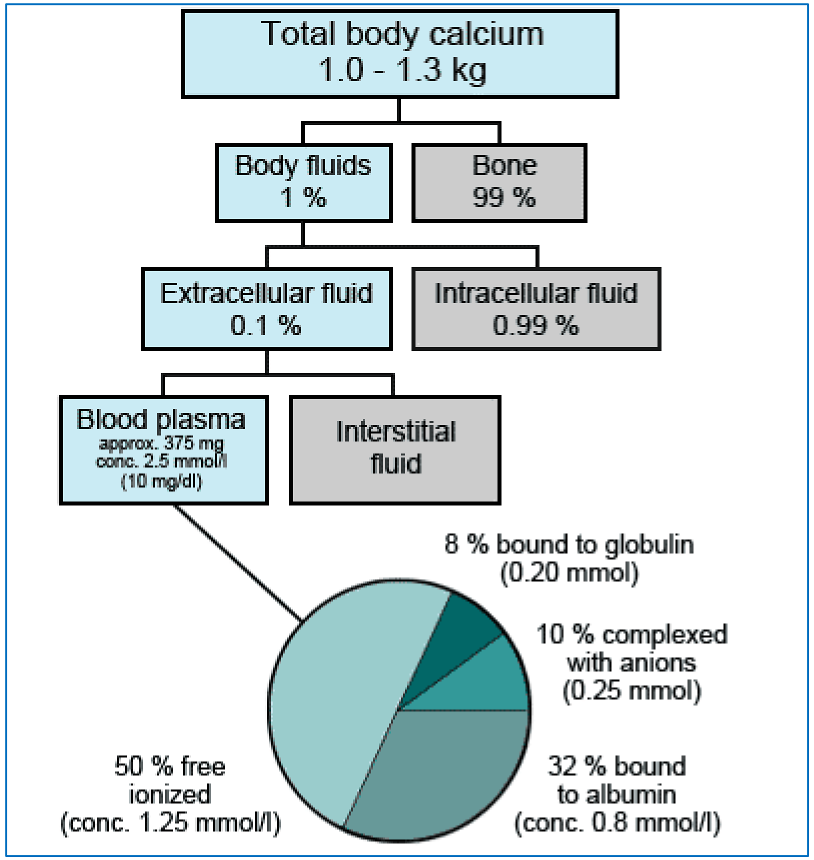
MUNI MED

Calcium

Metabolism, homeostasis disturbances

Physiology of Calcium

- 98% of the body calcium is in the skeleton
- Only 2% is in circulation and only half of this is free calcium (ionized Ca^{2+})
- This only is physiologically active
- The 1% is bound to proteins



Plasma calcium concentration

	mg/dL	meq/L	mmolL	% total
Free ionized	5.0	2.5	1.25	50
Protein-bound	4.2	2.1	1.05	44
Complexed	0.8	0.4	0.2	6
Total	10	5.0	2.50	100

↑ **Alkalosis:** increased calcium binding to protein; **decreased ionised fraction**

pH 7. 45

pH 7.35

Each 0.1 decrease in pH increases ionized calcium by 0.05 mmol/L

↓ **Acidosis:** decreased calcium binding to protein; **increased ionised fraction**

