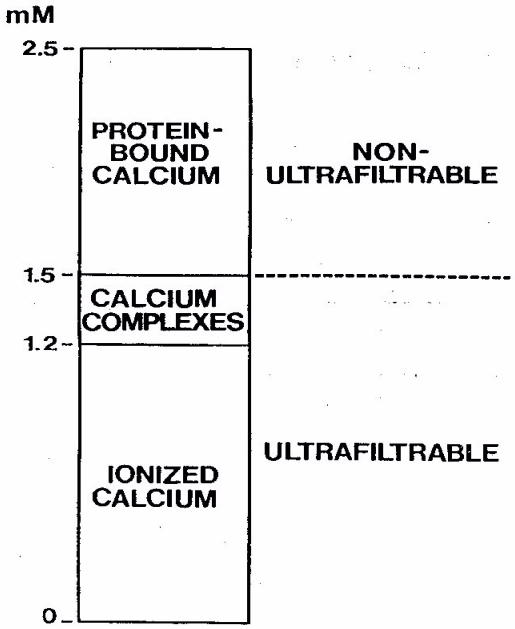
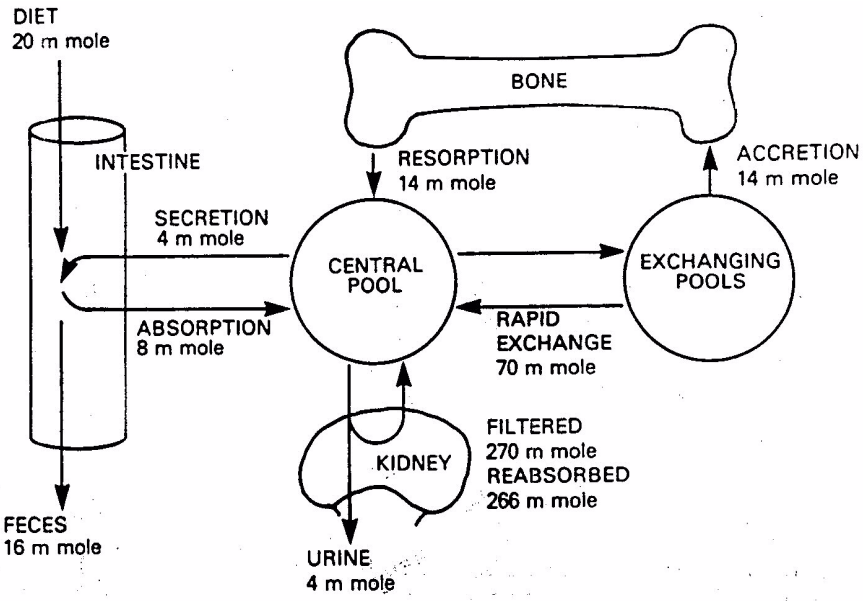
Calcium

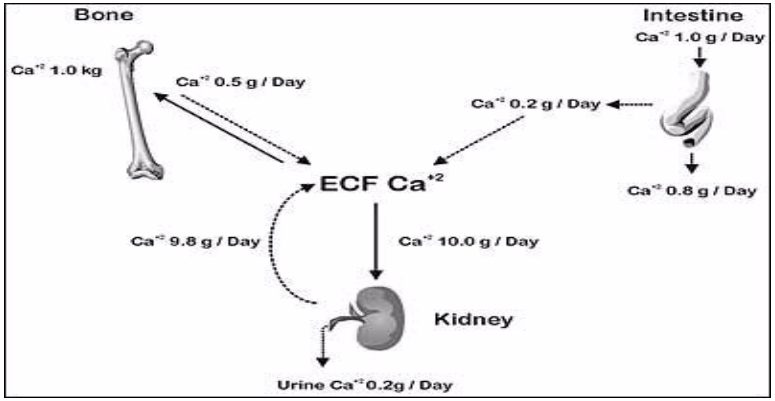
Metabolism, homeostatic disturbances



Calcium

- The skeleton, the gut and the kidney play a major role in assuring calcium homeostasis. Overall, in a typical individual, if 1000 mg of calcium are ingested in the diet per day, approximately 200 mg will be absorbed. Approximately 10 g of calcium will be filtered daily through the kidney and most will be reabsorbed with about 200 mg being excreted in the urine. The normal 24 hour excretion of calcium may however vary between 100 and 300 mg per day (2.5 to 7.5 mmoles per day). The skeleton, a storage site of about 1 kg of calcium, is the major calcium reservoir in the body. Ordinarily, as a result of normal bone turnover, approximately 500 mg of calcium is released from bone per day and the equivalent amount is accreted per day.





Calcium balance. On average, in a typical adult approximately 1g of elemental calcium (Ca+2) is ingested per day. Of this, about 200mg/day will be absorbed and 800mg/day excreted. Approximately 1kg of Ca+2 is stored in bone and about 500mg/day is released by resorption or deposited during bone formation. Of the 10g of Ca+2 filtered through the kidney per day only about 200mg appears in the urine, the remainder being reabsorbed.

Distribution of Calcium, Phosphorus, and Magnesium			
	Total body content, g	% in skeleton	% in soft tissues
Calcium	1000	99	1
Phosphorus	600	85	15
Magnesium	25	65	35

Regulation of Calcium and Skeletal Metabolism

Minerals
- Calcium (Ca)
- Phosphorus (P)
- Magnesium (Mg)

Organ Systems
- Skeleton
- Kidney
- GI tract
- Other

Hormones
- Calcitropic hormones
  - Parathyroid Hormone (PTH)
  - Calcitonin (CT)
  - Vitamin D [1,25(OH2)D]
  - PTHrP
- Other hormones
  - Gonadal and adrenal steroids
  - Thyroid hormones

Growth factor and cytokines

Multiple biological functions of calcium

- Cell signalling
- Neural transmission
- Muscle function
- Blood coagulation
- Enzymatic co-factor
- Membrane and cytoskeletal functions
- Secretion
- Biomineralization

