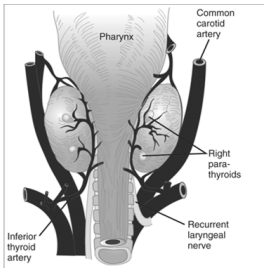
CALCIUM HOMEOSTASIS
PARATHYROID GLAND



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OBJECTIVES

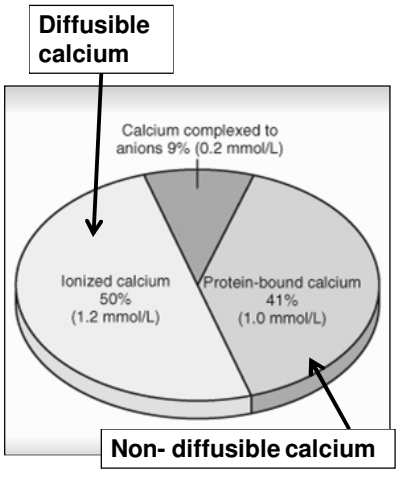
At the end of this lecture you should be able to:

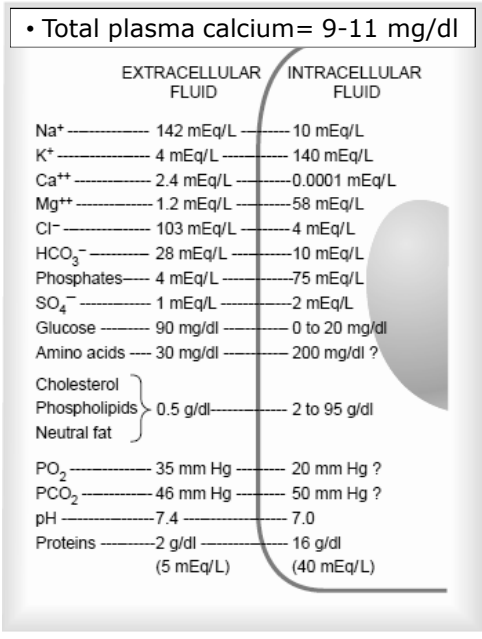
- **List functions of calcium**
- **Describe calcium metabolism**
- **Describe physiology of bone**
- **Understand and explain hormonal regulation of calcium metabolism**
  - **Parathyroid hormone**
  - **Calcitonin**
  - **Vitamine D_3**
- **Understand hypo and hyper-parathyroidism**

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
  - Blood coagulation
  - Hormonal secretion
  - Enzymatic regulation
  - Second messenger.
  - Milk production.
  - Maintains normal permeability of cell membranes.

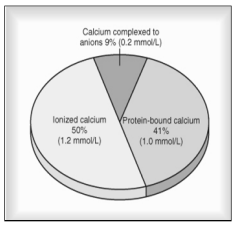
CALCUIM METABOLISM





PLASMA CALCIUM

9-11 mg/dl



Total diffusible	60%	1.34
Ionized (Ca^{2+})	50%	1.18
Complexed to HCO_3^-, citrate, etc	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

Calcuim metabolism cont…

Source

- milk
- dairy products

Daily requirements

- Infants & adults: 12.5 -25 mmol/day
- Pregnancy,
- lactation
- after menopause:

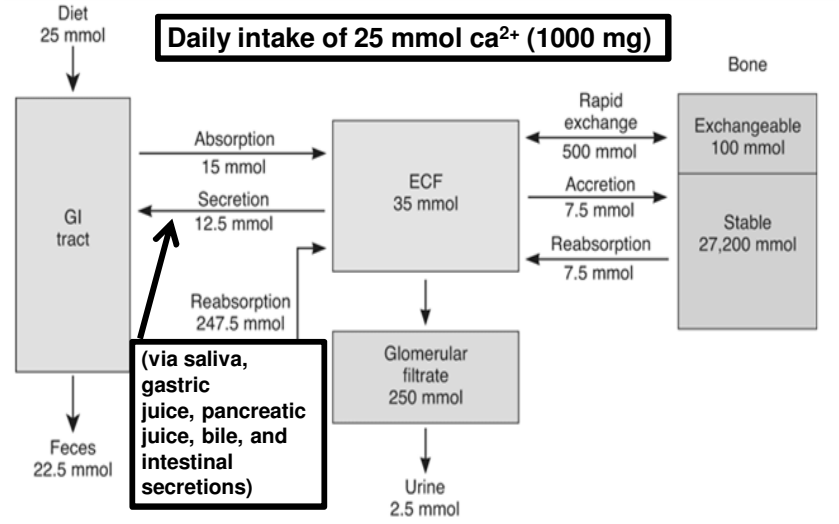
25-35 mmol/day

Absorption

- Duodenum: active transport
- small intestine: concentration gradient

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

Calcium metabolism in an adult human

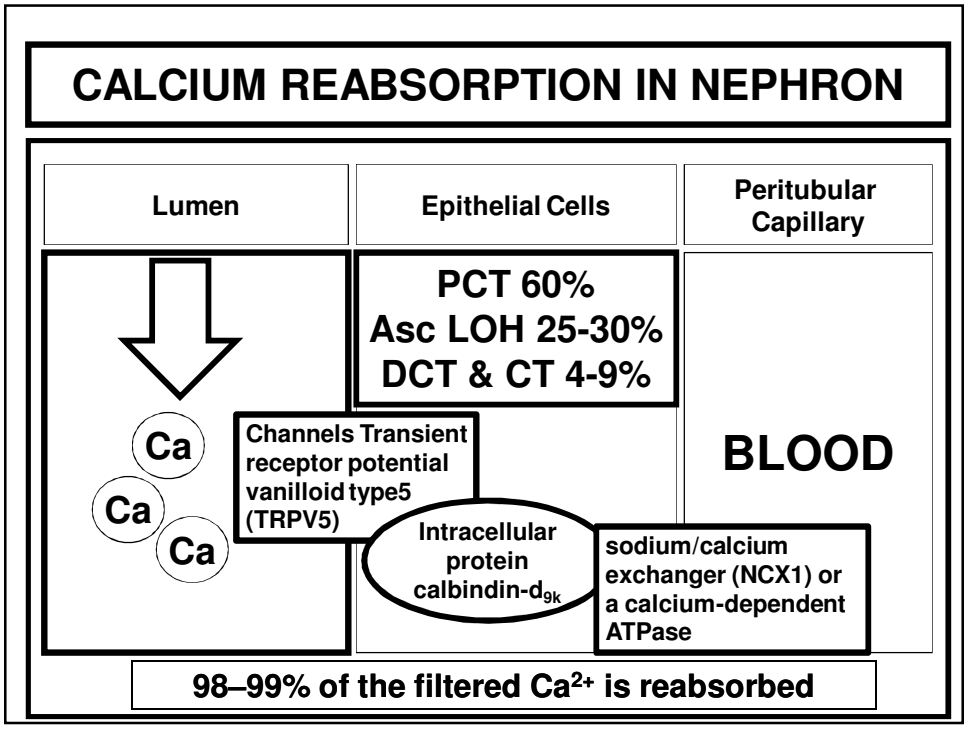


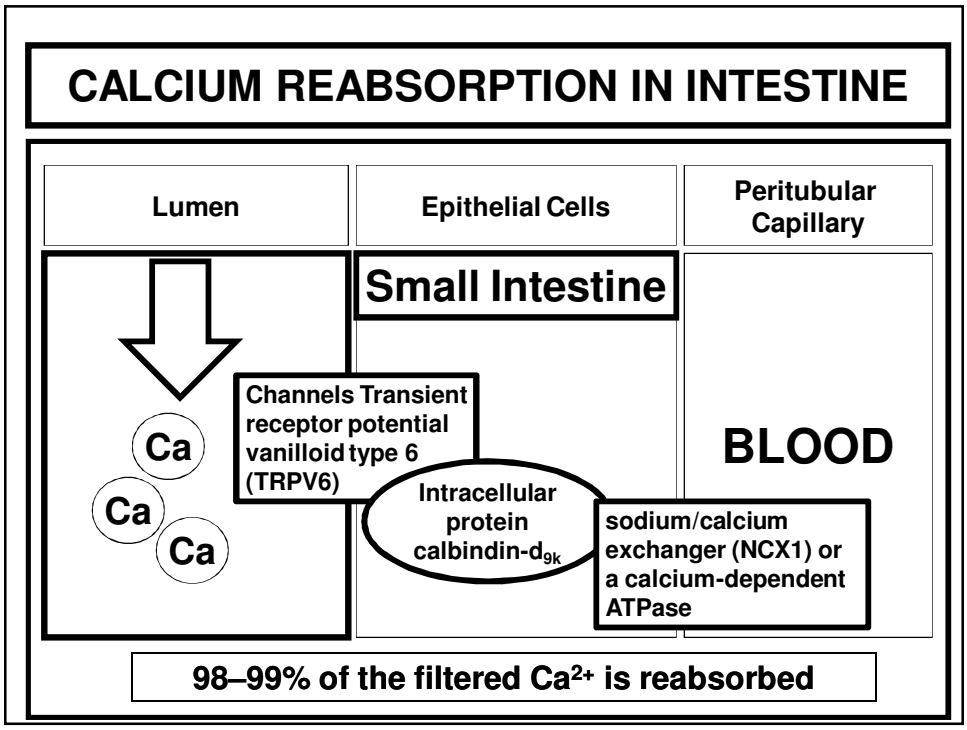
Distribution of Ca in Body

- **Skeleton & Teeth**
- **ICF** (Endoplasmic Reticulum)
- **ECF**

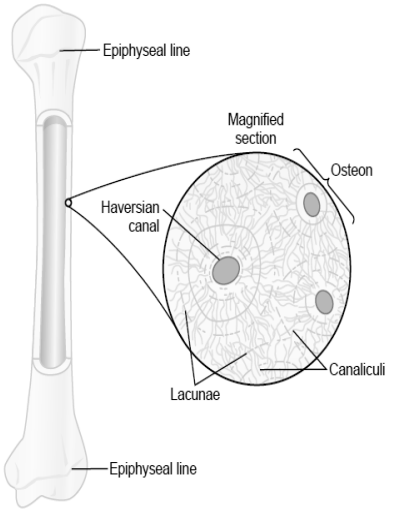
TABLE 36.1 Body Content and Tissue Distribution of Calcium and Phosphorus in a Healthy Adult

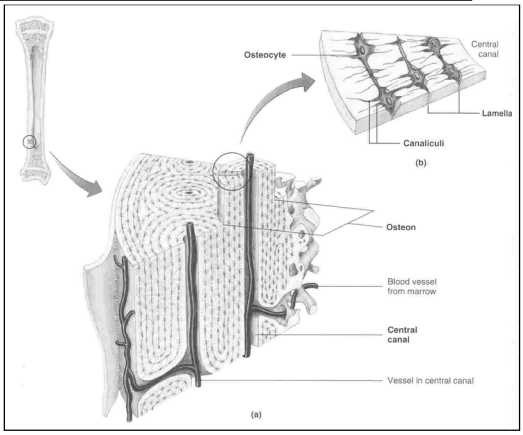
	Calcium	Phosphorus
Total Body Content	1,300 g	600 g
Relative Tissue Distribution (% of total body content)		
Bones and teeth	99%	86%
Extracellular fluid	0.1%	0.08%
Intracellular fluid	1.0%	14%


CALCIUM REABSORPTION IN NEPHRON
Lumen
Epithelial Cells
Peritubular Capillary
PCT 60%
Asc LOH 25-30%
DCT & CT 4-9%
BLOOD
Ca
Ca
Ca
Channels Transient receptor potential vanilloid type5 (TRPV5)
Intracellular protein calbindin-d_{9k}
sodium/calcium exchanger (NCX1) or a calcium-dependent ATPase
98–99% of the filtered Ca^{2+} is reabsorbed