Guyton & Hall Textbook of Medical physiology, 11th ed.; J.E.Hall; Chapter 79

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

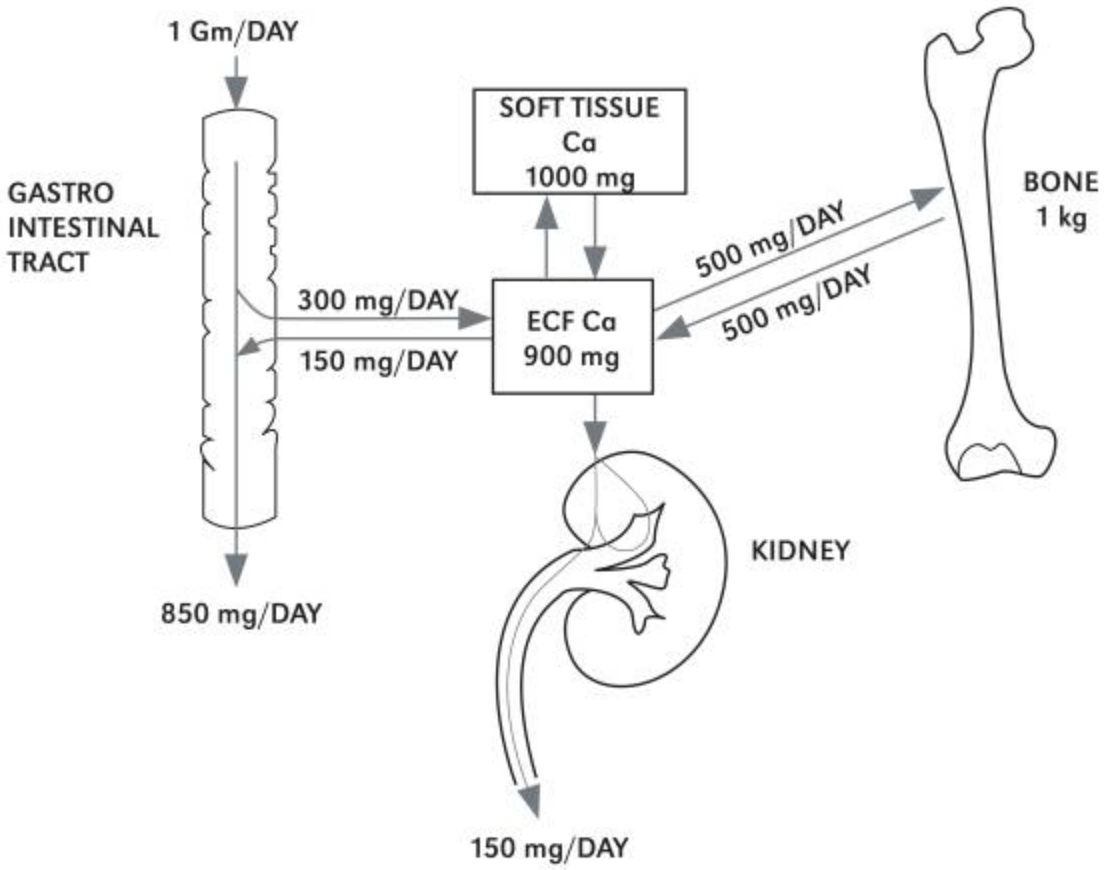
Blood Calcium - 10mgs/100 mls (2.5 mmoles/L)	Diet
Non diffusible - 3.5 mgs Albumin bound - 2.8 Globulin bound - 0.7 Diffusible - 6.5 mgs Ionized - 5.3 Complexed - 1.2 mgs bicarbonate - 0.6 mgs citrate - 0.3 mgs phosphate - 0.2 mgs other Close to saturation point tissue calcification kidney stones	Dietary 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

Balance per day



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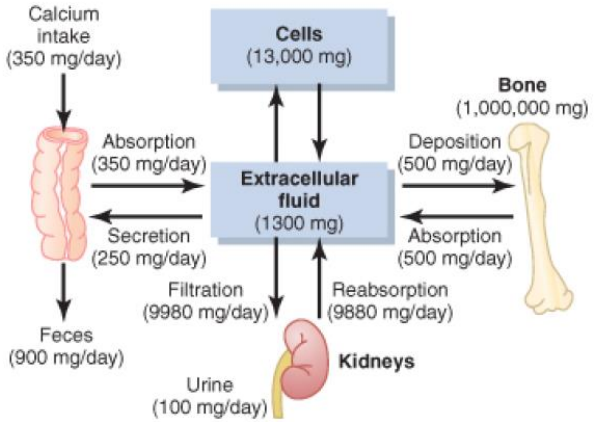
Regulation of Calcium and Skeletal Metabolism