Distribution of Calcium	Bone Structure (cellular and non-cellular)
Total body calcium- 1kg 99% in bone 1% in blood and body fluids Intracellular calcium Cytosol Mitochondria Other microsomes Regulated by "pumps" Blood calcium - 10mgs (8.5-10.5)/100 mls Non diffusible - 3.5 mgs Diffusible- 6.5 mgs	Inorganic (69%) Hydroxyapatite - 99% 3 $Ca_{10}(PO_4)_6(OH)_2$ Organic (22%) Collagen (90%) Non-collagen structural proteins proteoglycans sialoproteins gla-containing proteins a_2HS-glycoprotein Functional components growth factors cytokines

Blood Calcium - 10mgs/100 mls(2.5 mmoles/L)	Diet
Non diffusible - 3.5 mgs Albumin bound - 2.8 Globulin bound - 0.7 Diffusible - 6.5 mgs Ionized - 5.3 Complexed - 1.2 mgs bicarbonate - 0.6 mgs citrate - 0.3 mgs phosphate - 0.2 mgs other Close to saturation point tissue calcification kidney stones	Dietary calcium Milk and dairy products (1qt = 1gm) Dietary supplements Other foods Other dietary factors regulating calcium absorption Lactose Phosphorus

Calcium Absorption (0.4-1.5 g/d)	Mechanisms of GI Calcium Absorption
Primarily in duodenum 15-20% absorption Adaptative changes low dietary calcium growth (150 mg/d) pregnancy (100 mg/d) lactation (300 mg/d) Fecal excretion	Vitamin D dependent Duodenum > jejunum > ileum Active transport across cells calcium binding proteins (e.g., calbindins) calcium regulating membranomes Ion exchangers Passive diffusion

Urinary Calcium	Regulation of Urinary Calcium
Daily filtered load 10 gm (diffusible) 99% reabsorbed Two general mechanisms Active - transcellular Passive - paracellular Proximal tubule and Loop of Henle reabsorption Most of filtered load Mostly passive Inhibited by furosemide Distal tubule reabsorption 10% of filtered load Regulated (homeostatic) stimulated by PTH inhibited by CT vitamin D has small stimulatory effect stimulated by thiazides Urinary excretion 50 - 250 mg/day 0.5 - 1% filtered load	Hormonal - tubular reabsorption PTH - decreases excretion (clearance) CT - increases excretion (calciuretic) $1,25(OH)_2D$ - decreases excretion Diet Little effect Logarithmic Other factors Sodium - increases excretion Phosphate - decreases excretion Diuretics - thiazides vs loop thiazides - inhibit excretion furosemide - stimulate excretion

Regulation of the production and action of humoral mediators of calcium homeostasis

- **Parathyroid Hormone (PTH)**
- Regulation of Production
- PTH is an 84 amino acid peptide whose known bioactivity resides within the NH2-terminal 34 residues.
- The major regulator of PTH secretion from the parathyroid glands is the ***ECF calcium***. The relationship between ECF calcium and PTH secretion is governed by a steep inverse sigmoidal curve which is characterized by a maximal secretory rate at low ECF calcium, a midpoint or "set point" which is the level of ECF calcium which half-maximally suppresses PTH, and a minimal secretory rate at high ECF calcium.

Regulation of the production and action of humoral mediators of calcium homeostasis

- The parathyroid glands detect ECF calcium via a ***calcium-sensing receptor (CaSR***). This receptor has a large NH2-terminal extracellular domain which binds ECF calcium, seven plasma membrane-spanning helices and a cytoplasmic COOH-terminal domain.
- It is a member of the ***superfamily of G protein coupled receptors*** and in the parathyroid chief cells is linked to various intracellular second-messenger systems. Transduction of the ECF calcium signal via this molecule leads to alterations in PTH secretion.

Regulation of the production and action of humoral mediators of calcium homeostasis

- A rise in calcium will promote enhanced PTH degradation and a fall in calcium will decrease intracellular degradation so that more intact bioactive PTH is secreted.
- Bioinactive PTH fragments, which can also be generated in the liver, are cleared by the kidney. With sustained low ECF calcium there is a change in PTH biosynthesis.
- Low ECF calcium leads to increased transcription of the gene encoding PTH and enhanced stability of PTH mRNA. Finally sustained hypocalcemia can eventually lead to parathyroid cell proliferation and an increased total secretory capacity of the parathyroid gland.

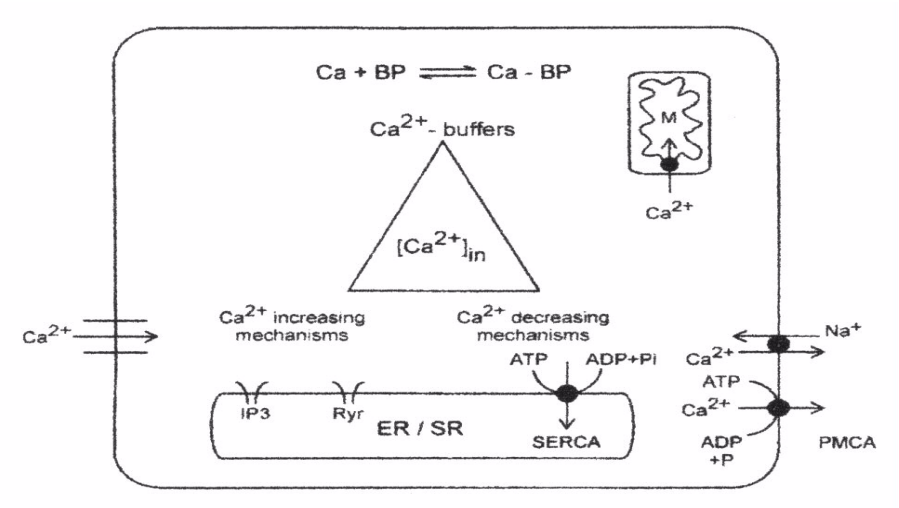
Regulation of the production and action of humoral mediators of calcium homeostasis

One of the most physiologically relevant regulator is 1,25(OH)2D3 which appears capable

- ❑ of tonically reducing PTH secretion
- ❑ of decreasing PTH gene expression
- ❑ of inhibiting parathyroid cell proliferation.