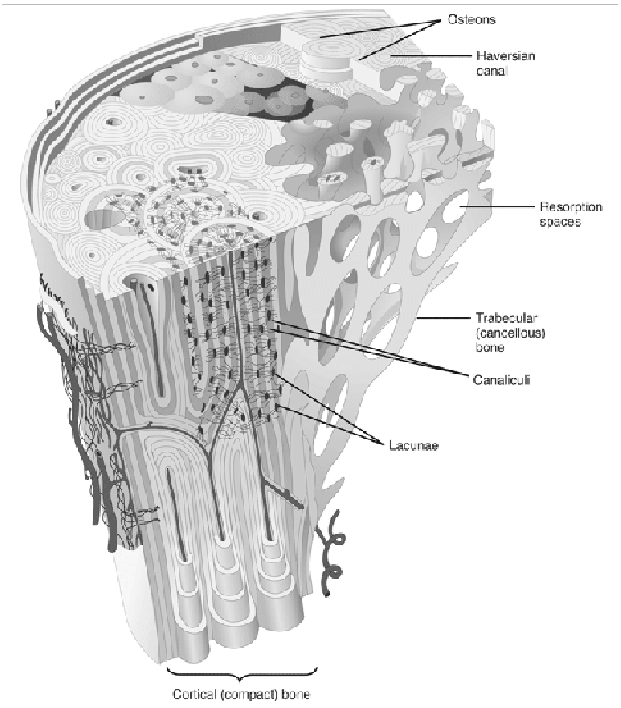

CALCIUM REABSORPTION IN INTESTINE
Lumen
Epithelial Cells
Peritubular Capillary
Small Intestine
BLOOD
Ca
Ca
Ca
Channels Transient receptor potential vanilloid type 6 (TRPV6)
Intracellular protein calbindin-d_{9k}
sodium/calcium exchanger (NCX1) or a calcium-dependent ATPase
98–99% of the filtered Ca^{2+} is reabsorbed

PHYSIOLOGY OF BONE

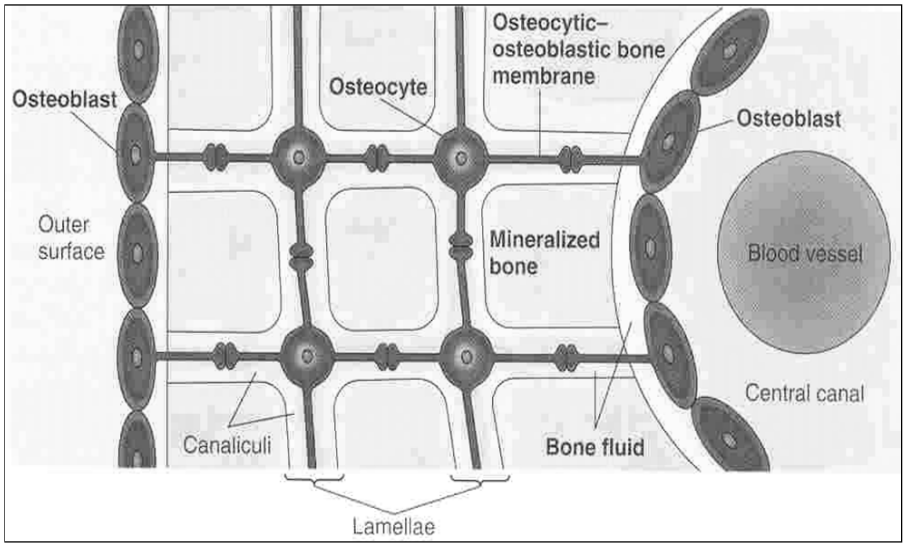


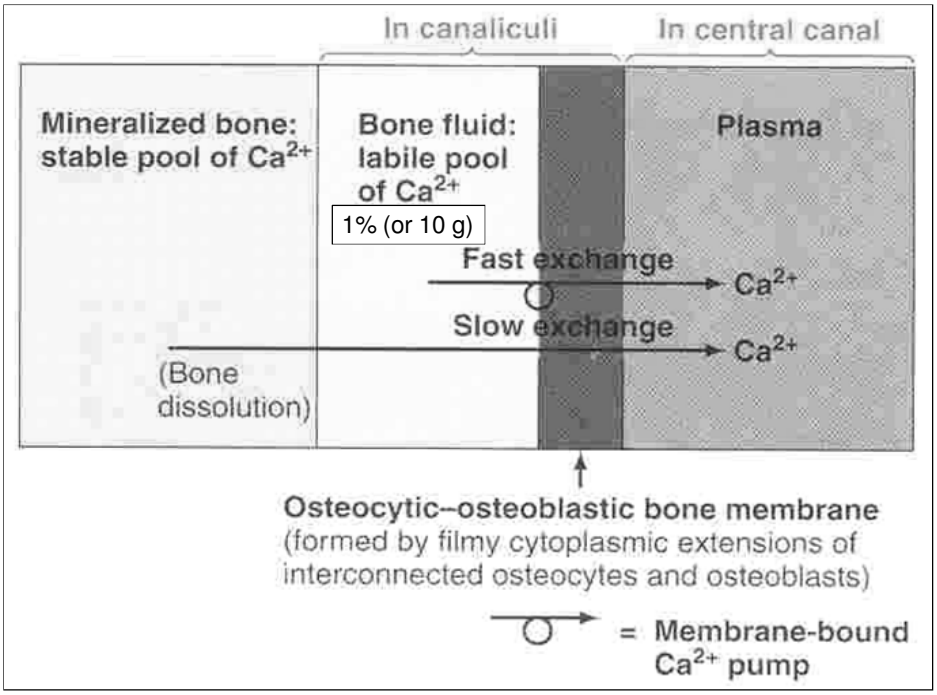


Structure of compact and trabecular bone



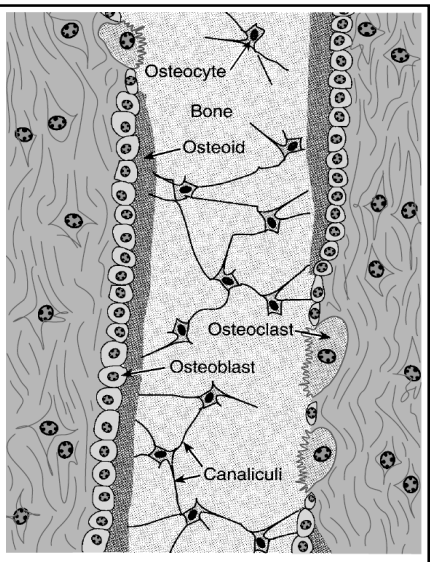
PHYSIOLOGY OF BONE





Bone & Ca^{++}

- **Organic Matrix 30%**
  - **Collagen Fibers**
  - **Ground Substance**
    - **ECF**
    - **Proteoglycans**
- **Bone Salts 70%**
  - **Salts of Ca & PO4**
    - **Amorphous form**
    - **Crystalline Form (Hydroxyapatite)**
- **Others: Mg, Na, K, Carbonate**



