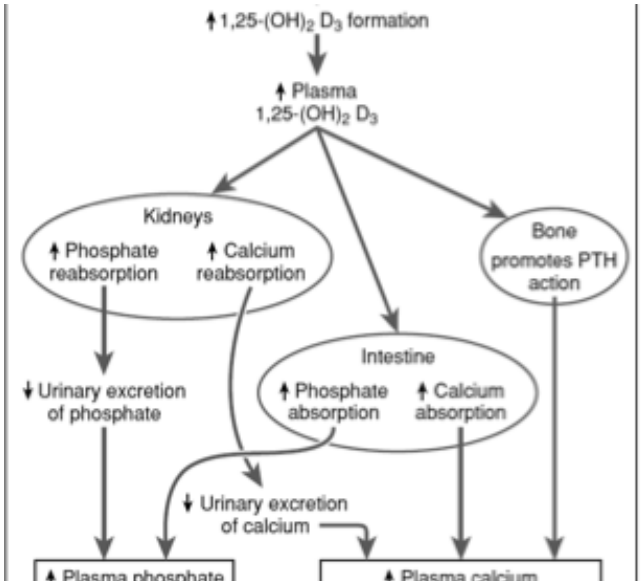
Net effect >> ↑ plasma P

-Mechanism of vit D. action on GIT & kidneys:

GIT: increase Ca-ATPase and **TRPV6** molecules **\ Kidneys: increase TRPV5 expression**

Also it induces synthesis of intracellular protein **calbindin**

In renal failure:
Kidneys don't activate enough vit D = no calcium reabsorption = low calcium and high PTH = bone diseases
That's why renal failure patients present with bone problems



PHOSPHATE: **Total body phosphorus is 500 to 800 g (16.1–25.8 mol), 85–90% of which is in the skeleton.**

- **Phosphate is found in ATP cyclicadenosinemonophosphate(cAMP), 2,3-diphosphoglycerate** & Many other proteins
- **Total plasma phosphorus is about 12 mg/dL, with two-thirds of this total in organic compounds and the remaining inorganic phosphorus (Pi) mostly in** PO_4^{3-}, HPO_4^{2-}, and $H_2PO_4^-$.
- **It is reabsorbed by cotransport with Na in PCT in luminal border (Na/Pi)**
- **Its reabsorption is Hormonally controlled**
- **Reabsorbtion increased by Vit D and decreased by Parathyroid Hormone. difference between PTH & Vit. D is PTH causes phosphaturia while Vit. D doesn't!!**

2nd: Parathyroid Hormone PTH

- **Source: Parathyroid Gland from chief cells.**
- **Chemistry: Polypeptide (84 aa)**
- **Molecular Weight:** 9500
- **Plasma Levels:** 10 to 55 pg/mL
- **Half Life: 10 min**
- **Fate Liver & Kidneys**

- **Actions of PTH: Targets are Bones & Kidneys and indirectly GIT**

1) On Calcium:

↑ **Absorption from Bone**

↓ **Renal Excretion** [↑reabsorption from DCT & CT]

↑ **Absorption from GIT** [indirectly via active vit. D] *

Net effect >> ↑ **plasma Ca**

2) On Phosphate:

↑ **Absorption from Bone**

↑ **Renal Excretion** [↓reabsorption] >> phosphaturia

↑ **Absorption from GIT**

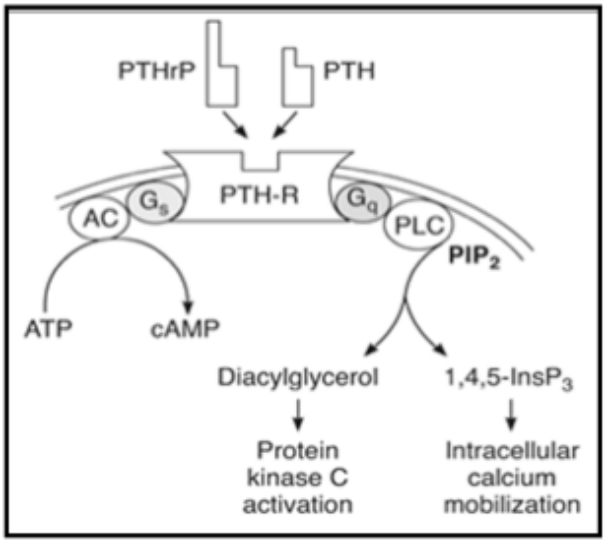
Net effect >> ↓ **plasma P**

absorbed P < excreted P

*PTH stimulates renal 1α-hydroxylase, the enzyme that converts 25-hydroxycholecalciferol to the active form, 1,25-dihydroxycholecalciferol. In turn, 1,25-dihydroxycholecalciferol stimulates intestinal Ca^{2+} absorption.

