CALCIUM METABOLISM

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15/01/2015

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OVERVIEW ABOUT CALCIUM

- about 99% of Ca in our bodies is found in bones. The concentration of Ca in plasma is higher than in the interstitial fluid, intracellular concentration of Ca is considerably less.

Interactions

- Phosphate: ↓ calcium excretion in the urine
- Caffeine: ↑ urinary and fecal excretion of calcium
- Sodium: ↑ sodium intake, ↑ loss of calcium in urine
- Iron: calcium might have inhibitory effect on iron absorption

Storage of Calcium

- The primary site of storage is our bones (about 1000 grams).
- Some calcium is stored within cells (endoplasmic reticulum and mitochondria).
- Bone is produced by osteoblast cells which produce collagen, which is then mineralized by calcium and phosphate (hydroxyapatite).
- Bone is remineralized (broken down) by osteoclasts, which secrete acid, causing the release of calcium and phosphate into the bloodstream.
- There is constant exchange of calcium between bone and blood.

Excretion of Calcium

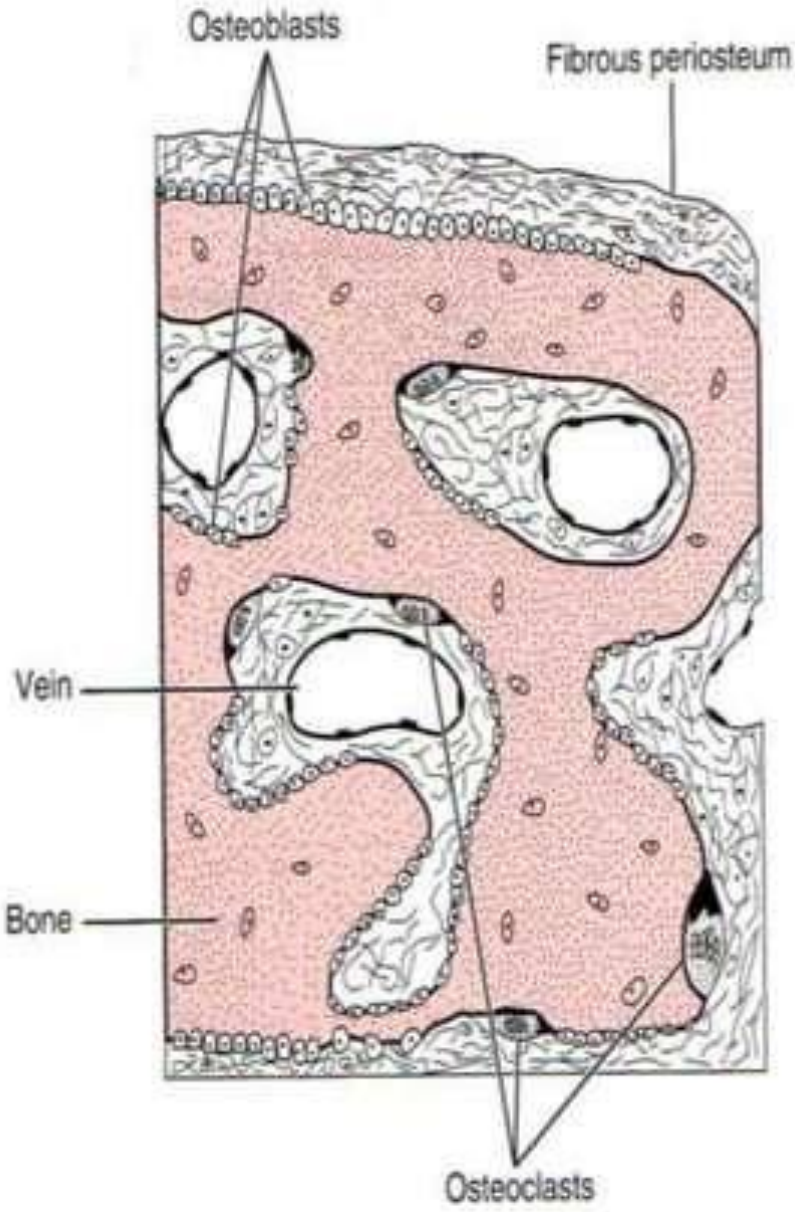
- The major site of Ca excretion in the body is the kidneys.
- The rate of Ca loss and reabsorption at the kidney can be regulated.
- Regulation of absorption, storage, and excretion of Ca results in maintenance of calcium homeostasis.

Calcium functions

- Major structural element in the vertebrate skeleton (bones and teeth) in the form of calcium phosphate ($Ca_{10}(PO_4)_6(OH)_2$ known as hydroxyapatatite
- Key component in the maintenance of the cell structure
- Membrane rigidity, permeability and viscosity are partly dependent on local calcium concs

Calcium functions (Bone)

- **Osteoclasts** (bone cells) remodel the bone by dissolving or resorbing bone
- **Osteoblasts** (bone forming cells) synthesize new bone to replace the resorbed bone
- Found on the outer surfaces of the bones and in the bone cavities



Calcium functions

Plays important regulatory roles in the body

A passive role:

- As a cofactor for many enzymes (e.g. Lipase) and proteins
- As component in the blood clotting cascade

An active role: as an intracellular signal

- In the relaxation and constriction of blood vessels
- In cell aggregation and movement
- In muscle protein degradation
- In secretion of hormones as insulin
- In cell division
- In nerve impulse transmission

Regulation of [Calcium]

- The important role that calcium plays in so many processes dictates that its concentration, both extracellularly and intracellularly, be maintained within a very narrow range.
- This is achieved by an elaborate system of controls

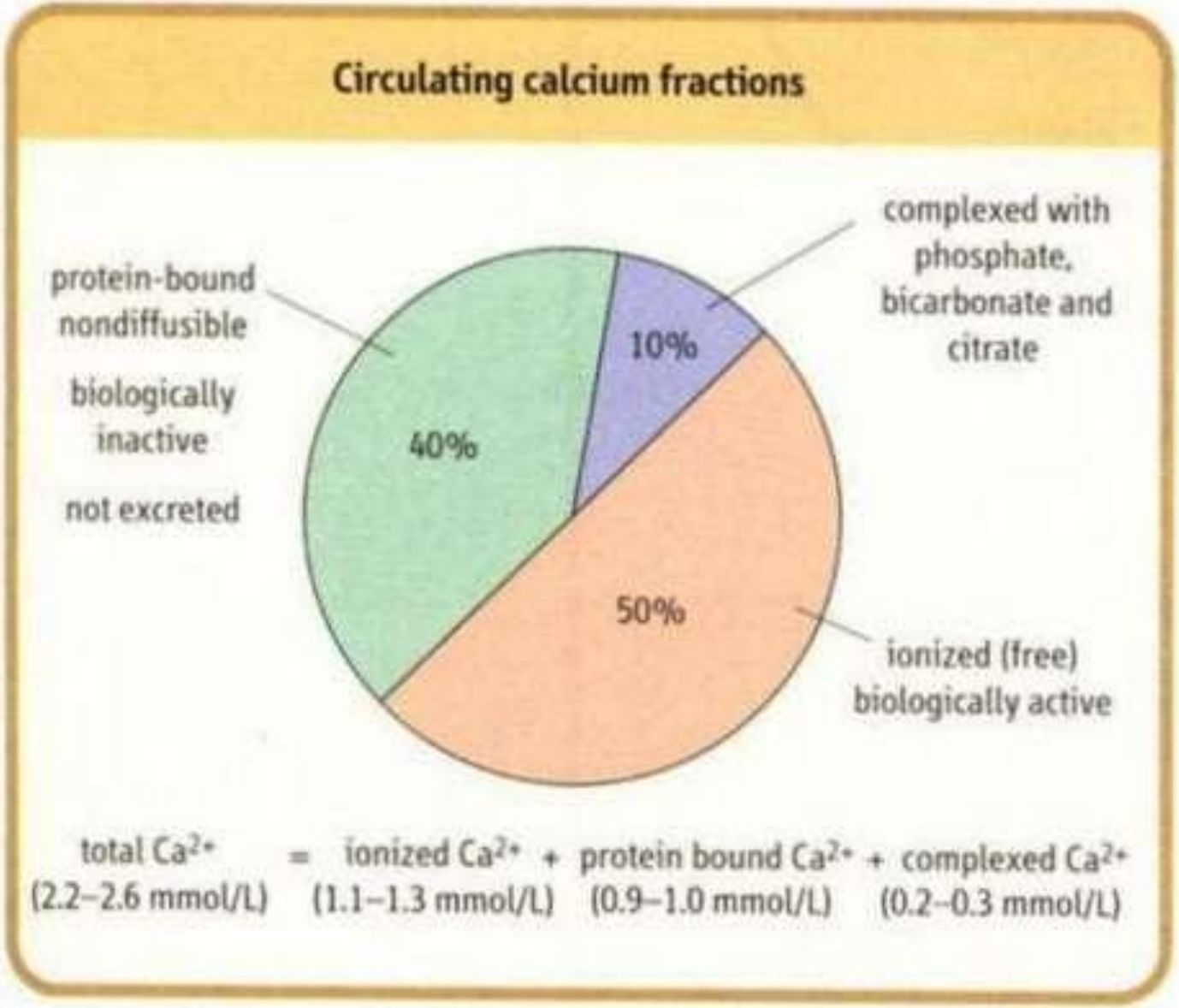
Regulation of Intracellular [Calcium]