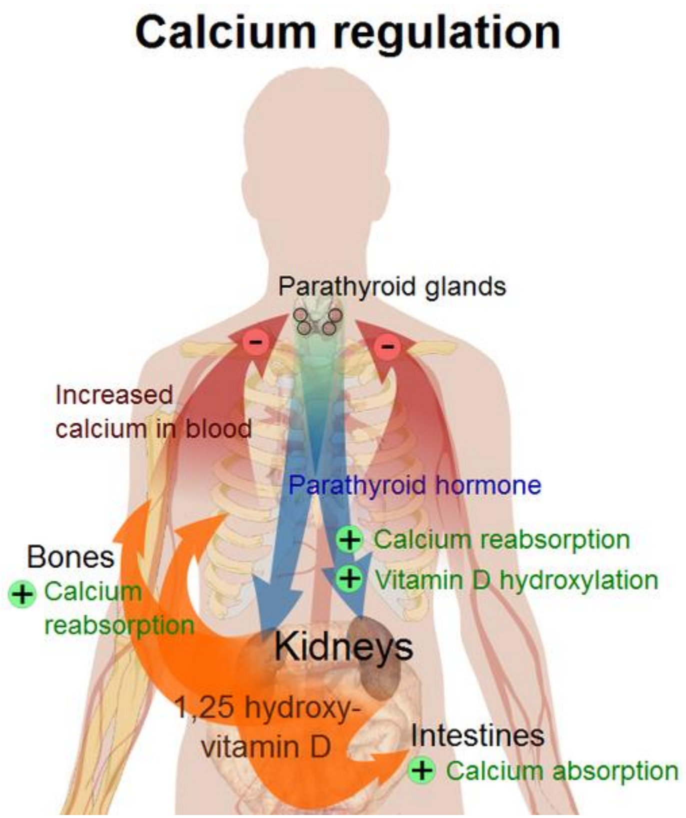
- Minerals
  - Calcium (Ca)
  - Phosphorus (P)
  - Magnesium (Mg)
- Organ Systems
  - Skeleton
  - Kidney
  - GI tract
  - Other
- Hormones
  - Calcitropic hormones
    - Parathyroid Hormone (PTH)
    - Calcitonin (CT)
    - Vitamin D [1,25(OH2)D]
    - PTHrP
  - Other hormones
    - Gonadal and adrenal steroids
    - Thyroid hormones
- Growth factor and cytokines