-Mechanism of PTH action:

Through two mechanisms; ① is adenylyl cyclase mechanism via Gs protein and cAMP as a 2nd messenger and ② phospholipase C mechanism via Gq protein and Ca as a 2nd messenger.



-Action of PTH on Bone:

Rapid Phase of Calcium and Phosphate Absorption—Osteolysis.

•Cell membranes of both osteoblasts and osteocytes have receptors for PTH
•PTH can activate the calcium pump strongly, causing rapid removal of calcium phosphate salts.
•PTH is believed to stimulate this pump by increasing the calcium permeability of the bone fluid side of the osteocytic membrane, thus allowing calcium ions to diffuse into the membrane cells from the bone fluid.
•Then the calcium pump on the other side of the cell membrane transfers the calcium ions the rest of the way into the extracellular fluid.

Slow Phase of Bone Absorption Release—Activation of the Osteoclasts

- Osteoclasts do not themselves have membrane receptor proteins for PTH Rather activated osteoblasts and osteocytes send a secondary but unknown "signal" to the osteoclasts
- Activation of the osteoclastic system occurs in two stages: (1) immediate activation of the osteoclasts that are already formed and (2) formation of new osteoclasts.
- After a few months of excess PTH, osteoclastic resorption of bone can lead to weakened bones and secondary [compensatory] stimulation of the osteoblasts Therefore, the late effect is actually to enhance both osteoblastic and osteoclastic activity.

Summary:

Rapid phase* = *Osteolysis

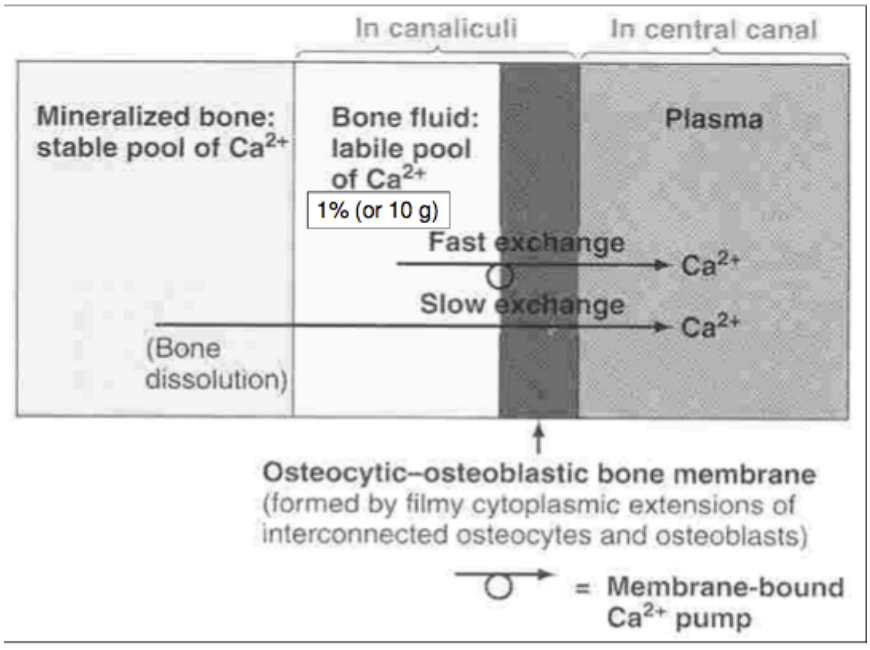
‣Through osteoblasts & osteocytes [osteoblastic osteocytic bone membrane]

‣PTH activate Ca pump causing absorption of Ca from bone fluid to plasma

Slow phase* = *activation of osteoclasts

‣Osteoclasts are activated by 2ndry signals from osteoblasts & osteocytes
‣New osteoclasts are formed

‣Those osteoclasts absorb Ca from mineralized bone to plasma



• **Regulation of PTH Secretion:**

-PTH secretion is regulated ONLY by plasma **Ca** concentration.