Additional factors including catecholamines and other ***biogenic amines, prostaglandins, cations (eg lithium and magnesium), phosphate per se and transforming growth factor alpha (TGFa)*** have been implicated in the regulation of PTH secretion.

Intracellular calcium homeostasis



Different possibilities of altered intracellular calciu homeostasis in different diseases

Basal $[Ca^{++}]_i$	$[Ca^{++}]_i$ response to stimulation	Example	Form
Gradually increasing	=/↓	Infarction, toxin-induced cellular death, acute pancreatitis	Acute
Increased, sustained	↑	Hypertension	Chronic
	↓	Idiopathic heart failure	Chronic
Normal, sustained	↑	Alzheimer´s disease	Chronic
	↓	Chronic inflammatory diseases (Crohn´s disease, rheumatoid arthritis)	Chronic

PTH actions

1. Renal Actions

- PTH has little effect on modulating calcium fluxes in the proximal tubule where 65% of the filtered calcium is reabsorbed, coupled to the bulk transport of solutes such as sodium and water.
- PTH binds to its cognate receptor, the **type I PTH/PTHrP receptor (PTHR**), a 7-transmembrane-spanning G protein-coupled protein which is linked to both the adenylate cyclase system and the phospholipase C system. Stimulation of adenylate cyclase is believed to be the major mechanism whereby PTH causes internalization of the type II Na+/Pi- (inorganic phosphate) co-transporter leading to decreased phosphate reabsorption and phosphaturia.

PTH actions

- PTH can, after binding to the PTHR, also stimulate the 25(OH)D3-1a hydroxylase, leading to increased synthesis of 1,25(OH)2D3.
- A reduction in ECF calcium can itself stimulate 1,25(OH)2D3 production but whether this occurs via the CaSR is presently unknown.
- Finally PTH can also inhibit Na+ and HC03- reabsorption in the proximal tubule by inhibiting the apical type 3 Na+/H+ exchanger, and the basolateral Na+/K+-ATPase as well as by inhibiting apical Na+/Pi-cotransport.

PTH actions

- About 20% of filtered calcium is reabsorbed in the cortical thick ascending limb of the loop of Henle (CTAL) and 15% in the distal convoluted tubule (DCT) and it is here that PTH also binds to the PTHR and again by a cyclic AMP-mediated mechanism, enhances calcium reabsorption.
- In the CTAL, at least, this appears to occur by increasing the activity of the Na/K/2Cl cotransporter that drives NaCl reabsorption and also stimulates paracellular calcium and magnesium reabsorption.

PTH actions

- The CaSR is also resident in the CTAL and can respond to an increased ECF calcium by activating phospholipase A2, reducing the activity of the Na/K/2Cl cotransporter and of an apical K channel, and diminishing paracellular calcium and magnesium reabsorption. Consequently a raised ECF calcium antagonizes the effect of PTH in this nephron segment and ECF calcium can in fact participate in this way in the regulation of its own homeostasis.
- The inhibition of NaCl reabsorption and loss of NaCl in the urine that results may contribute to the volume depletion observed in severe hypercalcemia. ECF calcium may therefore act in a manner analogous to "loop" diuretics such as furosemide.

PTH actions

In the distal convoluted tubule (DCT), PTH can also influence *transcellular calcium transport*. This is a multistep process involving

- transfer of luminal Ca+2 into the renal tubule cell via the transient receptor potential channel (TRPV5)
- translocation of Ca++2 across the cell from apical to basolateral surface a process involving proteins such as calbindin-D28K, and
- active extrusion of Ca++2 from the cell into the blood via a Na+/Ca++2 exchanger, designated NCX1.

PTH markedly stimulates Ca2+ reabsorption in the DCT primarily by augmenting NCX1 activity via a cyclic AMP-mediated mechanism.

PTH actions

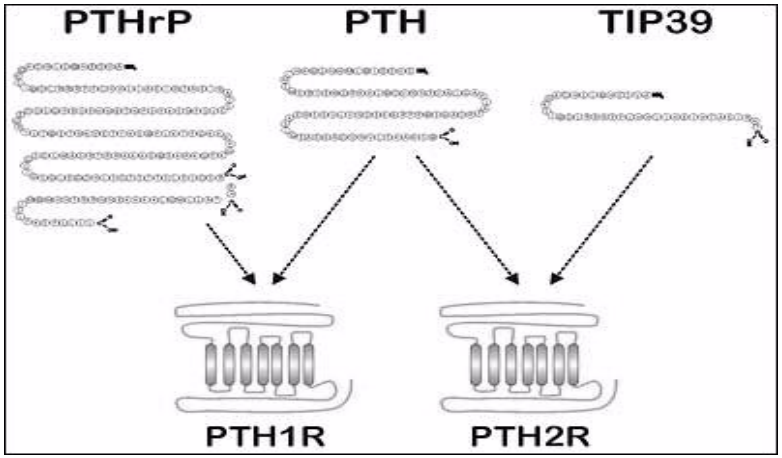
- **2. Skeletal Actions**
- In bone, the PTHR is localized on cells of the osteoblast phenotype which are of mesenchymal origin but not on osteoclasts which are of hematogenous origin.
- In the postnatal state the major physiologic role of PTH appears to be to maintain normal calcium homeostasis by enhancing osteoclastic bone resorption and liberating calcium into the ECF. This effect of PTH on increasing osteoclast stimulation is indirect, with PTH binding to the PTHR on pre-osteoblastic stromal cells and enhancing the production of the cytokine RANKL (receptor activator of NFkappaB ligand), a member of the tumor necrosis factor (TNF) family.