Calcium Homeostasis

- ↑ Bone Resorption
- ↑ Intestinal Absorption
- ↓ Renal Excretion



Calcium Homeostasis



- **Parathyroid Hormone**
- **1,25 DHC or Vitamin D_3**
- **Calcitonin**

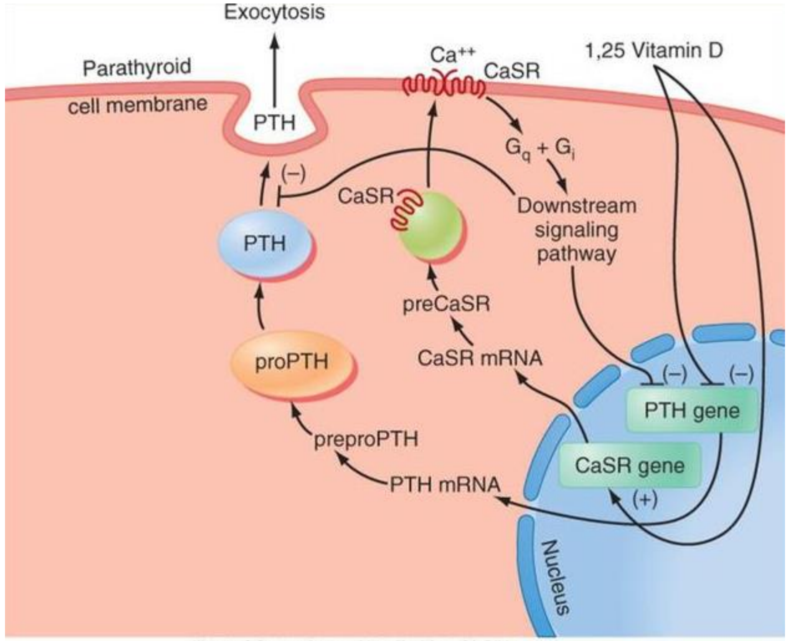
Control of Ca^{2+} Levels

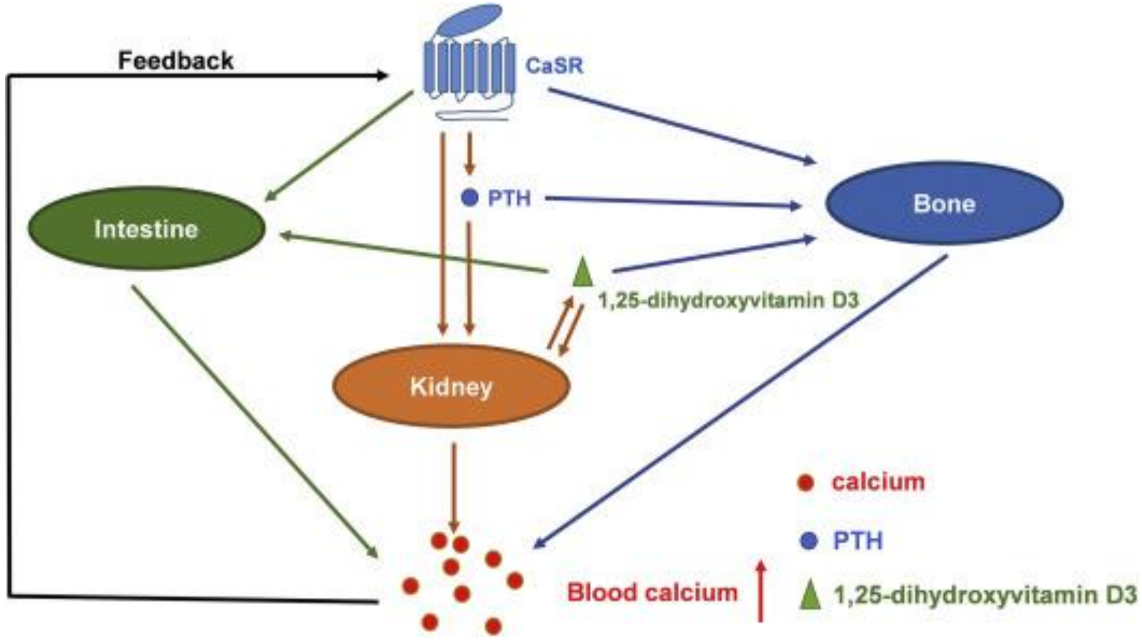
Hormone	**Effect**	**Bone**	**Gut**	**Kidney**
PTH	↑ Ca^{2+} ↓ Po4	Increases Osteoclasts	Indirect via Vit. D	Ca reab Po4 exr.
Vitamin D3	↑ Ca^{2+} ↑ Po4	No direct action	↑ Ca^{2+} ↑ Po4 absorption	No direct effect
Calcitonin	↓ Ca^{2+} ↓ Po4	Inhibits Osteoclasts	No direct effect	Ca^{2+} & Po4 excretion

Regulation of Ca^{2+} in ECT

- The parathyroid gland detects calcium levels in the ECT by the calcium sensing receptor – CaSR

- a member of the G protein-coupled receptor family with seven hydrophilic transmembrane helices anchored in the plasma membrane.