- Control of cellular Ca homeostasis is as carefully maintained as in extracellular fluids
- $[Ca^{2+}]_{cyt}$ is approximately 1/1000th of extracellular concentration
- Stored in mitochondria and ER
- "pump-leak" transport systems control $[Ca^{2+}]_{cyt}$

Extracellular Calcium

- When extracellular calcium falls below normal, the nervous system becomes progressively more excitable because of increase permeability of neuronal membranes to sodium.
- Binding of calcium to albumin is pH dependent
- Acute alkalosis increases calcium binding to protein and decreases ionized calcium

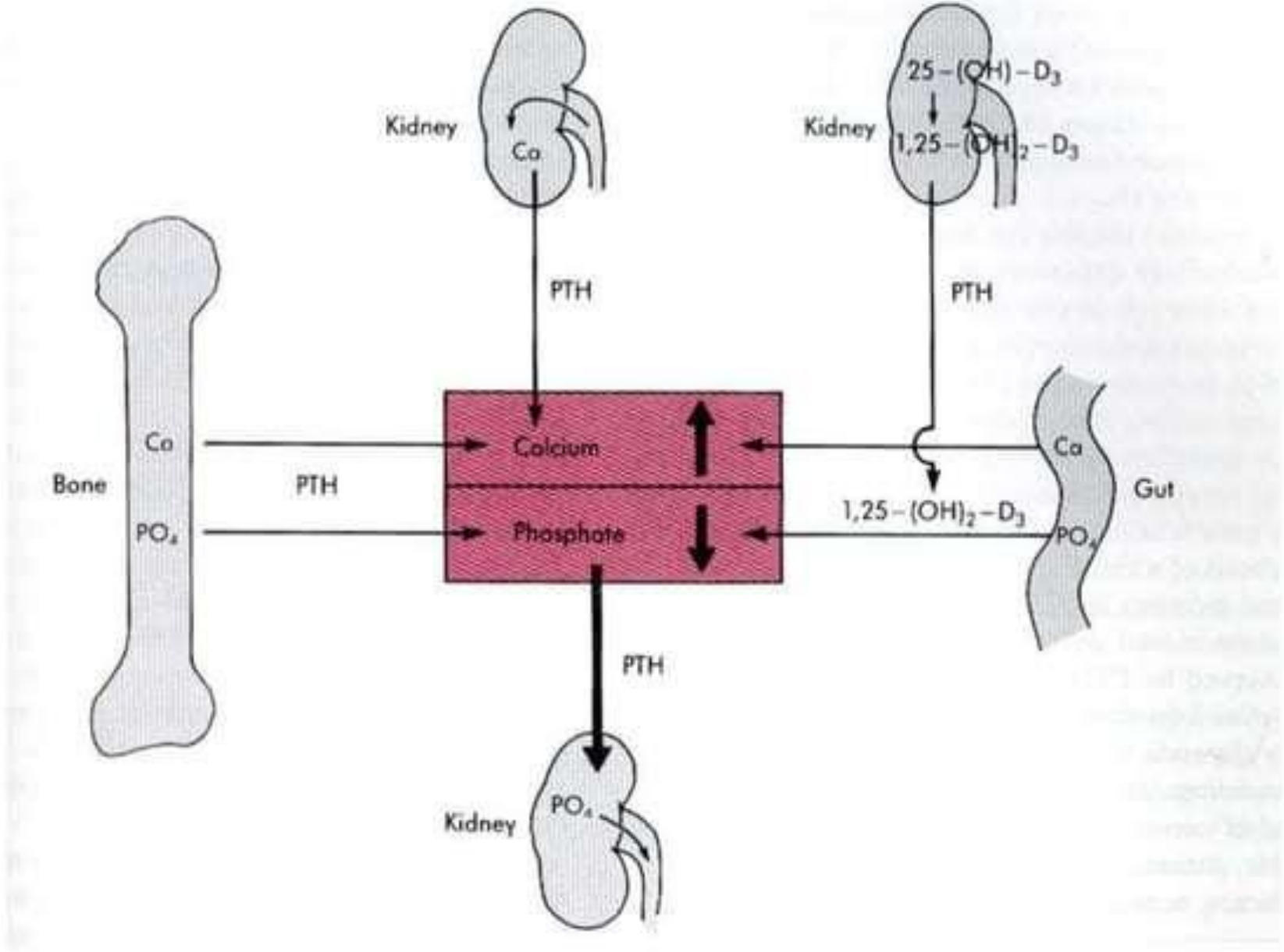
Three Forms of Circulating Ca^{2+}



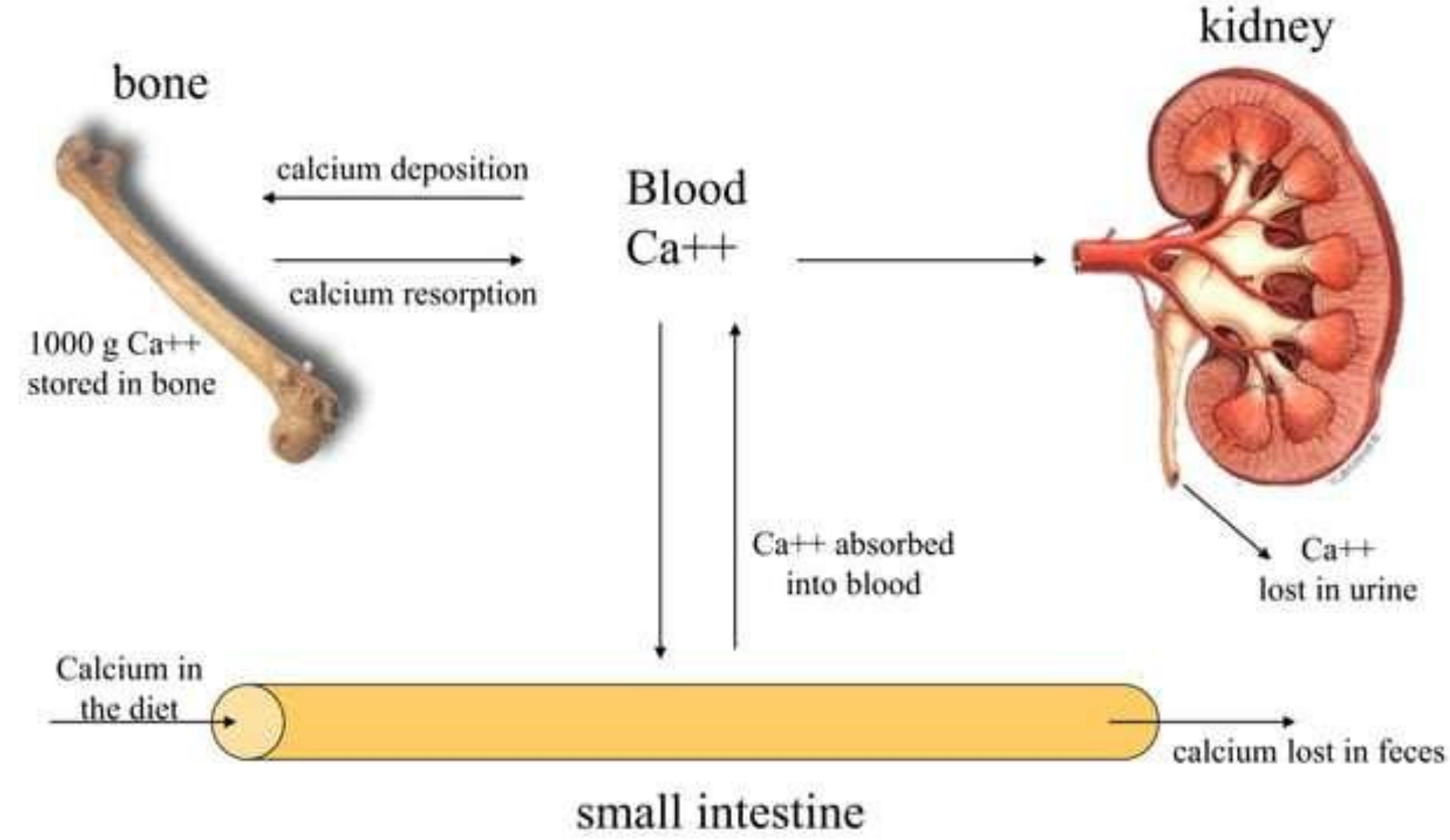
Regulation of Calcium Metabolism

- Minerals; serum concentration
  - Calcium (Ca^{2+}); 2.2-2.6 mM (total)
  - Phosphate (HPO_4^{2-}); 0.7-1.4 mM
  - Magnesium (Mg^{2+}); 0.8-1.2 mM
- Organ systems that play an import role in Ca^{2+} metabolism
  - Skeleton
  - GI tract
  - Kidney
- Calcitropic Hormones
  - Parathyroid hormone (PTH)
  - Calcitonin (CT)
  - Vitamin D (1,25 dihydroxycholecalciferol)
  - Parathyroid hormone related protein (PTHrP)