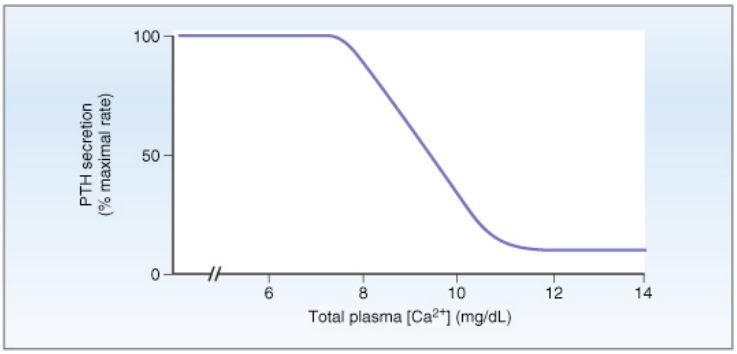
When **Ca** conc. is in the normal range (i.e., 10 mg/dL) or higher, PTH is secreted at a low (basal) level.

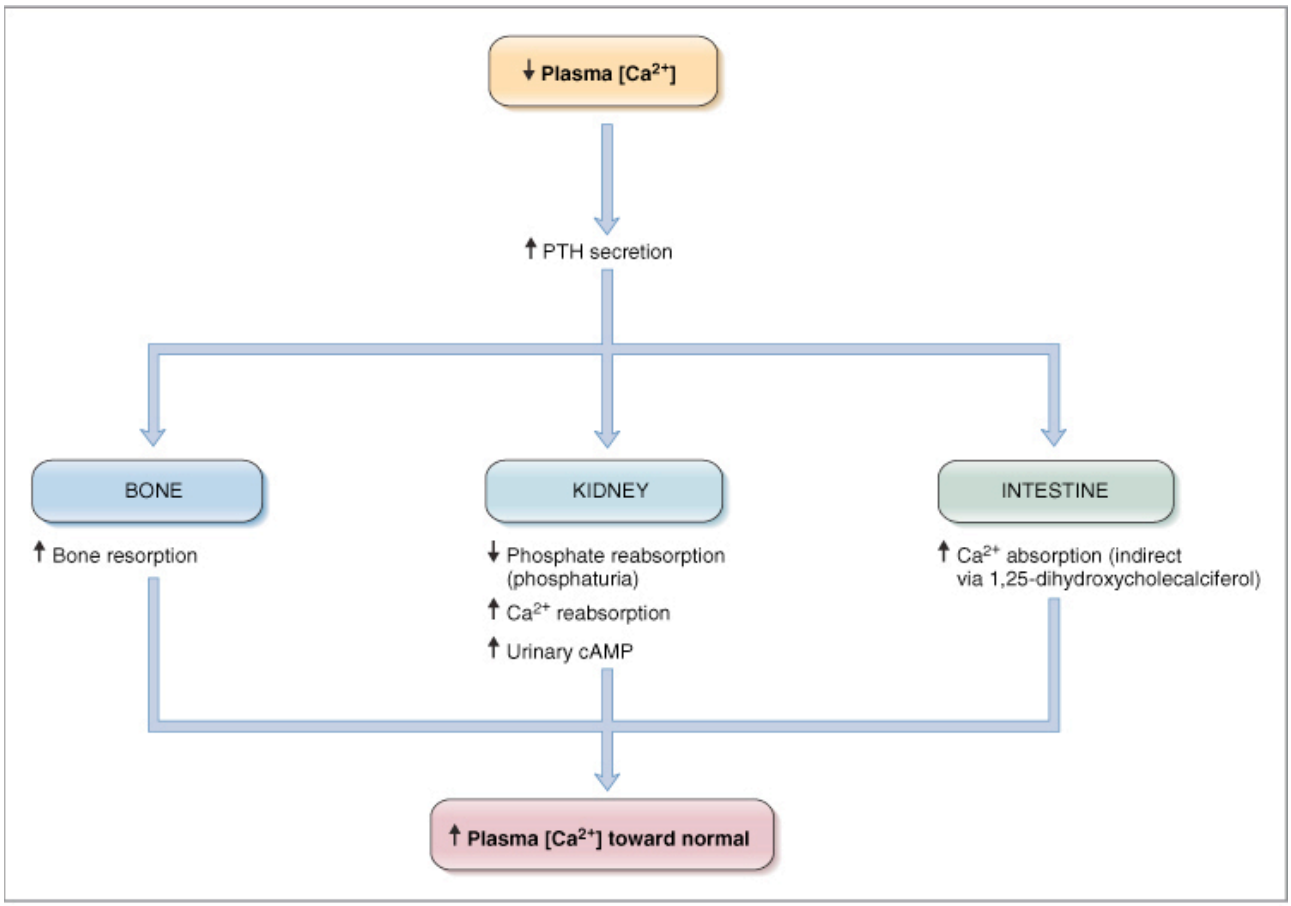
- However, when plasma **Ca** conc. decreases to less than 10 mg/dL, PTH secretion is stimulated, reaching maximal rates when the **Ca** concentration is 7.5 mg/dL.