PTH actions

- Levels of a soluble decoy receptor for RANKL, termed ***osteoprotegerin,*** are diminished facilitating the capacity for increased stromal cell-bound RANKL to interact with its cognate receptor, RANK, on cells of the osteoclast series. Multinucleated osteoclasts are derived from hematogenous precursors which commit to the monocyte/macrophage lineage, and then proliferate and differentiate as mononuclear precursors, eventually fusing to form *multinucleated osteoclasts*. These can then be activated to form *bone-resorbing osteoclasts.* RANKL can drive many of these proliferation/differentiation/fusion/activation steps although other cytokines, notably monocyte-colony stimulating factor (M-CSF) may participate in this process.

Parathyroid Hormone Relation Peptide (PTHrP)

- PTHrP was discovered as the mediator of the syndrome of ***"humoral hypercalcemia of malignancy" (HHM***). In this syndrome a variety of cancers, essentially in the absence of skeletal metastases, produce a PTH-like substance which can cause a constellation of biochemical abnormalities including ***hypercalcemia, hypophosphatemia*** and ***increased urinary cyclic AMP excretion***. These mimic the biochemical effects of PTH but occur in the absence of detectable circulating levels of this hormone.



PTH and PTHR gene families: PTHrP, PTH and TIP39 appear to be members of a single gene family. The receptors for these peptides, PTH1R and PTH2R, are both 7 transmembrane-spanning G protein-coupled receptors. PTHrP binds and activates PTH1R; it binds weakly to PTH2R and does not activate it. PTH can bind and activate both PTH1R and PTH2R.

PTHrP Actions

Effects of PTHrP can be grouped into those relating

- ❑ to ion homeostasis
- ❑ to smooth muscle relaxation;
- ❑ associated with cell growth, differentiation and apoptosis.
- ❑ necessary for normal fetal calcium homeostasis

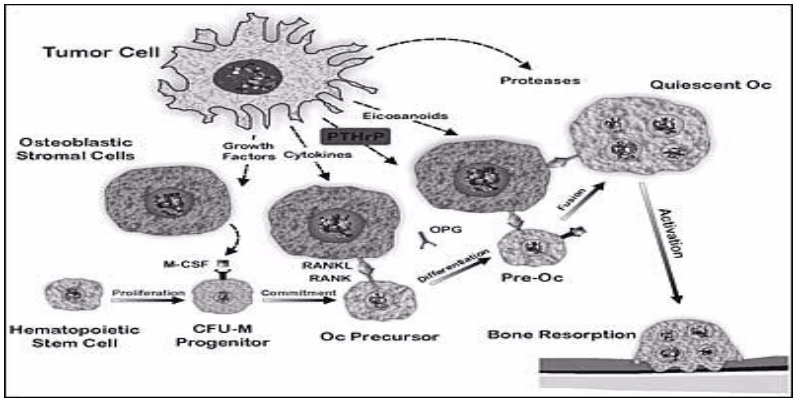
The majority of the physiological effects of PTHrP appear to occur by short-range ie paracrine/autocrine mechanisms rather than long-range ie endocrine mechanisms..

In the adult the major role in calcium and phosphorus homeostasis appears to be carried out by PTH rather than by PTHrP in view of the fact that PTHrP concentrations in normal adults are either very low or undetectable. This situation reverses when neoplasms constitutively hypersecrete PTHrP in which case PTHrP mimics the effects of PTH on bone and kidney and the resultant hypercalcemia suppresses endogenous PTH secretion.

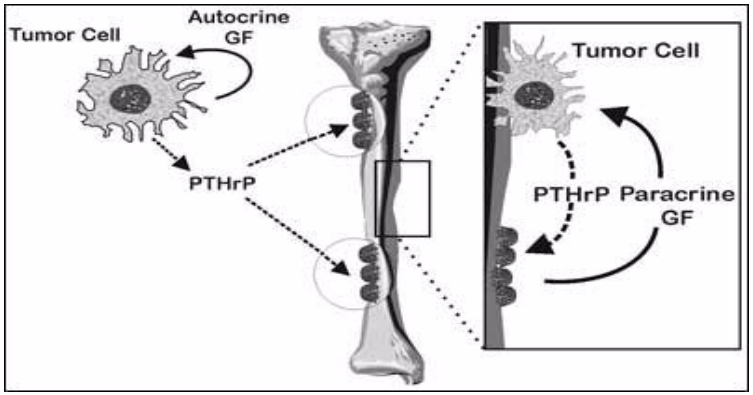
PTHrP Actions

PTHrP has been shown to modify

- ***cell growth, differentiated function and programmed cell death*** in a variety of different fetal and adult tissues. The most striking developmental effects of PTHrP however have been in the skeleton. The major alteration appears to occur in the cartilaginous growth plate where, in the absence of PTHrP, chondrocyte proliferation is reduced and accelerated chondrocyte differentiation and apoptosis occurs.
- ***increased bone formation***, apparently due to secondary hyperparathyroidism and the overall effect is a severely deformed skeleton.
- ***normal development of the cartilaginous growth plate***. In the fetus PTH has predominantly an anabolic role in trabecular bone whereas PTHrP regulates the orderly development of the growth plate. In contrast, in postnatal life, PTHrP acting as a paracrine/autocrine modulator assumes an anabolic role for bone whereas PTH predominantly defends against a decrease in extracellular fluid calcium by resorbing bone.



Production of bone resorbing substances by neoplasms. Tumor cells may release proteases which can facilitate tumor cell progression through unmineralized matrix. Tumors cells can also release PTHrP, cytokines, eicosanoids and growth factors (eg EGF) which can act on osteoblastic stromal cells to increase production of cytokines such as M-CSF and RANKL. RANKL can bind to its cognate receptor RANK in osteoclastic cells, which are of hepatopoietic origin, and increase production and activation of multinucleated osteoclasts which can resorb mineralized bone.



Growth factor-regulated PTHrP production in tumor states. Tumor cells at a distance from bone may be stimulated by autocrine growth factors (GF) to increase production of PTHrP which can then travel to bone via the circulation and enhance bone resorption. Tumor cells metastatic to bone (inset) may secrete PTHrP which can resorb bone and release growth factors which in turn can act in a paracrine manner to further enhance PTHrP production.