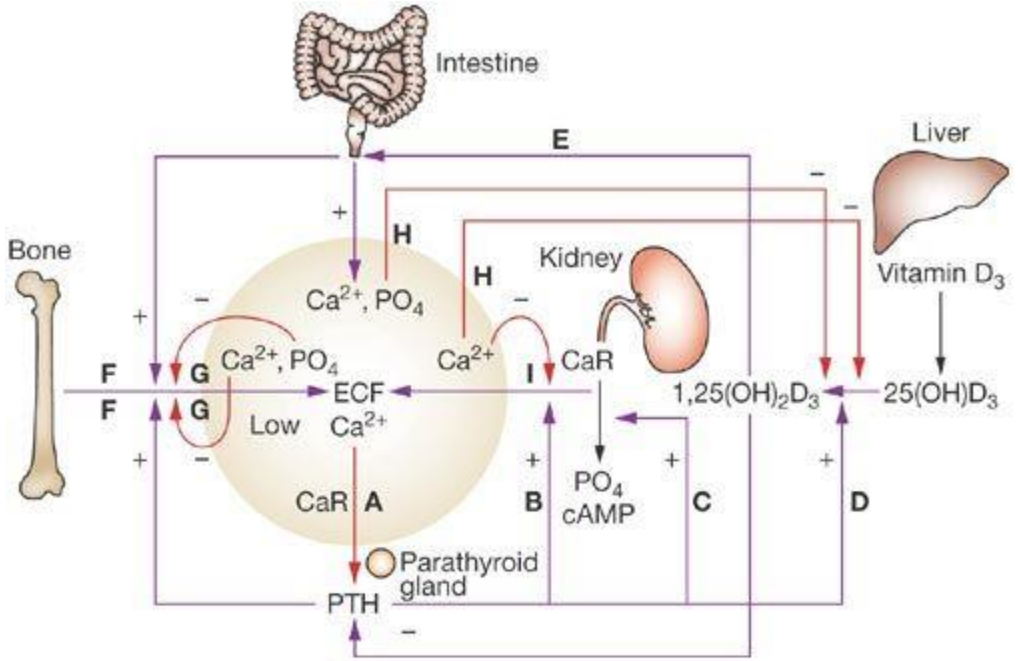




Expression of calcum sensor

- Parathyroid cells, thyroid C cells (control of PTH and calcitonin production).
- Kidney cells, osteoblasts, hematopoietic cells, mucosal cells of GIT.

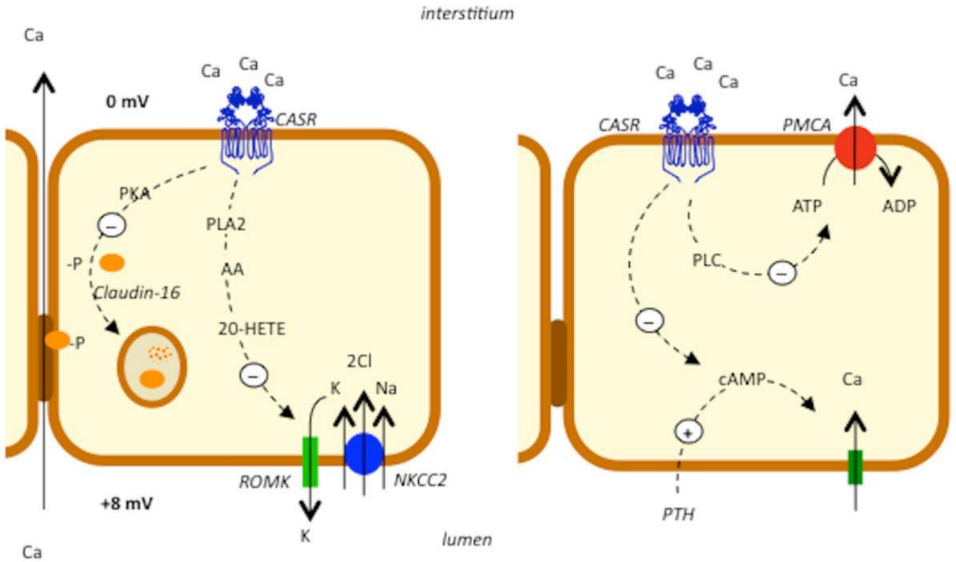
- All these cells respond to calcium levels in the blood.