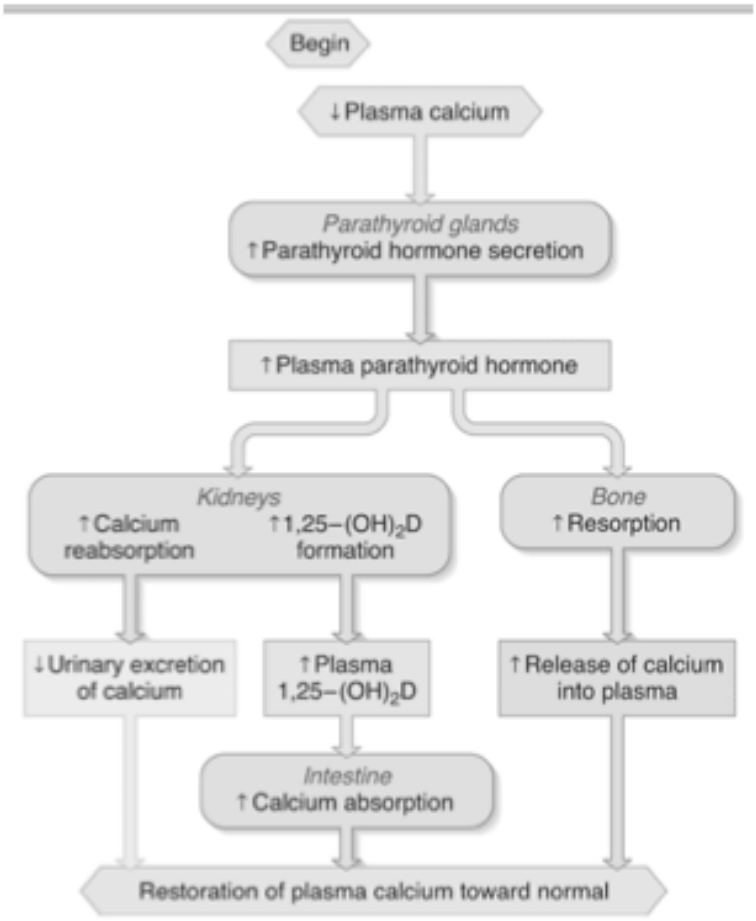
- The response of the parathyroid glands to a decrease in **Ca** concentration occurs within seconds. Furthermore, the faster the ionized **Ca** falls, the greater the PTH secretory response.

Summary

- **Normal plasma Ca = inhibition of PTH secretion**
- **↓ plasma Ca >> stimulation of PTH secretion**







3rd: Calcitonin

- **Source: Parafolicular [C Cells] of Thyroid Chemistry**
- **Chemistry: Peptide 32-amino acid**
- **Molecular weight: 3400**
- **Primary Target: Bone**

•Actions of Calcitonin:

✦The major action of calcitonin is inhibition of osteoclastic bone resorption >> ↓ plasma Ca concentration. Also it inhibits formation of new osteoclasts.