Manifestations of Hypercalcemia		
	Acute	**Chronic**
Gastrointestinal	Anorexia, nausea, vomiting	Dyspepsia, constipation, pancreatitis
Renal	Polyuria, polydipsia	Nephrolithiasis, nephrocalcinosis
Neuro-muscular	Depression, confusion, stupor, coma	Weakness
Cardiac	Bradycardia, first degree atrio-ventricular	Hypertension block, digitalis sensitivity

Hypercalcemic Disorders

A. Endocrine Disorders Associated with Hypercalcemia

1.Endocrine Disorders with Excess PTH Production
- •Primary Sporadic hyperparathyroidism
- •Primary Familial Hyperparathyroidism
  - •MEN I
  - •MEN IIA
  - •FHH and NSHPT
  - •Hyperparathyroidism - Jaw Tumor Syndrome
  - •Familial Isolated Hyperparathyroidism

2.Endocrine Disorders without Excess PTH Production
- •Hyperthyroidism
- •Hypoadrenalism
- •Jansen's Syndrome

Hypercalcemic Disorders

B. Malignancy-Associated Hypercalcemia (MAH)

1.MAH with Elevated PTHrP
- •Humoral Hypercalcemia of Malignancy
- •Solid Tumors with Skeletal Metastases
- •Hematologic Malignancies

2.MAH with Elevation of Other Systemic Factors
- •MAH with Elevated 1,25(OH)2D3
- •MAH with Elevated Cytokines
- •Ectopic Hyperparathyroidism
- •Multiple Myeloma

Hypercalcemic Disorders

C. Inflammatory Disorders Causing Hypercalcemia

1.Granulomatous Disorders
2.AIDS

D. Disorders of Unknown Etiology

1.Williams Syndrome
2.Idiopathic Infantile Hypercalcemia

E. Medication-Induced

1.Thiazides
2.Lithium
3.Vitamin D
4.Vitamin A
5.Estrogens and Antiestrogens
6.Aluminium Intoxication
7.Milk-Alkali Syndrome

Clinical Features Associated With Hypocalcemia

Neuromuscular inability

- •Chvostek's sign
- •Trousseau's sign
- •Paresthesias
- •Tetany
- •Seizures (focal, petit mal, grand mal)
- •Fatigue
- •Anxiety
- •Muscle cramps
- •Polymyositis
- •Laryngeal spasms
- •Bronchial spasms

Neurological signs and symptoms in hypocalcemia

Extrapyramidal signs due to calcification of basal ganglia
Calcification of cerebral cortex or cerebellum
Personality disturbances
Irritability
Impaired intelletual ability Nonspecific EEG changes
Increased intracranial pressure
Parkinsonism
Choreoathetosis
Dystonic spasms

Mental status in hypocalcemia

- Confusion
- Disorientation
- Psychosis
- Psychoneurosis

Ectodermal changes in hypocalcemia

- Dry skin
- Coarse hair
- Brittle nails
- Alopecia
- Enamel hypoplasia
- Shortened premolar roots
- Thickened lamina dura
- Delayed tooth eruption
- Increased dental caries
- Atopic eczema
- Exfoliative dermatitis
- Psoriasis
- Impetigo herpetiformis

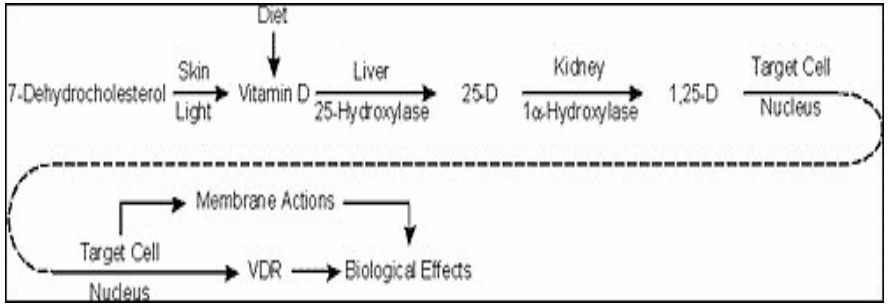
Smooth muscle involvement

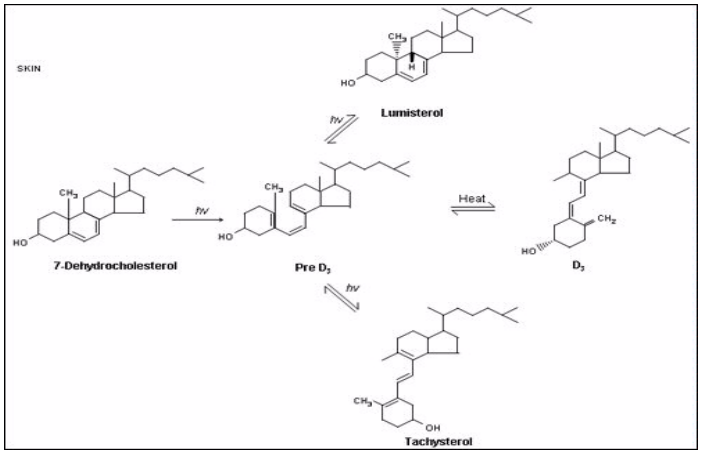
- Dysphagia
- Abdominal pain
- Biliary colic
- Dyspnea
- Wheezing

- **Ophthalmologic manifestations in hypocalcemia**
- Subcapsular cataracts
- Papilledema

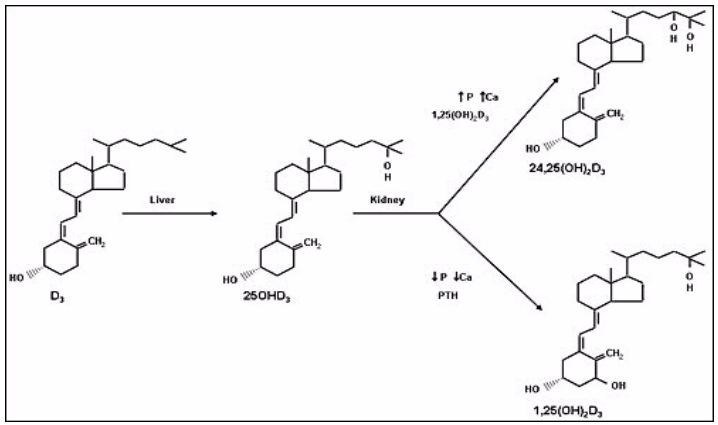
- **Cardiac manifestations in hypocalcemia**
- Prolonged QT interval in ECG
- Congestive heart failure
- Cardiomyopathy