Nature Clinical Practice Endocrinology & Metabolism **volume 3**, pages122–133(2007)

Functional consequences of the calcium sensor

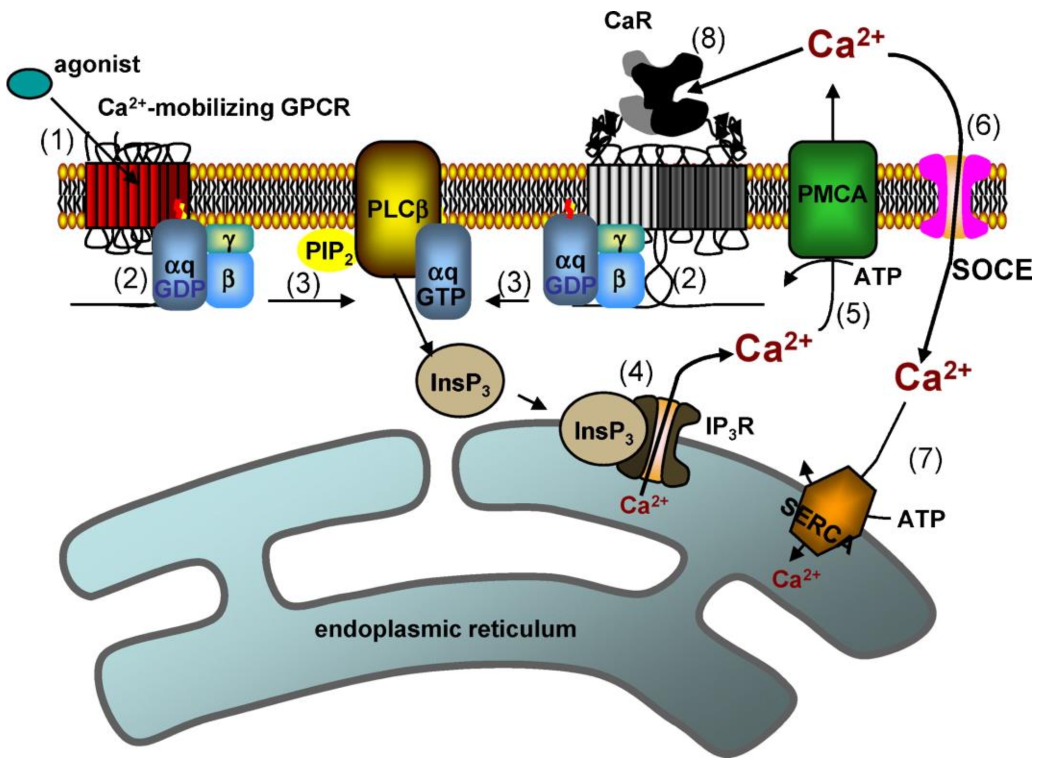
- CaSR is found throughout the tubular system
- CaSR in the thick part of the ascending arms of the Henle loop can respond to increased calcium levels in ECT by activating phospholipase A2, resulting in a reduction of Na / K / 2Cl co-transporter activity and apical channel activity for K + and a reduction in calcium and magnesium paracellular rebsorption.
- The increase in calcium in ECT antagonizes the effect of PTH on this segment of the nephron, so that calcium itself cooperates to maintain its own homeostasis. Inhibition of NaCl reabsorption and loss of urine NaCl in severe hypercalcaemia may then lead to hypovolaemia.