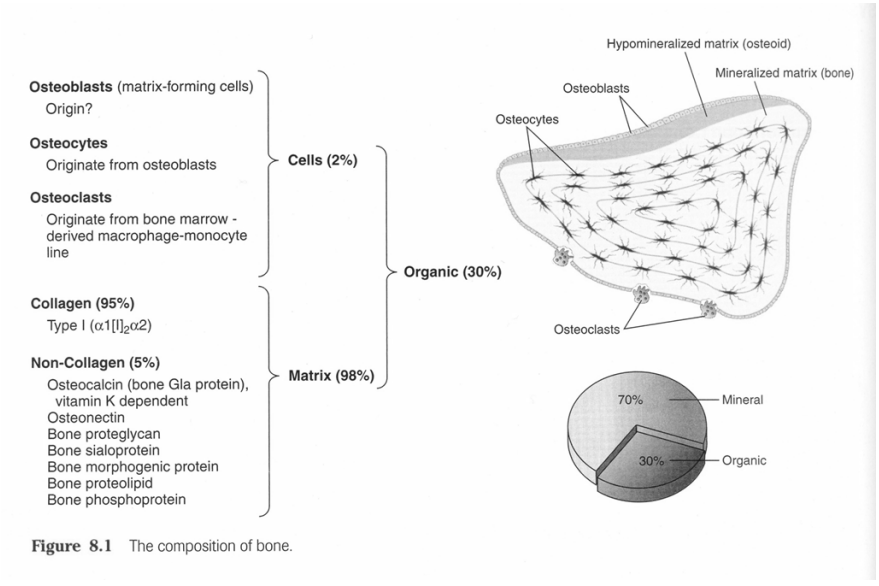


Figure 8.1 The composition of bone.

Bone & Ca Cont…

Types of Bone Cells

- **Osteoblasts**

  bone formation

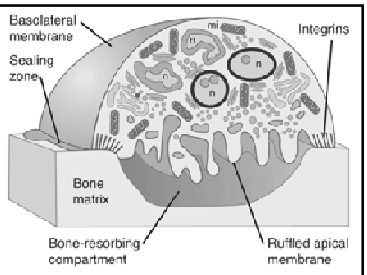
- **Osteoclasts**

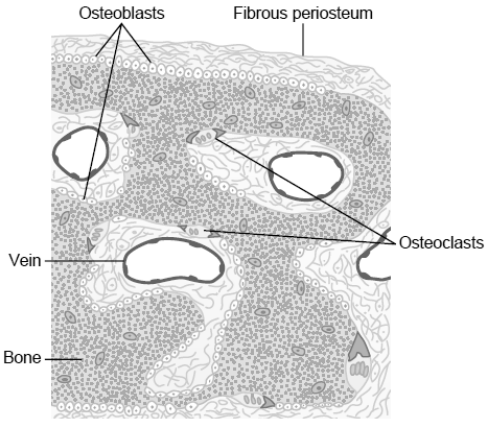
  bone resorption

- **Osteocytes**

  Quiescent Osteoblasts

  Source of Fast Pool of Ca





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 PO_4 CONCENTRATIONS

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

HORMONES REGULATING Ca^{++}

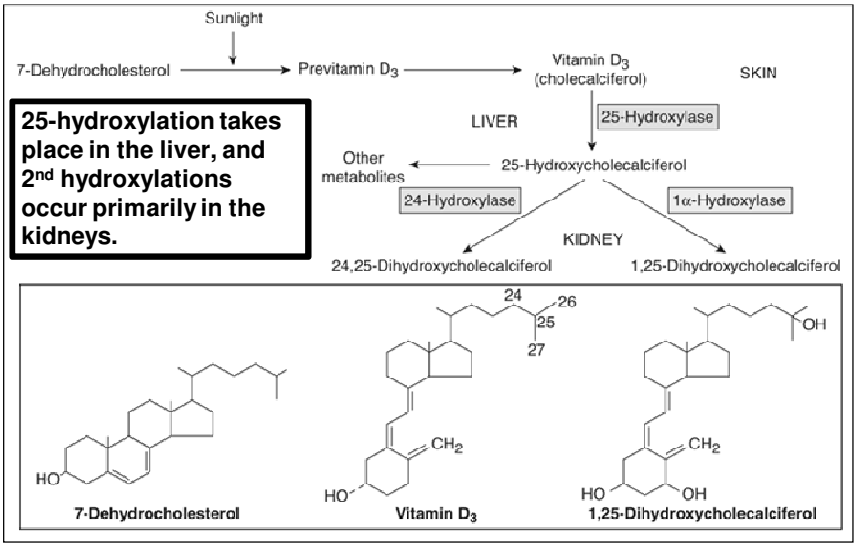
Three Hormones

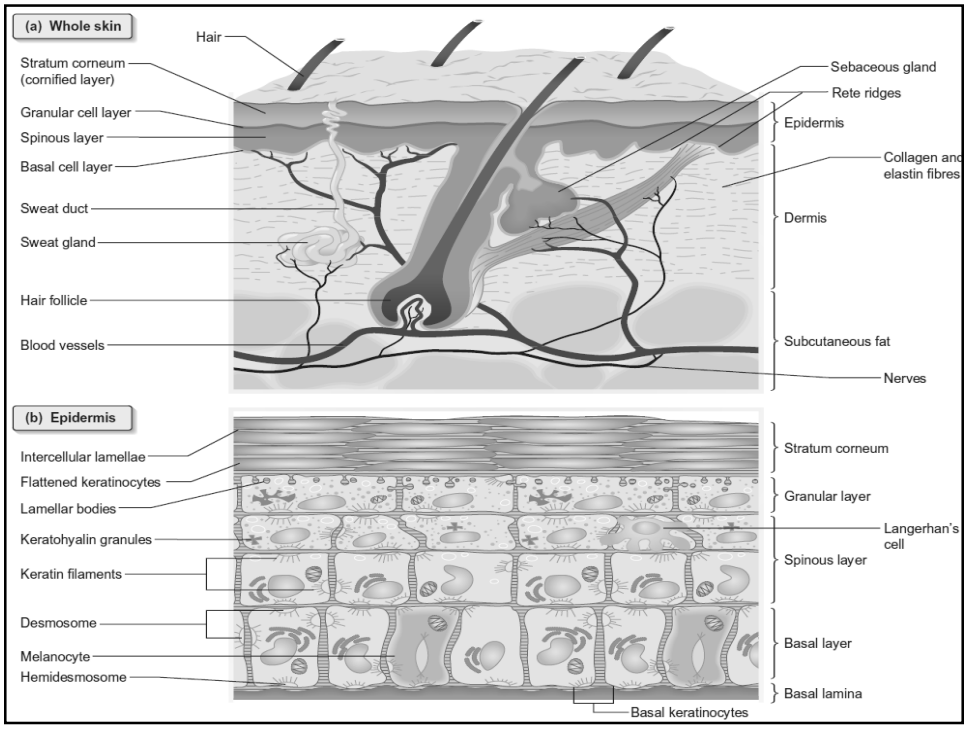
- Vitamin D
- Parathyroid Hormone
- Calcitonin

Role of Vit D in Ca Homeostasis

- **Source……..**
- **Chemistry……** Sterols
- **Molecular Weight**
- **Half Life**
- **Blood Levels**
- **Fate Skin, Liver & Kidneys**

Formation and hydroxylation of vit D3.