The Metabolic Activation of Vitamin D

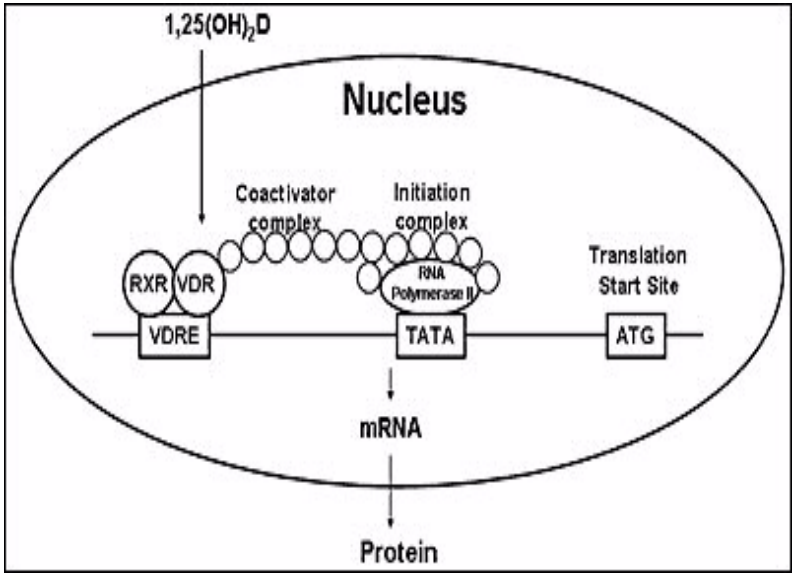




The production of vitamin D3 from 7-dehydrocholesterol in the epidermis. Sunlight (the ultraviolet B component) breaks the B ring of the cholesterol structure to form pre- D3. Pre-D3 then undergoes a thermal induced rearrangement to form D3. Continued irradiation of pre- D3 leads to the reversible formation of lumisterol3 and tachysterol3 which can revert back to pre-D3 in the dark.



The metabolism of vitamin D3. The liver converts vitamin D to 25OHD. The kidney converts 25OHD to 1,25(OH)2D and 24,25(OH)2D. Other tissues contain these enzymes, but the liver is the main source for 25-hydroxylation, and the kidney is the main source for 1a-hydroxylation. Control of metabolism of vitamin D to its active metabolite, 1,25(OH)2D, is exerted primarily at the renal level where calcium, phosphorus, parathyroid hormone, and 1,25(OH)2D regulate the levels of 1,25(OH)2D produced.



1,25(OH)2D-initiated gene transcription

- 1,25(OH)2D enters the target cell and binds to its receptor, VDR. The VDR then heterodimerizes with the retinoid X receptor (RXR). This increases the affinity of the VDR/RXR complex for the vitamin D response element (VDRE), a specific sequence of nucleotides in the promoter region of the vitamin D responsive gene. Binding of the VDR/RXR complex to the VDRE attracts a complex of proteins termed coactivators to the VDR/RXR complex. The coactivator complex spans the gap between the VDRE and RNA polymerase II and other proteins in the initiation complex centered at or around the TATA box (or other transcription regulatory elements). Transcription of the gene is initiated to produce the corresponding mRNA, which leaves the nucleus to be translated to the corresponding protein.

The Metabolic Activation of Vitamin D

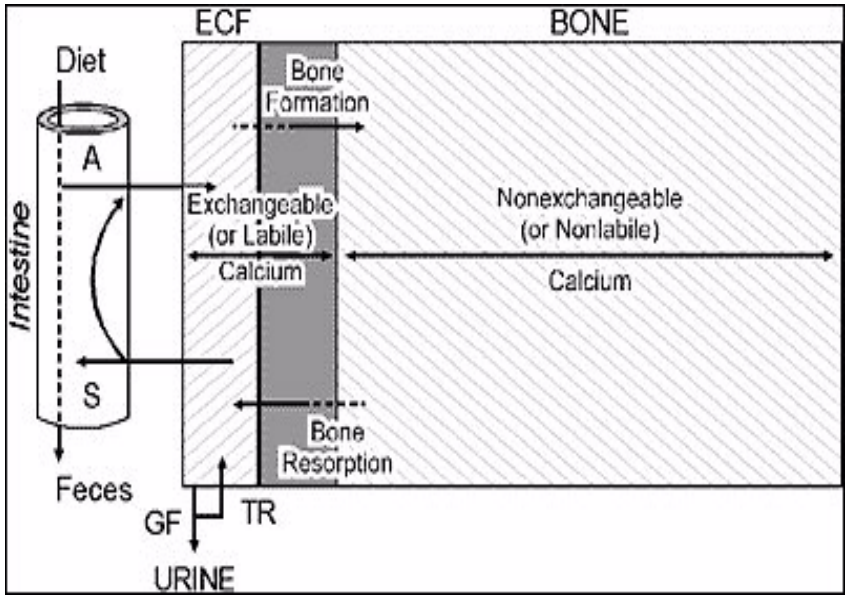
- Vitamin D from the diet or the conversion from precursors in skin through ultraviolet radiation (light) provides the substrate of the indicated steps in metabolic activation.
- The pathways apply to both the endogenous animal form of vitamin D (vitamin D3, cholecalciferol) and the exogenous plant form of vitamin D (vitamin D2, ergocalciferol), both of which are present in humans at a ratio of approximately 2:1.
- In the kidney, 25-D is also converted to 24-hydroxylated metabolites which may have unique effects on chondrogenesis and intramembranous ossification.
- The many effects of vitamin D metabolites are mediated through nuclear receptors or effects on target-cell membranes