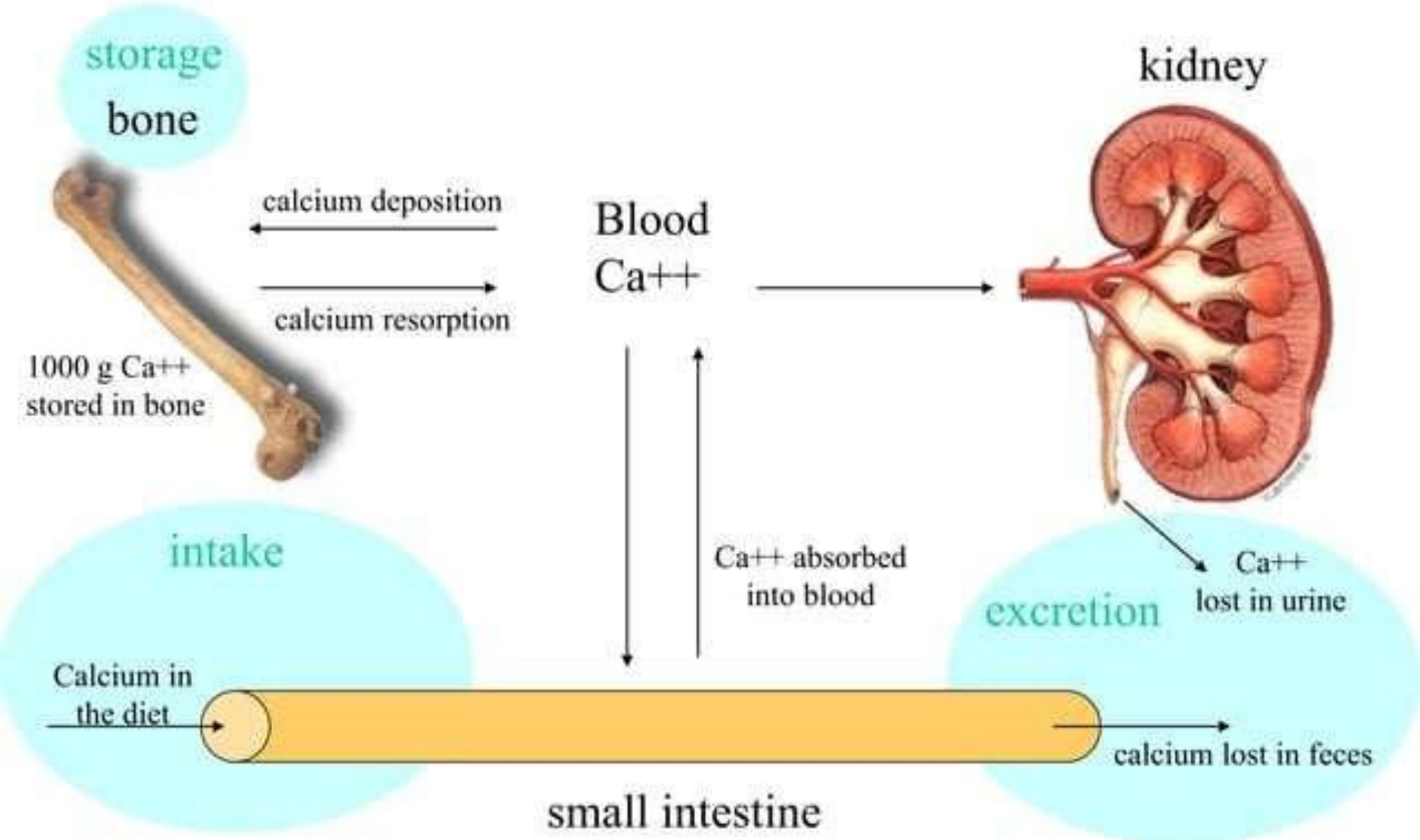
Calcium homeostasis



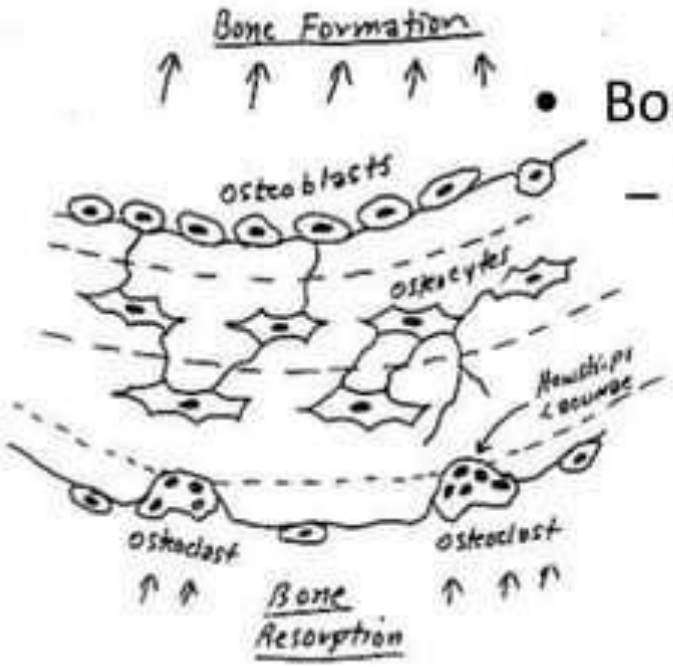
Calcium homeostasis



Calcium homeostasis

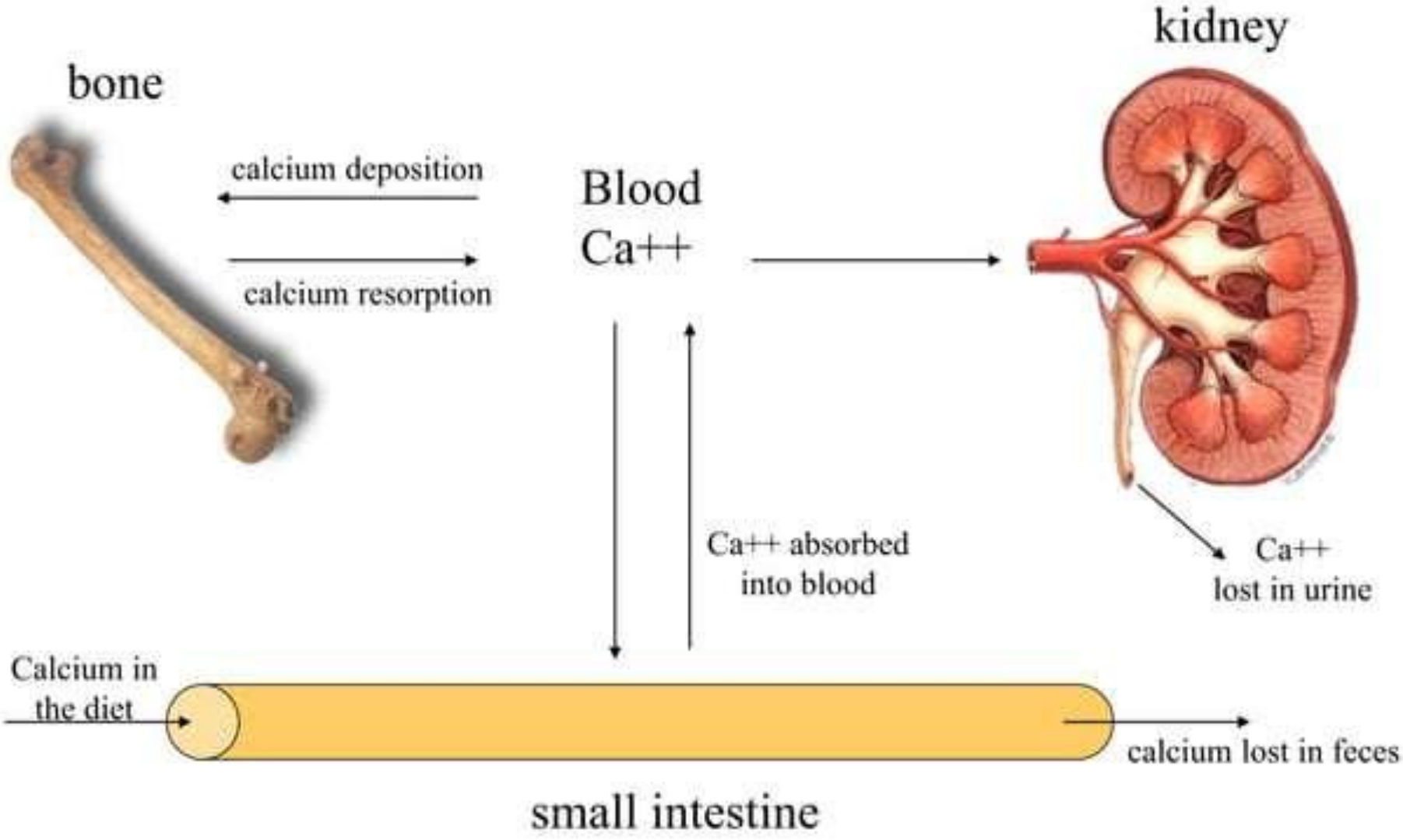


Calcium cycling in bone tissue



- Bone formation
  - Osteoblasts
    - Synthesize a collagen matrix that holds Calcium Phospate in crystallized form
    - Once surrounded by bone, become osteocyte
- Bone resorption
  - Osteoclasts
    - Change local pH, causing Ca++ and phosphate to dissolve from crystals into extracellular fluids

Calcium homeostasis



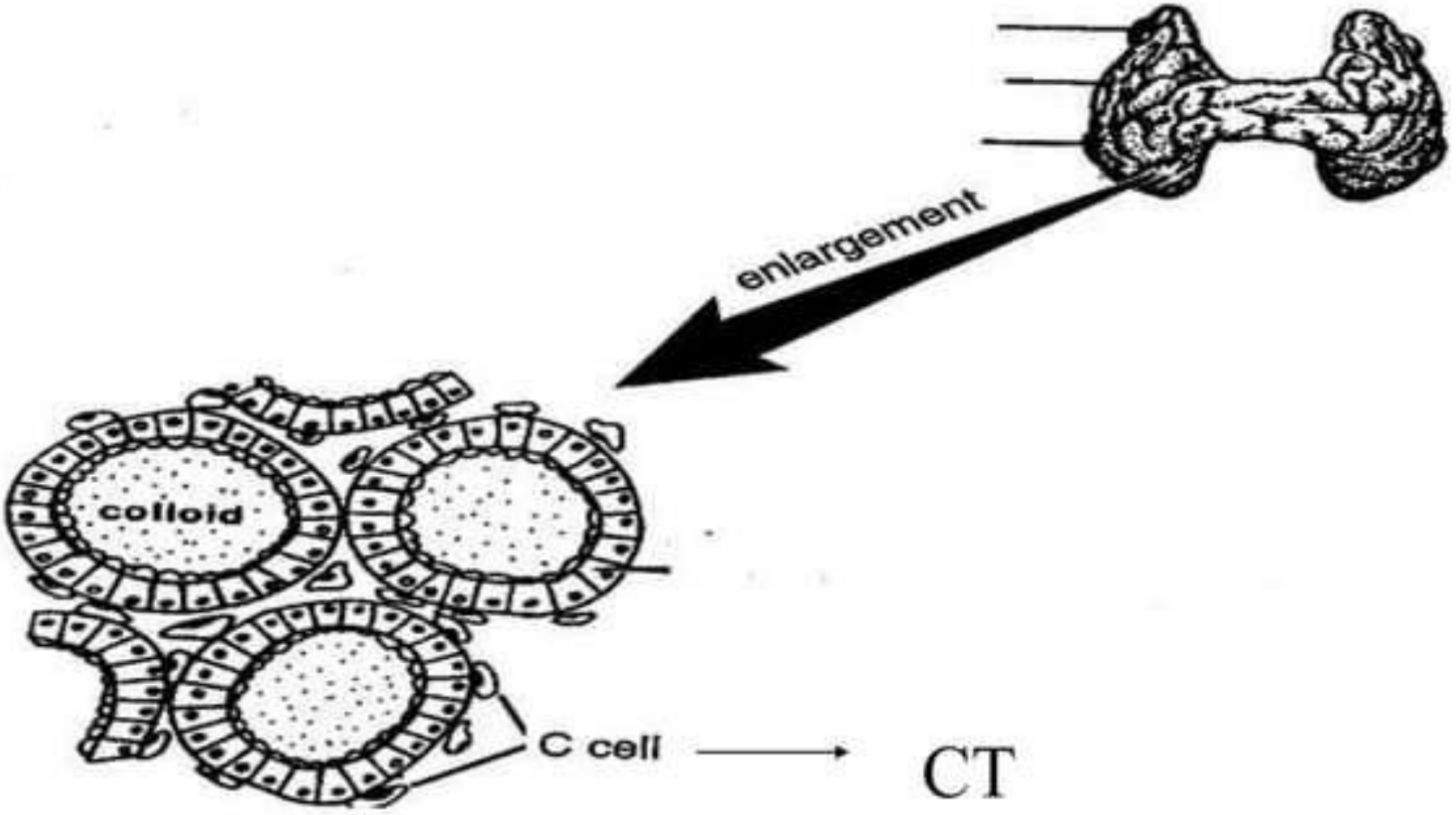
Calcitonin