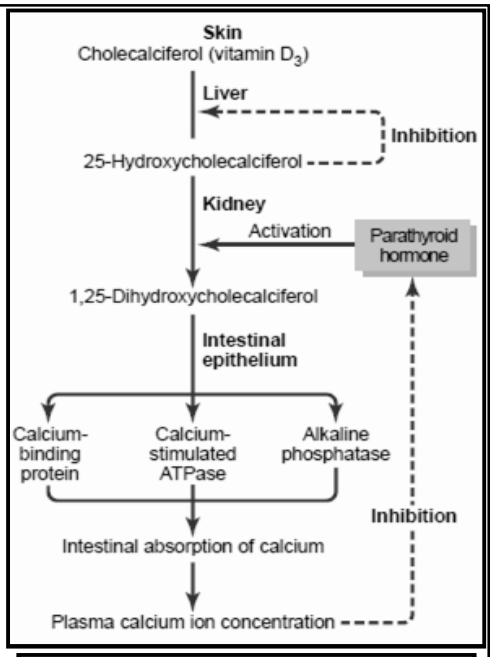




VITAMIN D3

Actions

- **Calcium**
  - ✓ ↑Absorption from Bone
  - ✓ ↓Renal Excretion
  - ✓ ↑ Absorption from GIT
- **Phosphate**
  - ✓ ↑ Absorption from Bone
  - ✓ ↓ Renal Excretion
  - ✓ ↑ Absorption from GIT



GIT: Ca^{2+}ATPase and TRPV6 molecules
Kidneys: TRPV5 expression

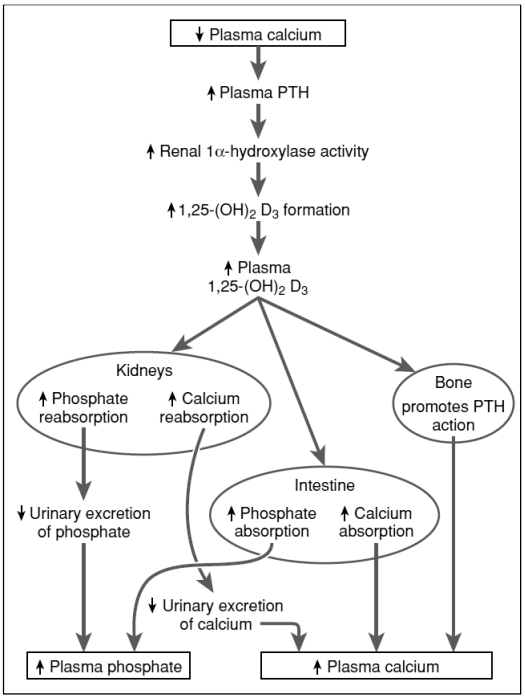
VITAMIN D3

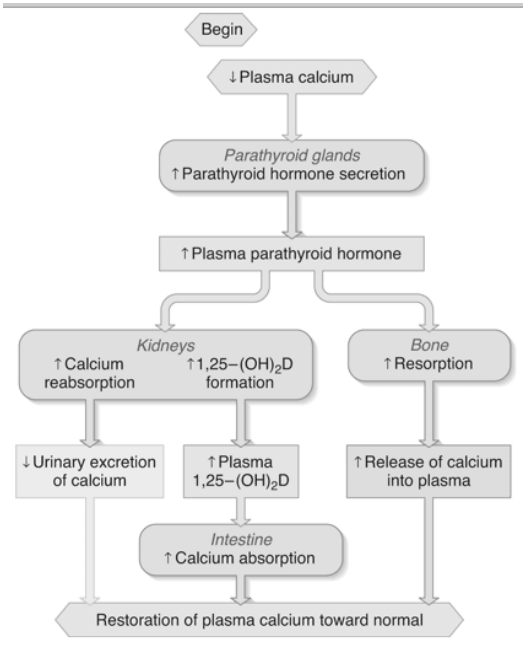
Actions

- Calcium
  - ↑Absorption from Bone
  - ↓Renal Excretion
  - ↑ Absorption from GIT
- Phosphate
  - ↑ Absorption from Bone
  - ↓ Renal Excretion
  - ↑ Absorption from GIT

Net Results

↑Plasma Cacium
↑Phosphate





Phosphorus

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**
- **cyclic adenosine monophosphate (cAMP)**
- **2,3-diphosphoglycerate**
- **Many other proteins**

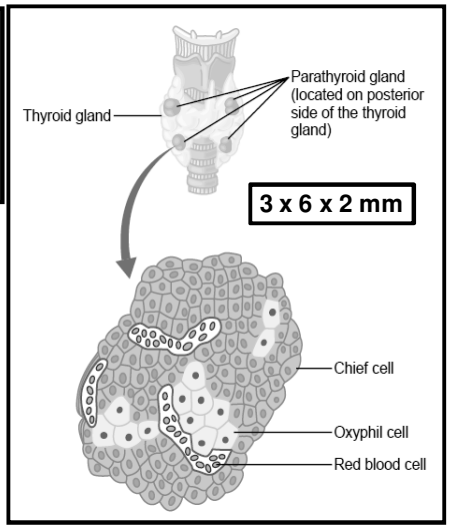
Total plasma phosphorus is about 12 mg/dL, with two-thirds of this total in organic compounds and the remaining inorganic phosphorus (P_i) mostly in PO_4^{3-}, HPO_4^{2-}, and $H_2PO_4^-$.