Net result is reduced osteoclastic and osteoblastic activity

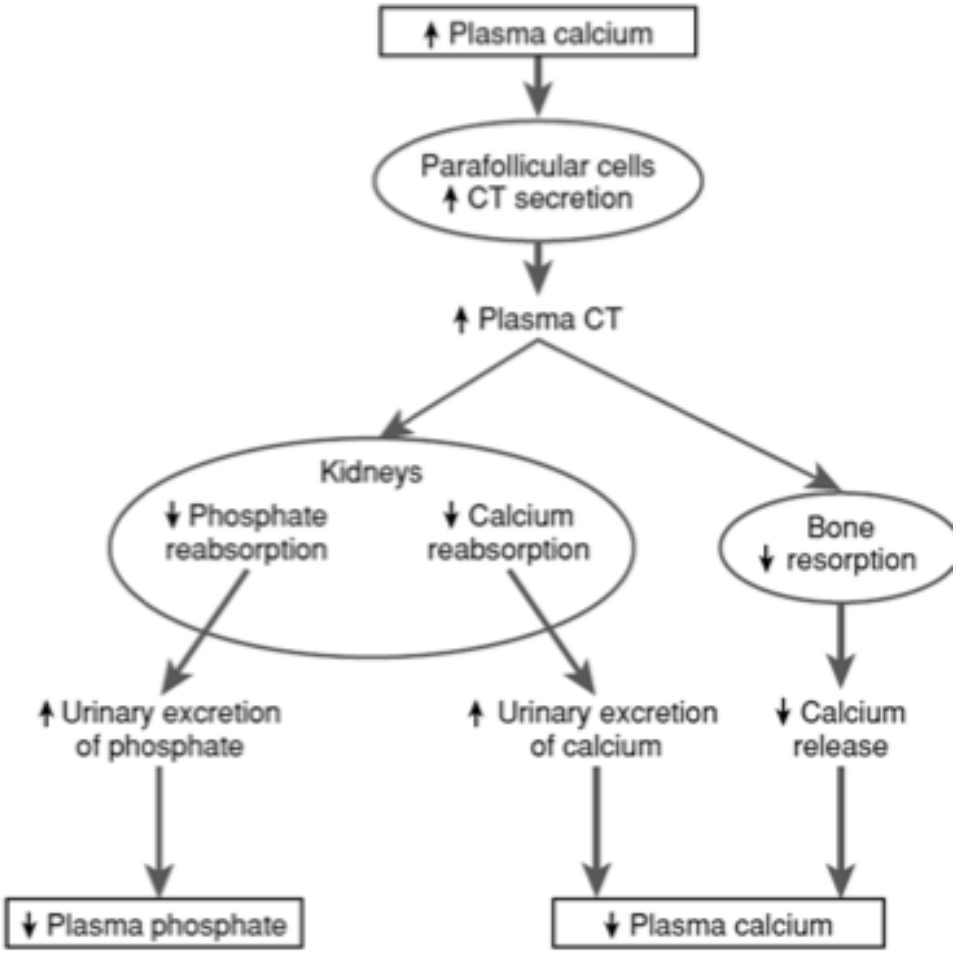
✦The minor action of calcitonin on Kidneys and GIT: ↓Calcium & ↓Phosphate reabsorption [increase Ca excretion]