- The major stimulus of calcitonin secretion is a rise in plasma Ca^{2+} levels
- Calcitonin is a physiological antagonist to PTH with regard to Ca^{2+} homeostasis

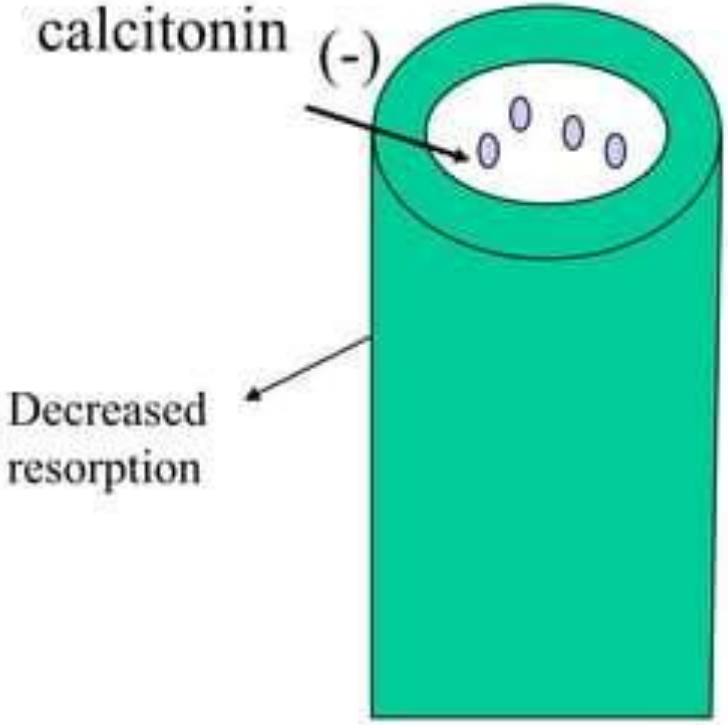
Calcitonin

- Calcitonin acts to decrease plasma Ca^{2+} levels.
- While PTH and vitamin D act to increase plasma Ca^{2+}-- only calcitonin causes a decrease in plasma Ca^{2+}.
- Promotes deposition of Ca++ into bone (inhibits osteoclasts)
- Calcitonin is synthesized and secreted by the parafollicular cells of the thyroid gland.

Calcitonin (CT)



Actions of Calcitonin



May be more important in regulating bone remodeling than in Ca2+ homeostasis.