PHOSPHATE

- **It is reabsorbed by cotransport with Na in PCT in luminal border (Na/Pi)**
- **Its reabsorption is Hormonally controlled**
- **It is increased by Vit D and decreased by Parathyroid Hormone**

PARATHYROID GLAND

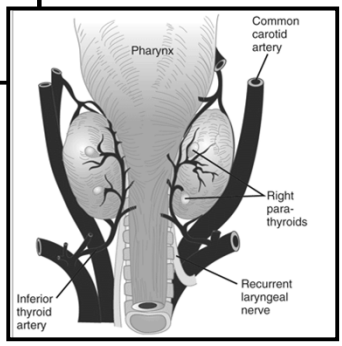
•**CHIEF CELLS (abundant) Secrete parathyroid hormone (PTH).**
•**OXYPHIL CELLS (less abundant) contain oxyphil granules. modified or depleted chief cells**



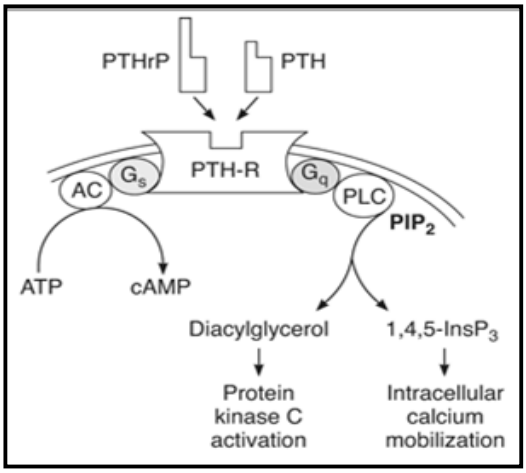
PARATHYROID HORMONE

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

Calcium-sensing and vitamin D receptors



PTH MECH OF ACTION

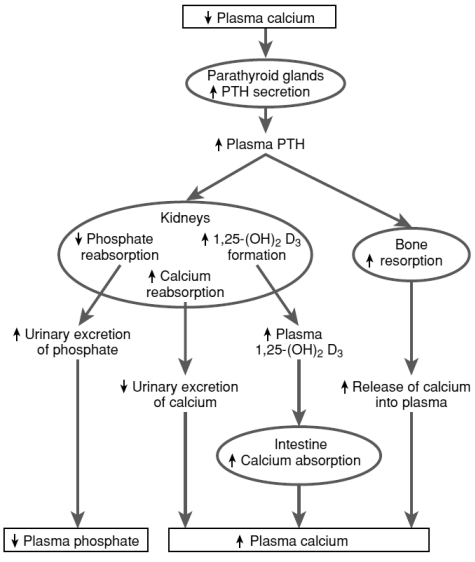


PARATHORMONE

Targets are Bones & Kidneys and indirectly GIT

Actions

- **Calcium**
  - ✓ ↑**Absorption from Bone**
  - ✓ ↓**Renal Excretion**
  - ✓ ↑ **Absorption from GIT**
- **Phosphate**
  - ✓ ↑ **Absorption from Bone**
  - ✓ ↑ **Renal Excretion**

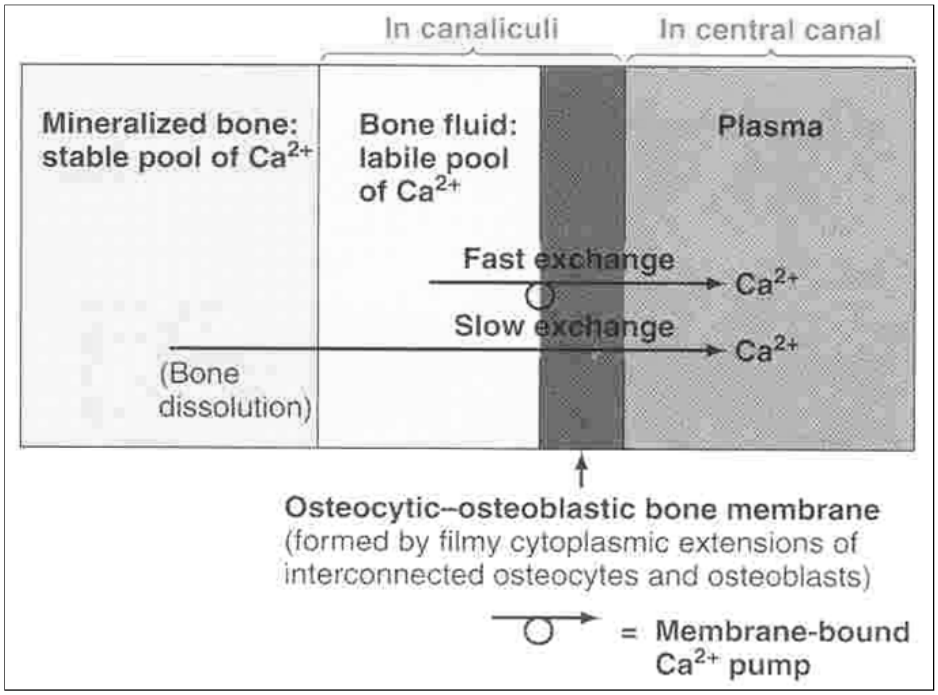


Rapid Phase of Calcium and Phosphate Absorption—Osteolysis.

- Cell membranes of both the osteoblasts and the osteocytes have receptor proteins for binding PTH
- PTH can activate the calcium pump strongly, thereby 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.

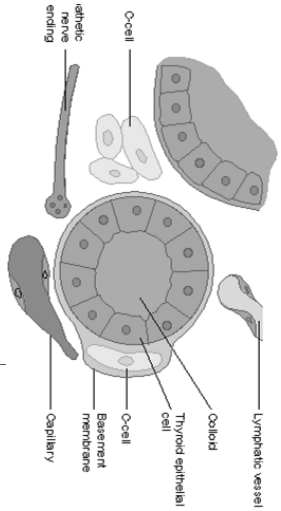
Slow Phase of Bone Absorption Release—Activation of the Osteoclasts

- 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 stimulation of the osteoblasts that attempt to correct the weakened state. Therefore, the late effect is actually to enhance both osteoblastic and osteoclastic activity.