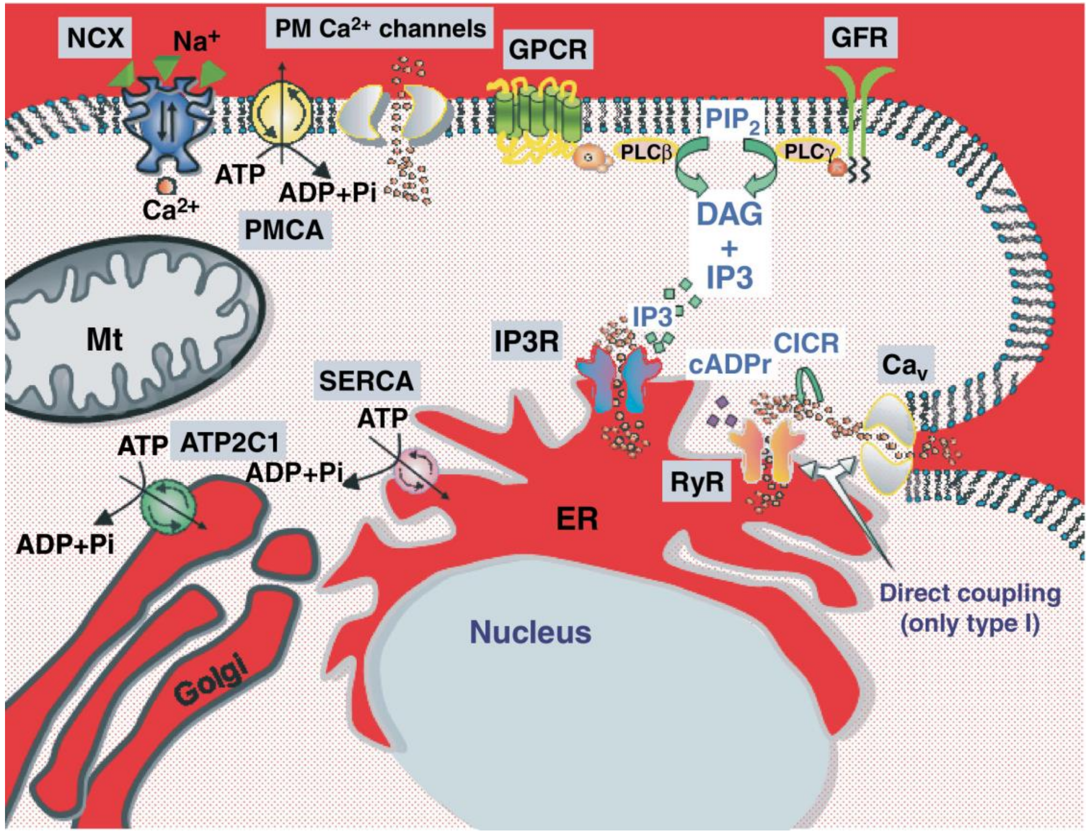


Journal of Translational Medicine **volume 9**, Article number: 201 (2011)

Activation of the calcium sensor has two major signal transduction effects:

- Activation of phospholipase C, which leads to activation of second messengers of diacylglycerol and inositol trisphosphate.
- Inhibition of adenylate cyclase, which leads to a decrease in intracellular cAMP concentration.
- The sensor can also activate mitogen-activated protein kinase (MAPK)