Used in treatment of hypercalcemia

Hormonal Regulators

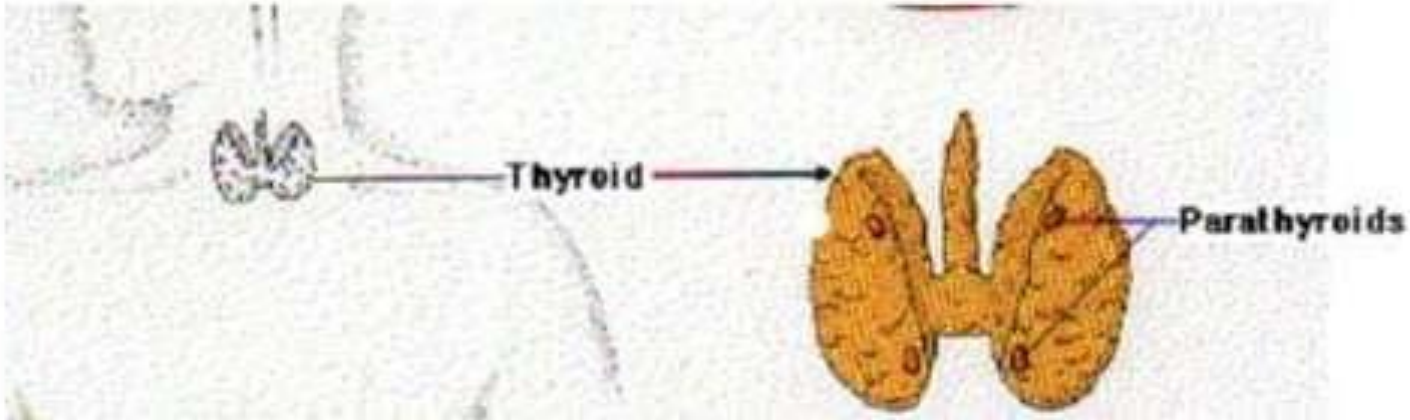
- Calcitonin (CT)
  - Lowers Ca++ in the blood
  - Inhibits osteoclasts
- Parathormone (PTH)
- 1,25 Vitamin D3

Parathyroid Hormone

- PTH is synthesized and secreted by the parathyroid gland which lie posterior to the thyroid glands.
- The Chief Cells in the parathyroid gland are the principal site of PTH synthesis.
- It is THE MAJOR of Ca homeostasis in humans.

(PTH)

- Increases Ca++ in blood
- Increases Ca++ resorption from the bone
  - Stimulates osteoclasts
  - Increases number of osteoclasts
- Increases Ca++ reabsorption from nephron
- Control of secretion:
- Necessary for fine control of Ca++ plasma levels

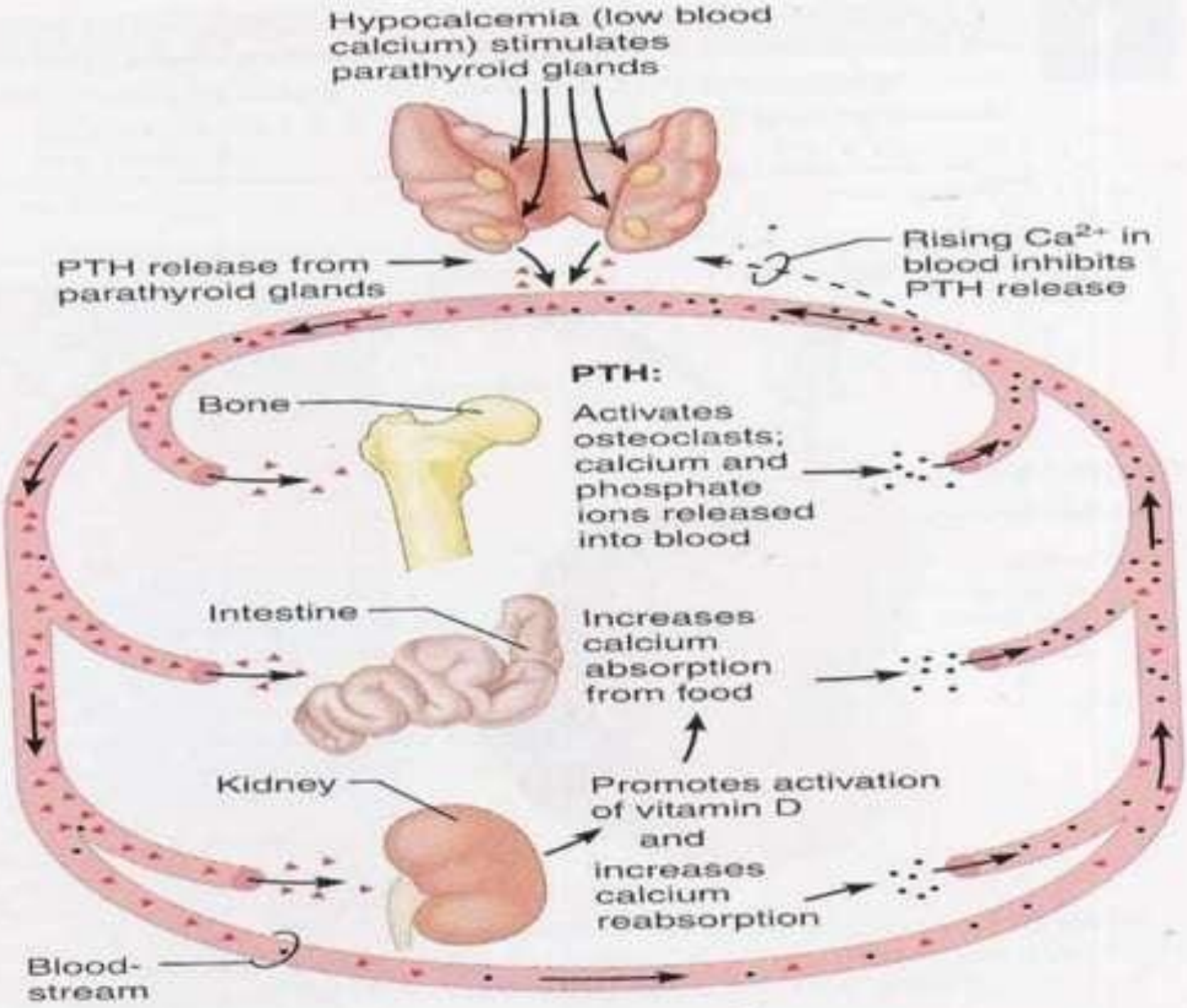


Regulation of PTH

- The dominant regulator of PTH is plasma Ca^{2+}.
- Secretion of PTH is inversely related to $[Ca^{2+}]$.
- Maximum secretion of PTH occurs at plasma Ca^{2+} below 3.5 mg/dL.
- At Ca^{2+} above 5.5 mg/dL, PTH secretion is maximally inhibited.

Regulation of PTH

- When Ca^{2+} falls, cAMP rises and PTH is secreted.
- 1,25-$(OH)_2$-D inhibits PTH gene expression, providing another level of feedback control of PTH.
- Despite close connection between Ca^{2+} and PO_4, no direct control of PTH is exerted by phosphate levels.


Hypocalcemia (low blood calcium) stimulates parathyroid glands
PTH release from parathyroid glands
Rising Ca^{2+} in blood inhibits PTH release
PTH:
Bone
Activates osteoclasts; calcium and phosphate ions released into blood
Intestine
Increases calcium absorption from food
Kidney
Promotes activation of vitamin D and increases calcium reabsorption
Blood-stream
Key:
= Ca^{2+} ions
= PTH molecules