CALCITONIN

Source: Parafolicular C Cells of Thyroid
Chemistry: Peptide 32-amino acid
Molecular weight: 3400
Prim Target: Bone



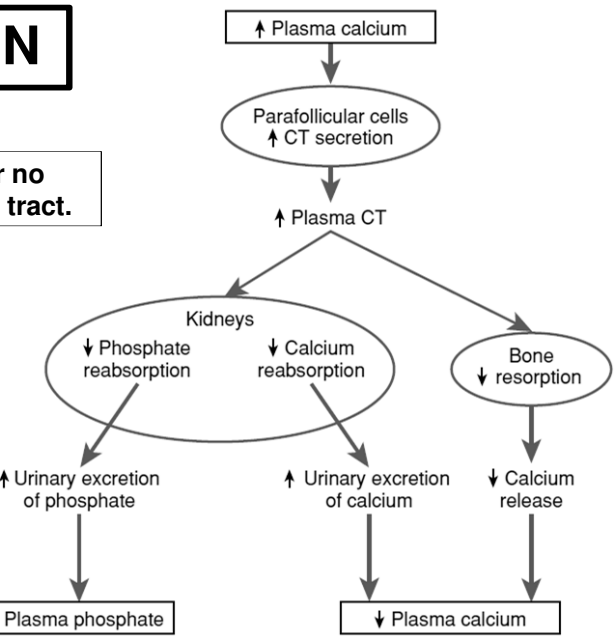
Actions

Calcium-sensing

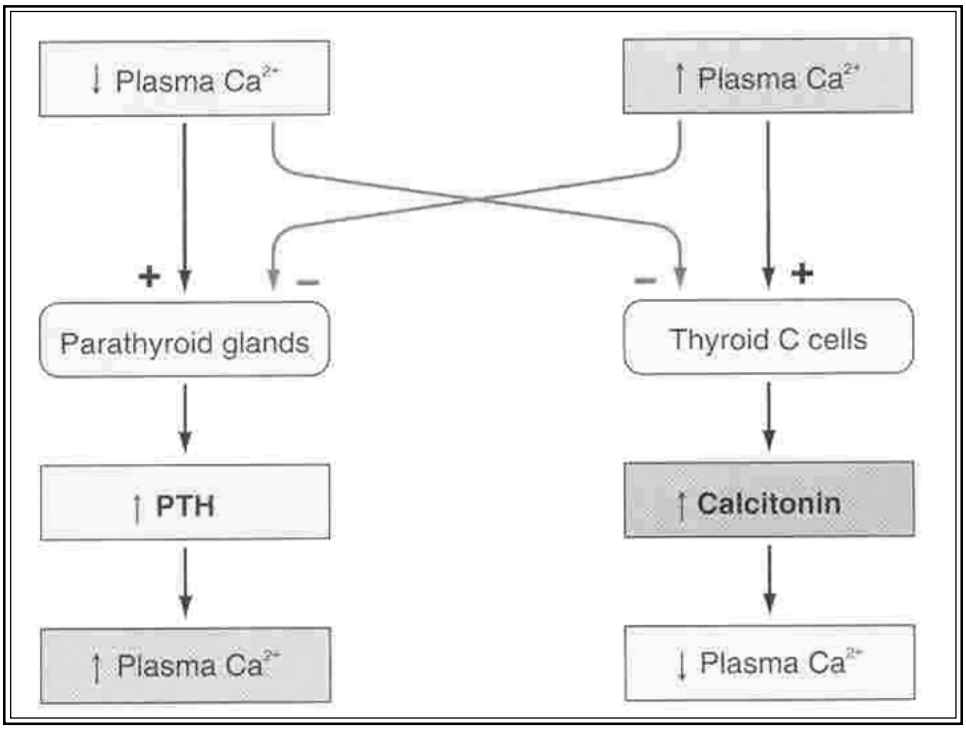
- **Immediate effect**
  - **Osteoclastic Activity ↓**
- **Prolonged Effect**
  - **Formation of new Osteoclasts ↓**
- **On Kidneys and GIT: ↓Calcium & ↓Phosphate reabsorption (minor effect)**

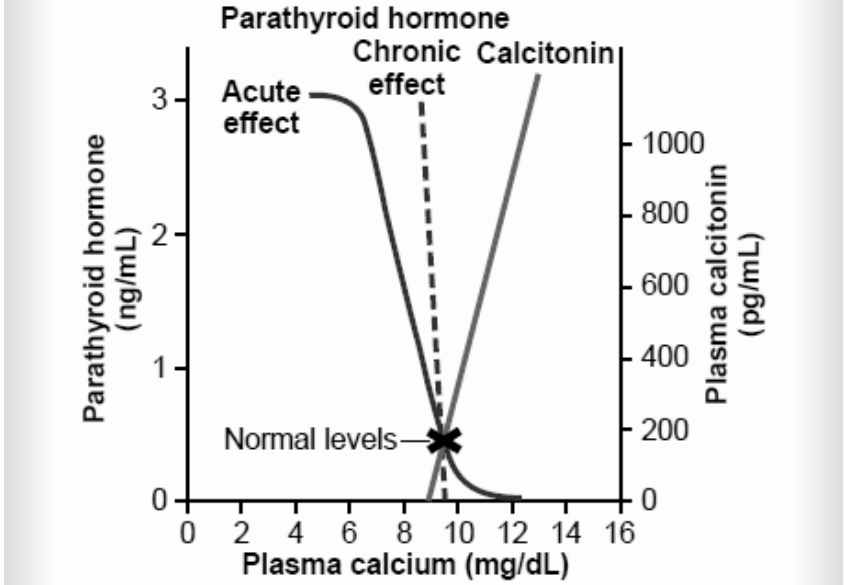
CALCITONIN

Calcitonin has little or no direct effect on the GI tract.

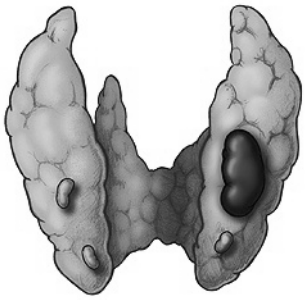


Net result is reduced osteoclastic and osteoblastic activity





DISORDERS OF PARATHYROID HORMONE SECRETION



Hypoparathyroidism

Causes

Injury to the parathyroid glands (surgery) & Autoimmune.

Signs & symptoms (due to hypocalcaemia)

- **Tingling in the lips, fingers, and toes**
- **Dry hair, brittle nails, and dry, coarse skin**
- **Muscle cramps and pain in the face, hands, legs, and feet**
- **Cataracts on the eyes**
- **Malformations of the teeth, including weakened tooth enamel.**
- **Loss of memory, Headaches**
- **sever muscle spasms(tetany) and convulsions**

Treatment Calcium carbonate and vitamin D supplements

Figure 79–2

Hypocalcemic tetany in the hand, called carpopedal spasm.