Net effect >> ↓ plasma Ca

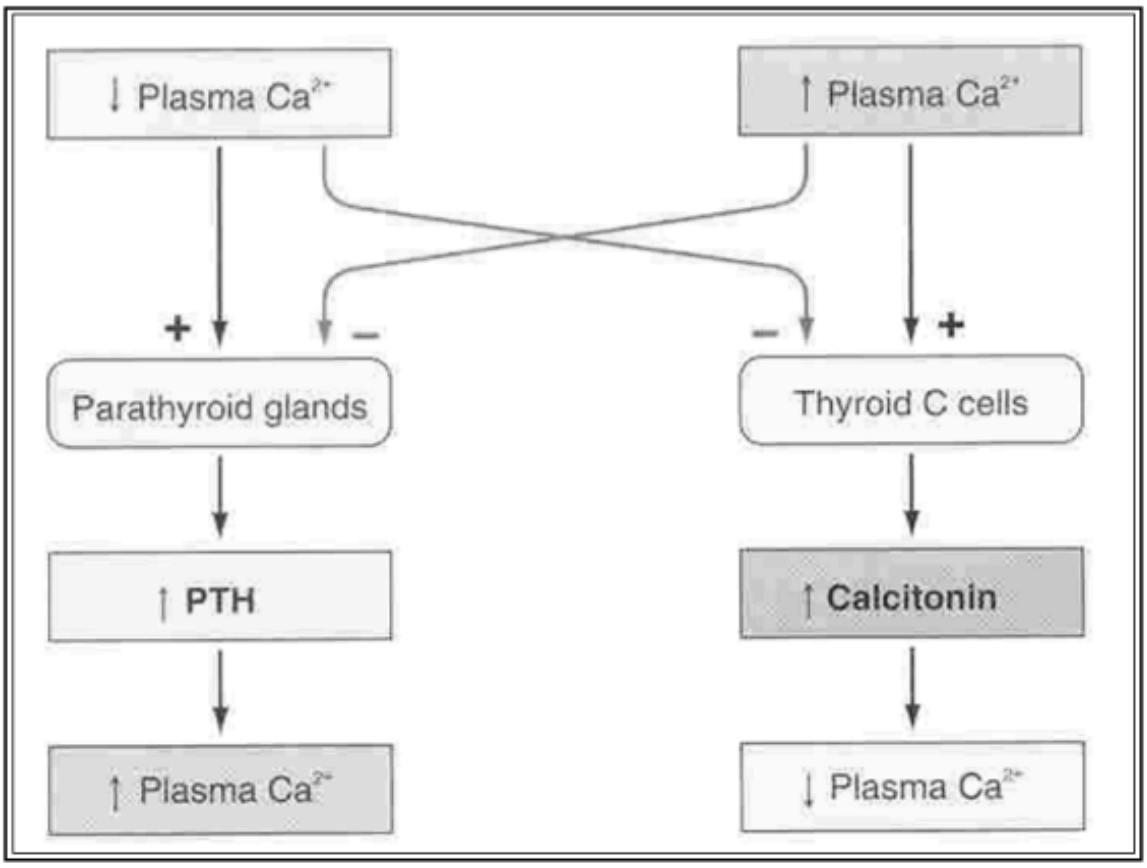
Because it only affects osteoclasts [slow exchange], calcitonin does not participate in the minute-to-minute regulation of the plasma Ca

• Regulation of Calcitonin Secretion:

The major stimulus for calcitonin secretion is increased plasma Ca concentration



Summary of PTH & Calcitonin Regulation:



DISORDERS OF PARATHYROID HORMONE SECRETION

Hypoparathyroidism

Causes Injury to the parathyroid glands (thyroid surgery) & Autoimmune.
[↓plasma calcium accompanies ↑plasma phosphate]

Signs & symptoms (due to **hypocalcaemia**)

1. **Tingling in the lips, fingers, and toes**
2. **Muscle cramps and pain in the face, hands, legs, and feet**
3. Dry hair, brittle nails, and dry, coarse skin
4. Cataracts on the eyes
5. Malformations of the teeth, including weakened tooth enamel
6. Loss of memory, Headaches
7. **sever muscle spasms(tetany) and convulsions**
8. **Death usually from respiration muscles spasm**

1,2&7 are due to hyperexcitability of muscles & nerves

Hypoparathyroidism :
specific indicators :
1-chvostek sign: twiching of the facial muscles elicited by tapping on the facial nerve.

2-Trousseau sign: carpopedal spasm upon inflation of a blood pressure cuff.

Treatment Calcium carbonate and vitamin D supplements

Hyperparathyroidism

- Causes - Primary hyperparathyroidism PTH secreting adenomas
  - Secondary hyperparathyroidism physiological **compensatory hypertrophy** of all parathyroids **because of chronic hypocalcaemia,** such as occurs in renal failure or vitamin D deficiency.

★ In Secondary hyperparathyroidism:

1) **PTH levels are raised but calcium levels are low or normal**
2)PTH falls to normal after correction of the cause of hypocalcaemia where this is possible.
3) Possible causes of 2ndry hyprPTHism: 1) Low calcium diet 2) Pregnancy 3) Lactation 4) Rickets 5) Osteomalcia 6) Chronic renal failure

a) Phosphateretention [hyperphosphatenemia]
b) ↓ 1,25(OH) – D3 synthesis

★ In Primary hyperparathyroidism Manifestations are:

- Hypercalcemia ↑ **Ca**
- Hypophosphemia ↓Po4
- Hypercalciuria: although PTH >>↓ Renal Excretion of Ca but high plasma **Ca** will be filtrated and excreted leading to high amount of **Ca** in urine. and what does **Ca** do in urine?
  Calcium stones in kidney
- Demineralization of bone >> multiple bone cysts (osteitis fibrosa cystic)
- Precipitation of calcium in soft tissues occur when **Ca** > 17mg/dl.