Hormonal Regulators

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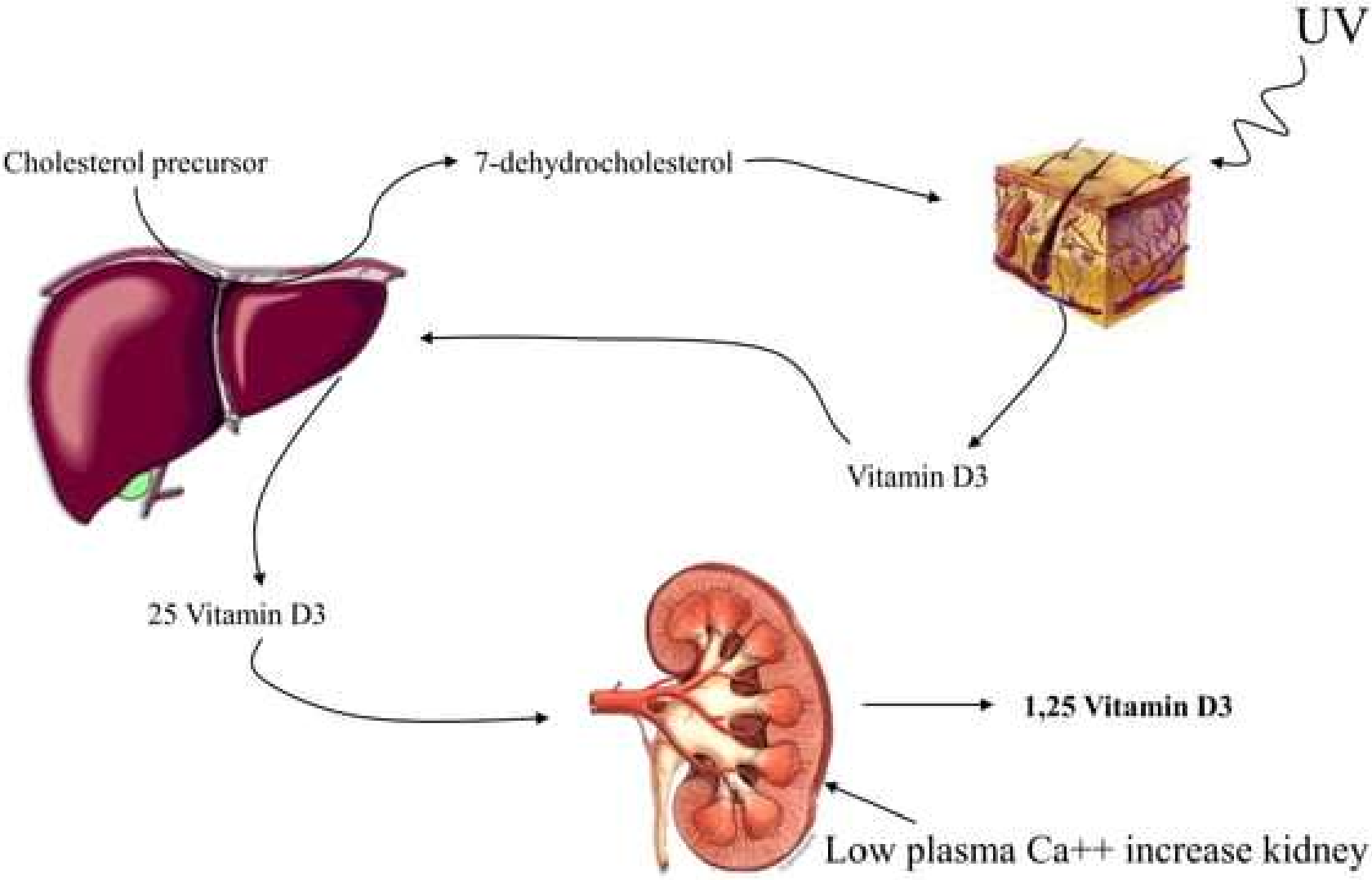
  - Lowers Ca++ in the blood
  - Inhibits osteoclasts
- Parathormone (PTH)
  - Increases Ca++ in the blood
  - Stimulates osteoclasts
- 1,25 Vitamin D3

1,25 Vitamin D3

- Increases Ca++ uptake from the gut
  - Increase transcription and translation of Ca++ transport proteins in gut epithelium
- Minor roll: also stimulates osteoclasts
  - Increase Ca++ resorption from the bone

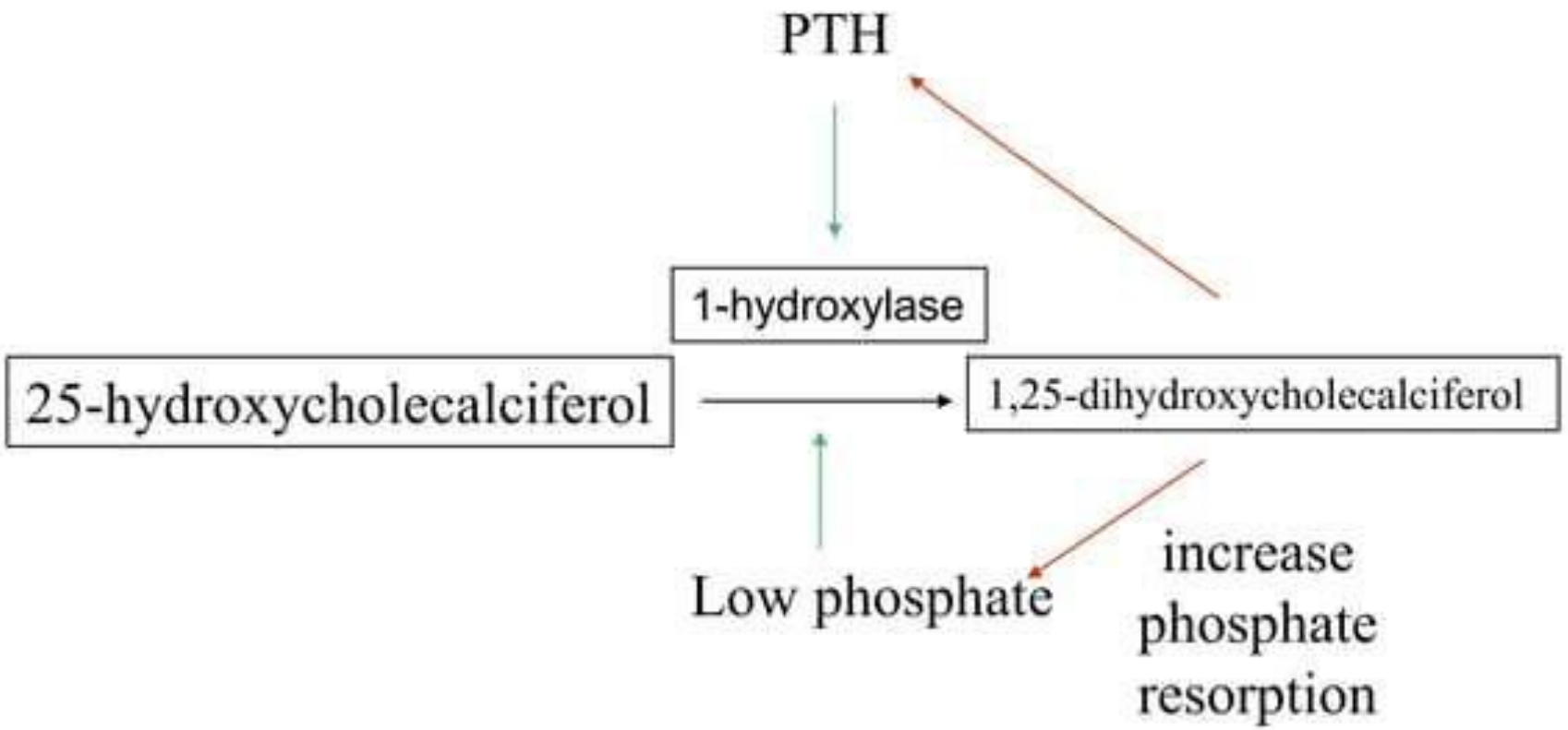
1,25 Vitamin D3



Synthesis of Vitamin D

- Humans acquire vitamin D from two sources.
- Vitamin D is produced in the skin by ultraviolet radiation and ingested in the diet.
- Vitamin D is not a classic hormone because it is not produced and secreted by an endocrine "gland." Nor is it a true "vitamin" since it can be synthesized *de novo*.
- Vitamin D is a true hormone that acts on distant target cells to evoke responses after binding to high affinity receptors

Regulation of Vitamin D by PTH and Phosphate Levels



Vitamin D action

- The main action of 1,25-$(OH)_2$-D is to stimulate absorption of Ca^{2+} from the intestine.
- 1,25-$(OH)_2$-D induces the production of calcium binding proteins which sequester Ca^{2+}, buffer high Ca^{2+} concentrations that arise during initial absorption and allow Ca^{2+} to be absorbed against a high Ca^{2+} gradient