Cellular bone mineral transport

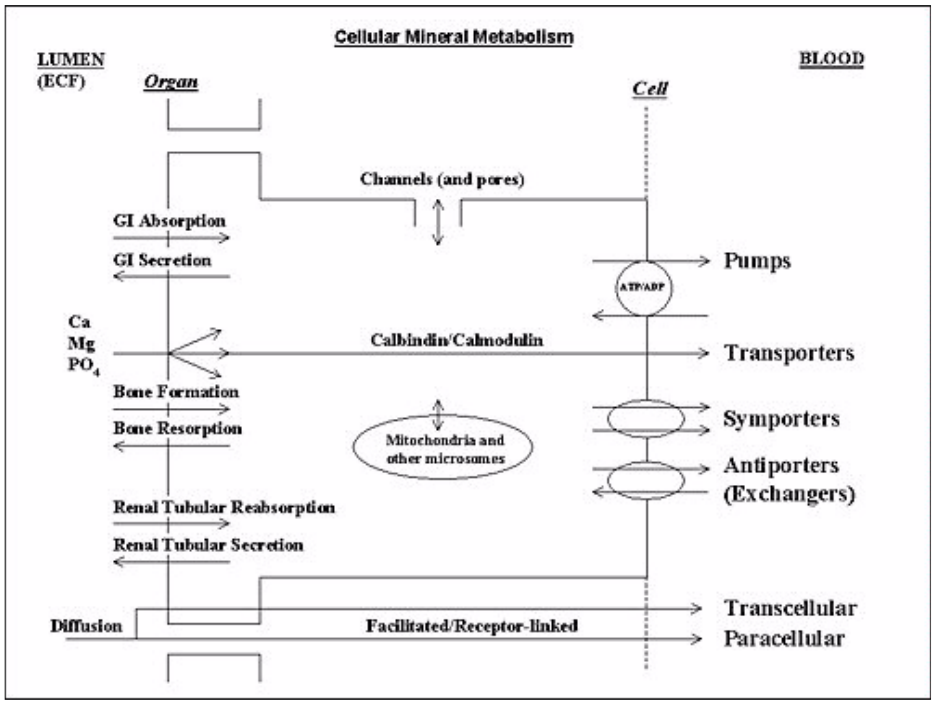
- For calcium, the transcellular transport is ferried by the interaction among a family of proteins that include ***calmodulin, calbindin, integral membrane protein,*** and ***alkaline phosphatase;*** the latter three are vitamin D dependent.
- Cytoskeletal interactions are likely important for transcellular transport as well. Exit from the cell is regulated by membrane structures similar to those that mediate entry. There do not appear to be any corresponding binding proteins for phosphorous, so diffusional gradients and cytoskeletal interactions seem to regulate cellular transport.

Hormonal regulation of cellular bone mineral transport

- The molecular details of the hormonal regulation of cellular bone mineral transport have not been fully elucidated.
- ***Parathormon, calcitonin and vitamin D*** regulate these molecular mechanisms through their biological effects on the participating membrane structures and transport proteins.
- For the enterocyte, vitamin D is central in enhancing the movement of calcium into the cell through its stimulation of calbindin synthesis.
- For kidney tubules, PTH is the key regulator in a corresponding manner for the transport of phosphate and calcium.
- For bone, PTH and CT are the major regulators of cellular calcium and phosphate transport, while vitamin D provides appropriate concentrations of these minerals through its renal and GI actions.

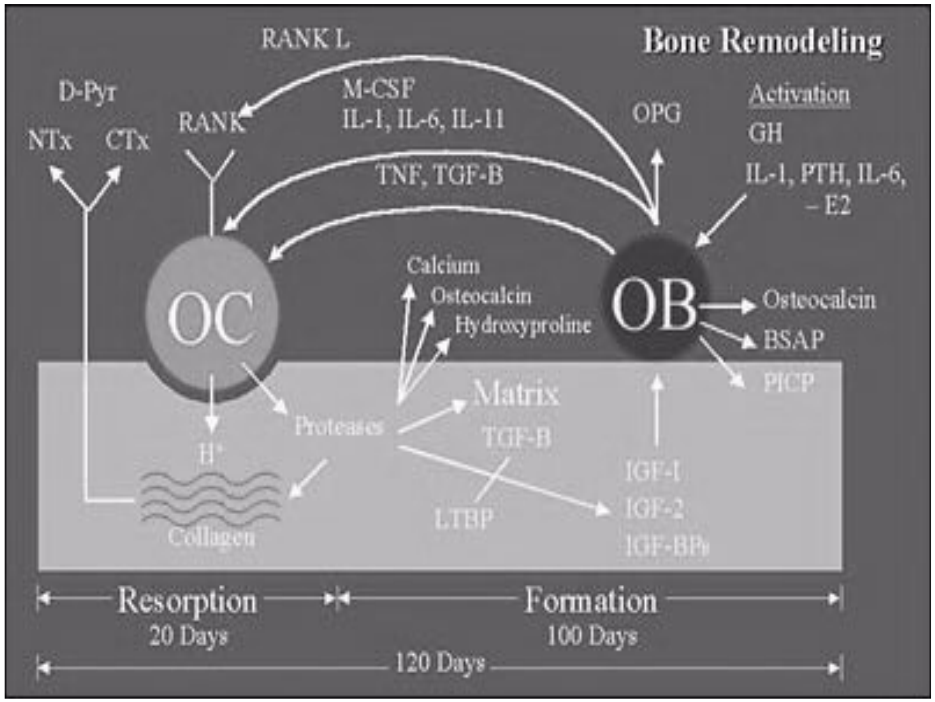


Schematic Representation of Calcium and Skeletal Metabolism



To the previous figure:

- It provides a simplified version of the cellular regulation of bone mineral metabolism and transport.
- Mineral homeostasis requires the transport of calcium, magnesium, and phosphate across their target cells in bone, intestine, and kidney.
- This transport can be across cells ***(transcellular)*** and around cells ***(pericellular).*** The pericellular transport is usually diffusional, down a gradient , and not hormonally regulated. Diffusion can also occur through cell channels, which can be gated. Transport across cells is more complex and usually against a gradient. This active transport is energized by either ATP hydrolysis or electrochemical gradients and involves membrane structures that are generally termed porters, exchangers, or pumps.
- Three types of porters have been described, ***uniporters*** of a single substance; ***symporters*** for more than one substance in the same direction; and ***anti-porters*** for more than one substance in opposite directions.