Positive Chvostek's sign is facial nerve irritability/spasms elicited by tapping the nerve

Hyperparathyroidism

- Primary hyperparathyroidism adenomas
- Secondary hyperparathyroidism

  physiological compensatory hypertrophy of all parathyroids because of hypocalcaemia, such as occurs in renal failure or vitamin D deficiency. PTH levels are raised but calcium levels are low or normal, and PTH falls to normal after correction of the cause of hypocalcaemia where this is possible.

Hyperparathyroidism (PTH Excess)

Primary

Manifestations:

- **Hypercalcemia ↑ Ca^{2+}**
- **Hypophosphemia ↓Po4**
- **Hypercalciuria**
- **Calcium stones in kidney**
- **Demineralisation of bone multiple bone cysts (osteitis fibrosa cystic)**
- **Precipitation of calcium in soft tissues occur when Ca > 17mg/dl.**

Secondary (compensatory)

Due to ↓Ca^{2+} in ECF

Causes:

1) **Low calcium diet**
2) **Pregnancy**
3) **Lactation**
4) **Rickets**
5) **Osteomalcia**
6) **Chronic renal failure**
   a) **Phosphate retention**
   b) **↓ 1,25(OH) – D3 synthesis**

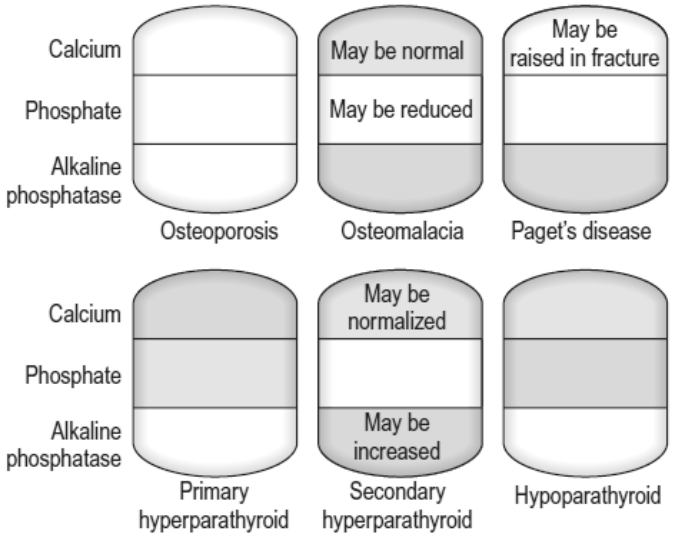


Fig. 10.35 **Changes in serum calcium, phosphate and alkaline phosphatase in main bone disorders.** Shading represents increased (red), reduced (blue) or normal (white) levels.

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
- Defect in vitamin D availability or metabolism
- Plasma Concentrations of Calcium and Phosphate Decrease in Rickets

Causes of rickets/osteomalacia

- Deficient intake or absorption of vitamin D
- Inadequate synthesis in skin, Low dietary intake, Malabsorption
- Defective 25-hydroxylation
- Chronic cholestasis (e.g. primary biliary cirrhosis) & Anticonvulsant therapy
- Defective 1-alpha hydroxylation
- Chronic kidney disease, Tubular disorders,Vitamin D-dependent rickets types I and II
- Inhibitors of mineralization
- Fluoride, aluminium, bisphosphonates
- Miscellaneous

❑**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 →

❑**Treatment of Rickets**

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

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.

blood level of calcium falls below 7 mg/dl

→ signs of tetany: (positive Chvostek's sign)

→Death: tetanic respiratory spasm

❑Osteomalacia-"Adult Rickets".
(rare).

• serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat)

• almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

Osteoporosis—Decreased Bone Matrix

•Osteoporosis is the most common of all bone diseases in adults, especially in old age.

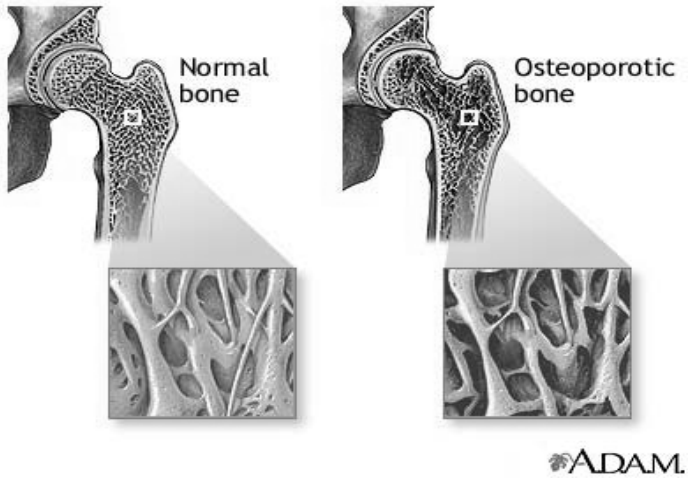
•Osteoporosis involves a reduction in total bone mass with an equal loss of both bone mineral and organic matrix.

•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 of Osteoporosis

(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

Osteoporosis—Decreased Bone Matrix



Dual energy X-ray absorptiometry (DXA) measures

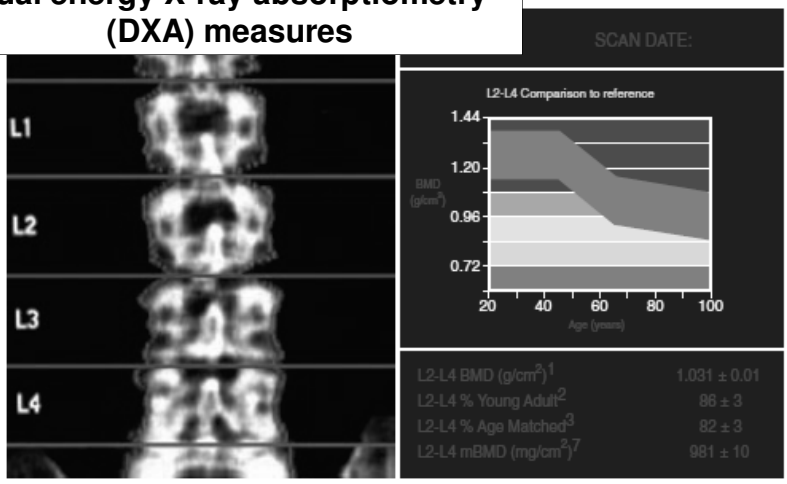


Fig. 10.39 **Dual energy X-ray absorptiometry of the lumbar spine.** The AP image of the lumbar spine is shown on the left and on the right, the patient's value is expressed in relation to the reference range.

Osteoporosis—Decreased Bone Matrix