Clinical application

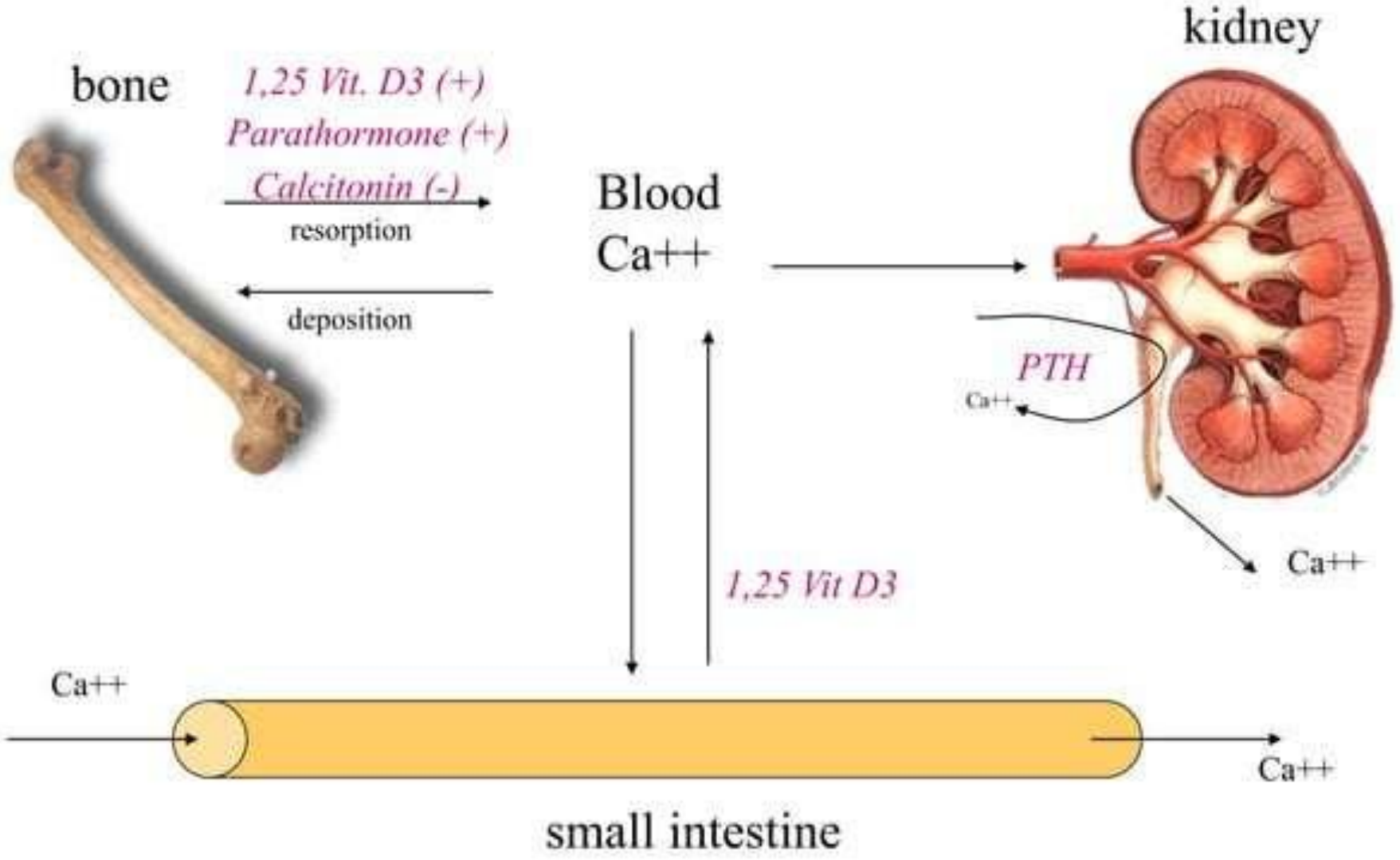
Vitamin D-dependent rickets type II

- Mutation in 1,25-(OH)2-D receptor
- Disorder characterized by impaired intestinal calcium absorption
- Results in rickets or osteomalacia despite increased levels of 1,25-(OH)2-D in circulation

Hormonal Regulators

- Calcitonin (CT)
  - Lowers Ca++ in the blood
  - Inhibits osteoclasts
- Parathormone (PTH)
  - Increases Ca++ in the blood
  - Stimulates osteoclasts
- 1,25 Vitamin D3
  - Increases Ca++ in the blood
  - Increase Ca++ uptake from the gut
  - Stimulates osteoclasts