To the previous figure:

- The bone remodeling cycle. The osteoblast (OB) orchestrates the orderly process of bone remodeling through activation signals from systemic factors including growth hormone (GH) interleukins (IL-1,IL-6) Parathyroid hormone (PTH) and withdrawal of estrogen (-E2). M-CSF and RANKL are the two major OB mediated factors which regulate the recruitment and differentiation of the osteoclast (OC). Osteoprotogerin (OPG) is also synthesized by OBs and serves as a soluble decoy receptor blocking activation of RANK. Inhibition or knockout of these signals from OB-OC results in reduction in bone resorption. The IGFs are released during bone resorption and serve as coupling factors to recruit new OBs to the surface. These peptides may also be important for osteoclast activity.

Mediators of Bone Remodeling

Normal adult bone is constantly undergoing "turnover" or remodeling . This is characterized by sequences of

- activation of osteoclasts followed by
- osteoclastic bone resorption followed by
- osteoblastic bone formation.

These sequential cellular activities occur in focal and discrete packets in both trabecular and cortical bone and are termed bone remodeling units. This coupling of osteoblastic bone formation to bone resorption may occur via the action of growth factors released by resorbed bone eg TGFb, IGF-1 and fibroblast growth factor (FGF) which can induce osteoclast apoptosis and also induce osteoblast chemotaxis proliferation and differentiation at the site of repair.

Mediators of Bone Remodeling

A number of systemic and local factors regulate the process of bone remodelling. In general those factors which enhance bone resorption may do so

- by creating an imbalance between the depth of osteoclastic bone erosion and the extent of osteoblastic repair
- by increasing the numbers of remodeling units which are active at any given time ie by increasing the activation frequency of bone remodeling.

One predominant example in which osteoblastic activity does not completely repair and replace the defect left by previous resorption is in multiple myeloma; such an imbalance can occasionally also occur in association with some advanced solid malignancies.

Mediators of Bone Remodeling

- *Systemic hormones such as **PTH, PTHrP and 1,25(OH)2D3*** all initiate ***osteoclastic bone resorption*** and increase the activation frequency of ***bone remodeling***.
- ***Thyroid hormone receptors*** are present in osteoblastic cells and triiodothyronine can stimulate osteoclastic bone resorption and produce a high turnover state in bone
- ***Vitamin A*** has a direct stimulatory effect on osteoclasts and can induce bone resorption as well.

Mediators of Bone Remodeling

- A variety of local factors are critical for physiologic bone resorption and regulation of the normal bone-remodeling sequence.
- ***Interleukin-1 (IL-1)*** and M-CSF can be produced by both osteoblastic cells and by cells of the osteoclastic lineage.
- ***TNFa*** is released by monocytic cells
- ***TNFb*** (lymphotoxin) by activated T lymphocytes
- ***Interleukin-6 (IL-6)*** by osteoclastic cells.

Mediators of Bone Remodeling

All can enhance osteoclastic bone resorption.

- ***Leukotrienes*** can also induce osteoclastic bone resorption.
- ***Prostaglandins,*** particularly of the E series, may also stimulate bone resorption in vitro but appear to predominantly increase formation in vivo.
- The inappropriate production of these regulators in pathologic conditions such as cancer may contribute to altered bone dynamics, altered calcium fluxes through bone and ultimately in altered ECF calcium homeostasis.

Biochemical parameters of mineral and bone metabolism in patients with rickets and/or osteomalacia, by etiology

	Serum levels				
Etiology	Calcium	Phosphorous	iPTH	Bone specific alk. phos	24h urinary calcium excretion
Hypocalcemic e.g. vitamin D deficiency	Low to low normal	Low	Elevated	Elevated	Low
Hypophosphatemice.g. X-linked hypophosphatemia	Normal	Low	Normal to low normal	Elevated	Low to elevated
No abnormality in mineral homeostasis e.g. hypophosphatasia	Normal	Normal	Normal	Low	Normal

Alk. phos. alkaline phosphatase activity

Etiology of Osteoporosis in Men		
Etiology	Age-yrs	Clinical Features
Hypogonadism	30-80	low Test, low E2, inc resorption
Alcoholism	40-80	low test, E2+/-, +/- turnover
Glucocorticoids	20-80	+/- test, E2 +/-,inc resorption Decreased formation
Hypercalcuria	30-80	Test, E2 nl;inc resorption, Hypercalcuria, inc PTH,kidney stones
Idiopathic Osteoporosis-	40-80	fractures, low formation, low IGF1
Sprue	20-80	low 25OHD,turnover increased
Endocrine Disorders	20-80	Inc PTH in PHPT,increased resorption
PHPT,Thyrotoxicosis		in all cases; Dec PTH in thyrotoxicosis Cushings
E2- estradiol, Inc- increased, Test-testosterone PTH-parathyroid hormon, PHPT-primary hyperparathyroidism		

Effects of Glucocorticoids on Bone Mass		
Response to Glucocorticoids	**Effects on Bone Remodeling**	**Effects on Bone Mass**
Increased PTH secretion	Increased bone resorption ?decreased bone formation	rapid loss of bone
Decreased LH/FSH secretion	Increased bone resorption due Loss of estrogen	loss of bone
Impaired calcium absorption Due to decreased 1,25 D resorption	Increased PTH, increase bone	loss of bone
Increased calcium loss in urine	Secondary increase in PTH- Increased bone resorption	loss of bone
Acute suppression of Osteoblasts and apoptosis	reduced bone formation	gradual bone loss
Stimulation of osteoclastogenesis	increased bone resorption rapid	loss of bone