RICKETS AND OSTEOMALACIA

•Rickets (in children) and osteomalacia (in adults) result from **inadequate mineralization of new bone matrix (osteoid) such that the ratio of bone mineral to matrix is reduced. [loss of mineralized bone NOT matrix]**

•Defect in vitamin D availability or metabolism

•Plasma Concentrations of Calcium and Phosphate Decrease in Rickets due to decreased absorption of **Ca** [recall Vit. D action]

•In Vit. d deficiency, Plasma calcium is slightly depressed but plasma phosphate level is greatly depressed because parathyroid gland prevent calcium level level from falling by promoting bone absorption and increased parathyroid activity increases the excretion of phosphate in the urine.

• Causes:

-Deficient intake or absorption of vitamin D

Inadequate synthesis in skin, Low dietary intake, Malabsorption

-Defective 25-hydroxylation in liver

Chronic cholestasis (e.g. primary biliary cirrhosis) & Anticonvulsant therapy [hepatotoxic]

-Defective 1-alpha hydroxylation [activation] in kidney

Chronic kidney disease, Tubular disorders,Vitamin D-dependent rickets types I and II

-Inhibitors of mineralization

Fluoride, aluminium, bisphosphonates

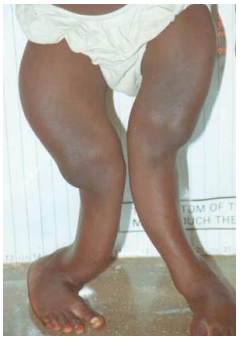
• Tetany in Rickets:

✦ **early stages: no tetany (PTH stimulate osteoclastic absorption of bone).**

✦**When the bones finally become exhausted of calcium >> Calcium level falls rapidly** during prolonged rickets, the compensatory PTH production causes extreme osteoclastic absorption of the bone)

✦**blood level of calcium falls below 7 mg/dl → signs of tetany:** (positive Chvostek's sign)

✦→**Death: tetanic respiratory spasm**



• Rickets (In children):

Results from calcium/phosphate deficiency in ECF. usually caused by lack of vitamin D.

Bowing of the long bones in the legs

• Osteomalacia-"Adult Rickets"(rare).

- serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat >> deficiency in lipid-soluble vitamins A-D-E-K)
- almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

• Treatment of Rickets Supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D.

OSTEOPOROSIS

•Osteoporosis is the most common of all bone diseases in adults, especially in old age.
•Osteoporosis involves a reduction in total bone mass with an equal loss of both bone mineral and organic matrix.
•The osteoblastic activity in the bone usually is less than normal, and consequently the rate of bone osteoid deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.

• Causes:

(1) Lack of physical stress on the bones because of inactivity
(2) Malnutrition (3) Lack of vitamin C
(4) Postmenopausal lack of estrogen
(5) Old age (6) Cushing's syndrome [hypercortisolism]

•Dual energy X-ray absorptiometry (DXA) measures is used in diagnosis.

Extra from Linda Costanzo's book:
Some factors that alter the form of Ca in plasma :

1) Changing in plasma protein concentration : will lead to alter the concentration of total Ca in the same direction (if it increased it will increased too)..

2) Changing in anion concentration : will lead to alter the ionized (free) Ca concentration , so if anions increased in blood the Ca will bind more to it which lead to decrease the free Ca in blood (opposite direction)

3) Acid-base abnormalities : will lead to alter the ionized (free) Ca concentration , in acidemia the (H) will bind more to albumin so the free Ca will increase , in alkalemia the (H) will be low so more Ca will bind to albumin and thus decrease the free Ca concentration.

Calcitonin is not the major controller of calcium in humans.
Thus, reduction of calcitonin secretion by removing the thyroid, or excess of calcitonin via c-cell tumors has little impact on plasma calcium (tumor marker)

Source: Physiology by Linda Costanzo

Ganong's Review of Medical Physiology