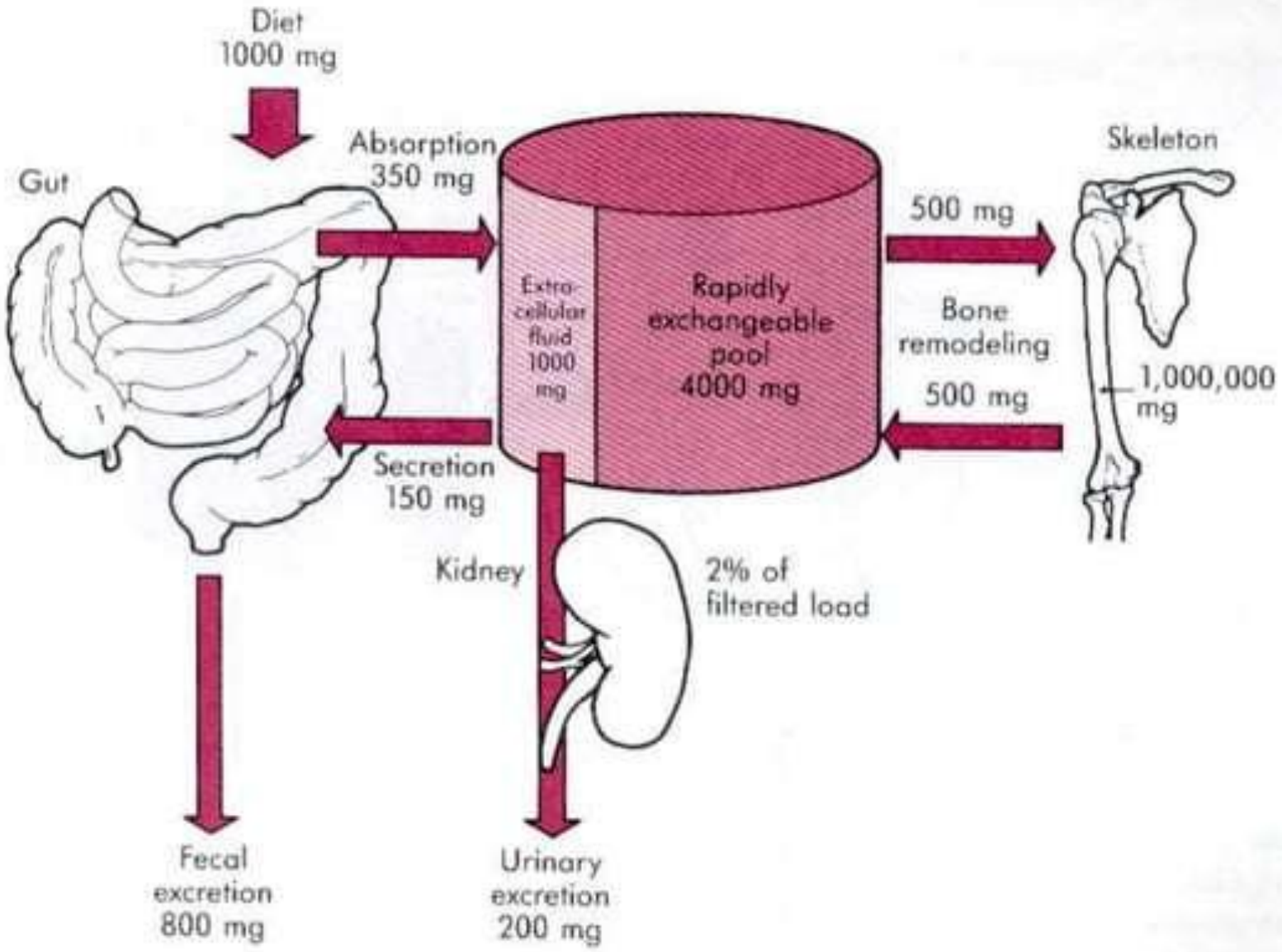
Calcium homeostasis



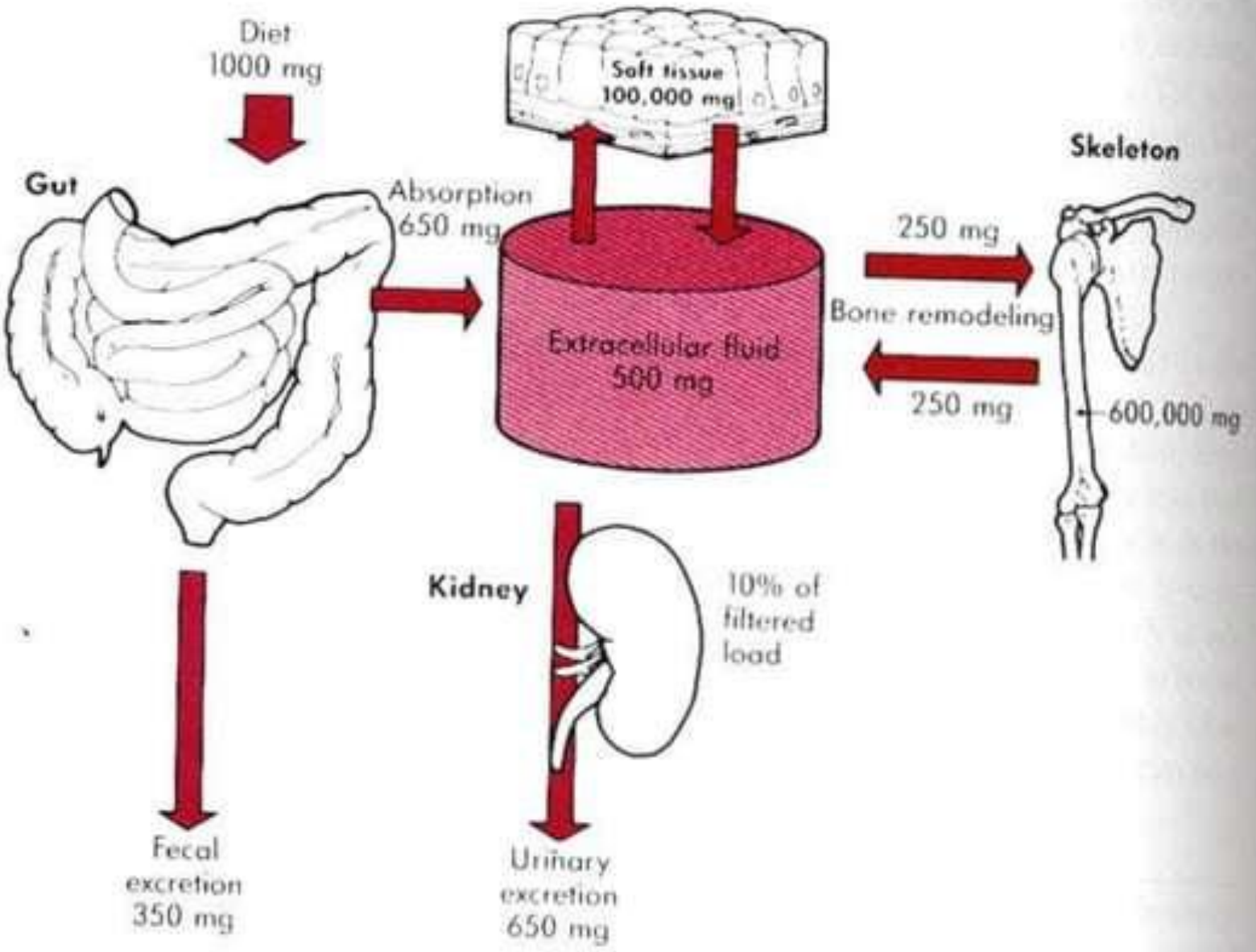
Calcium and Phosphorous

- Ca is tightly regulated with P in the body.
- P is an essential mineral necessary for ATP, cAMP 2nd messenger systems, and other roles

Calcium Turnover



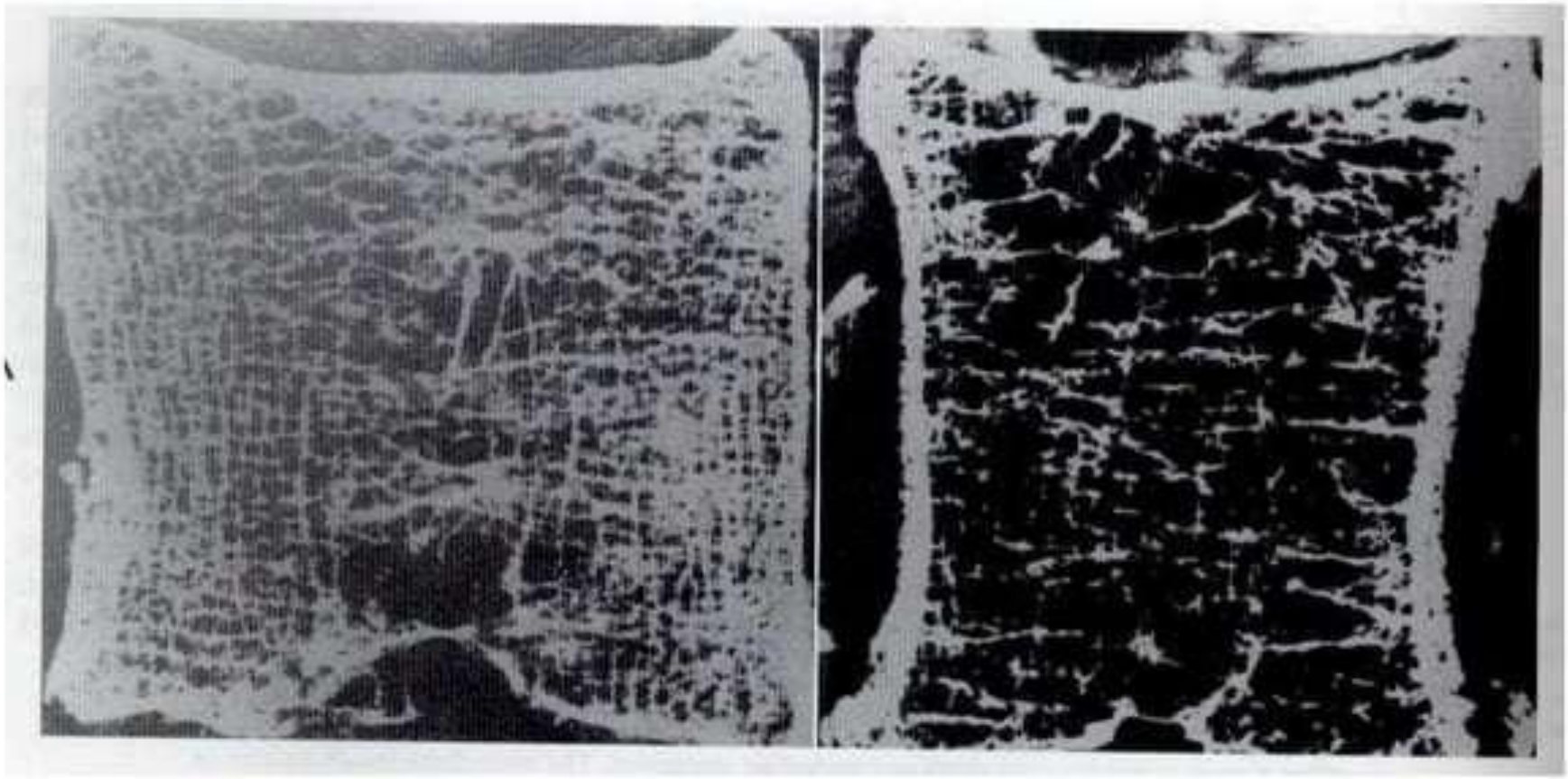
Phosphate Turnover



Calcium, Bones and Osteoporosis

- The total bone mass of humans peaks at 25-35 years of age.
- Men have more bone mass than women.
- A gradual decline occurs in both genders with aging, but women undergo an accelerated loss of bone due to increased resorption during perimenopause.
- Bone resorption exceeds formation.

Age related bone density changes



Calcium, Bones and Osteoporosis

- Reduced bone density and mass: **osteoporosis**
- Susceptibility to fracture.
- Earlier in life for women than men but eventually both genders succumb.
- Reduced risk:
  - **Calcium in the diet**
  - **habitual exercise**
  - **avoidance of smoking and alcohol intake**
  - **avoid drinking carbonated soft drinks**

Influences of Growth Hormone

- Normal GH levels are required for skeletal growth.
- GH increases intestinal calcium absorption and renal phosphate resorption.
- Insufficient GH prevents normal bone production.
- Excessive GH results in bone abnormalities (acceleration of bone formation AND resorption).

Influence of Thyroid Hormones

- Thyroid hormones are important in skeletal growth during infancy and childhood (direct effects on osteoblasts).
- Hypothyroidism leads to decreased bone growth.
- Hyperthyroidism can lead to increased bone loss, suppression of PTH, decreased vitamin D metabolism, decreased calcium absorption. Leads to osteoporosis.

DISORDERS OF CALCIUM METABOLISM

- PTH receptor deficiency
- Hyper/hypoparathyroidsm
- Hypercalcemia of malignancy
- Hypercalcemia
- Hypocalcemia

PTH receptor deficiency

- Rare disease known as Jansen's metaphyseal chondrodysplasia
- Characterized by ***hypercalcemia, hypophosphotemia, short-limbed dwarfism***
- Due to activating mutation of PTH receptor
- Rescue of PTH receptor knock-out with targeted expression of "Jansen's transgene"

Hyperparathyroidsm

- Calcium homeostatic loss due to excessive PTH secretion
- Due to excess PTH secreted from adenomatous or hyperplastic parathyroid tissue
- ***Hypercalcemia*** results from combined effects of PTH-induced bone resorption, intestinal calcium absorption and renal tubular reabsorption
- Pathophysiology related to both PTH excess and concomitant excessive production of 1,25-(OH)2-D.

Hypoparathyroidsm

- ***Hypocalcemia*** occurs when there is inadequate response of the Vitamin D-PTH axis to hypocalcemic stimuli
- Hypocalcemia is often multifactorial
- Hypocalcemia is invariably associated with hypoparathyroidism
- Bihormonal—concomitant decrease in 1,25-(OH)2-D

Hypercalcemia of malignancy

- Underlying cause is generally excessive bone resorption by one of three mechanisms
- 1,25-(OH)2-D synthesis by lymphomas
- Local osteolytic hypercalcemia
  - 20% of all hypercalcemia of malignancy
- Humoral hypercalcemia of malignancy
  - Over-expression of PTH-related protein (PTHrP)

References

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