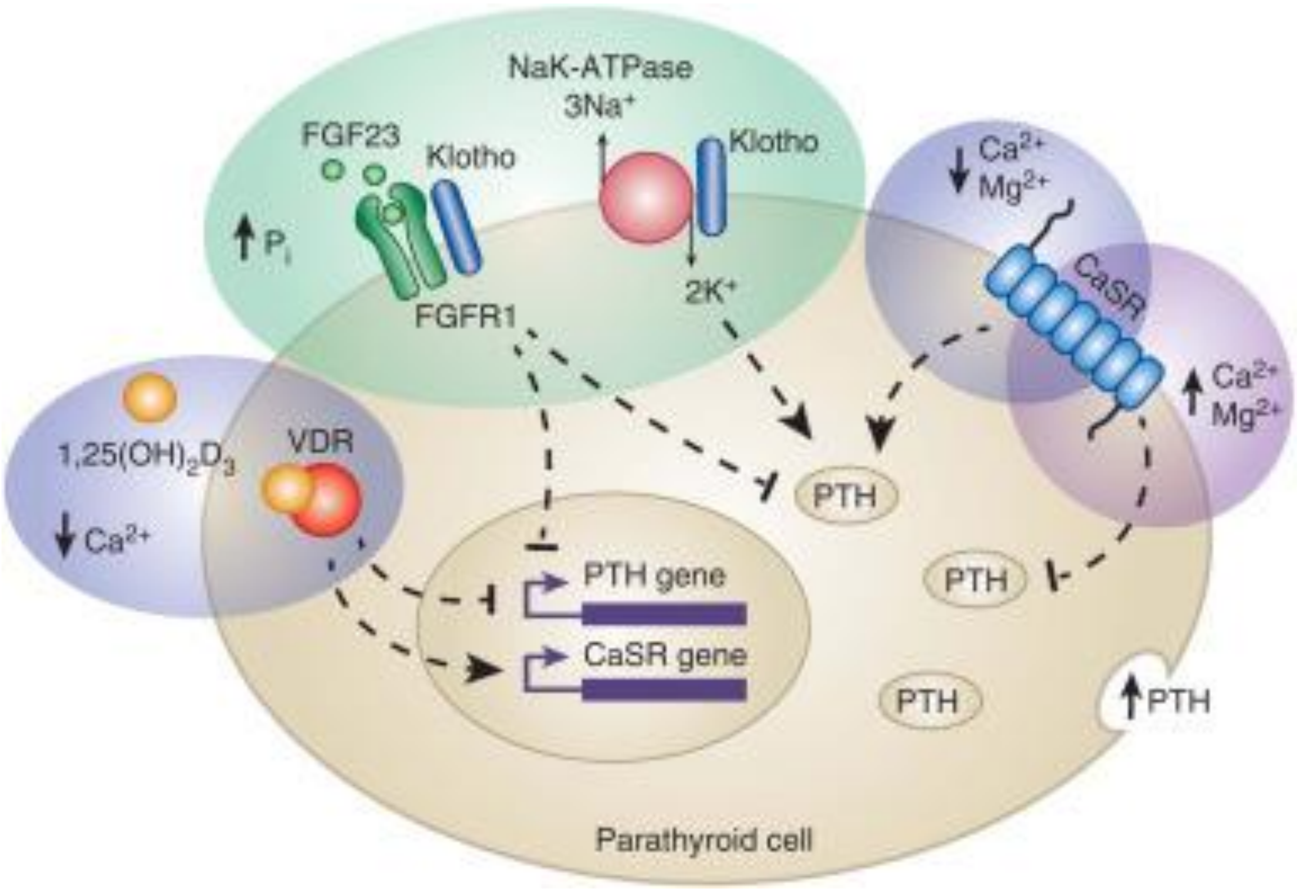


Scheme of an idealized mammalian cell with localization of the major mechanisms of Ca homeostasis.
PM Ca2+ channels, generic plasma membrane Ca2+ channels (voltage-, ligand- or second messenger–operated);
GPCR, G protein–coupled receptor; PLC, phospholipase C; PIP2, phosphatidylinositol 4,5 bisphosphate; DAG, diacylglycerol; GFR, growth factor receptor; ATP2C1, Golgi-resident Ca2+ ATPase; cADPR, cyclic ADP ribose; CICR, Ca2+ induced Ca2+ release; Mt, mitochondrion.

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

Magnesium

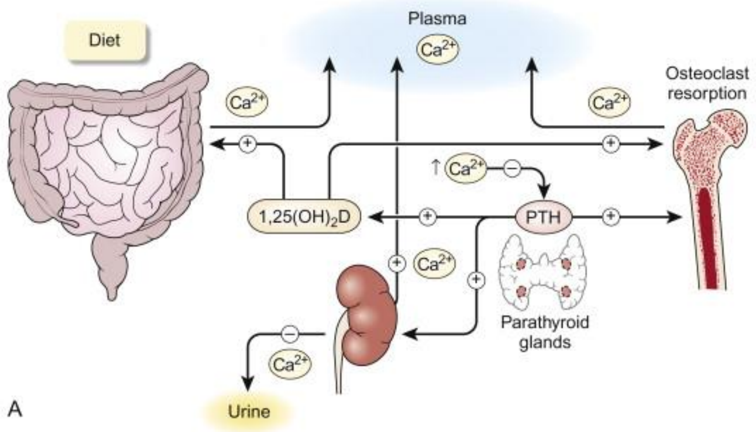
- Magnesemia negatively affects PTH secretion
- However, the rate of secretion activation is up to 3 times less than that of calcium

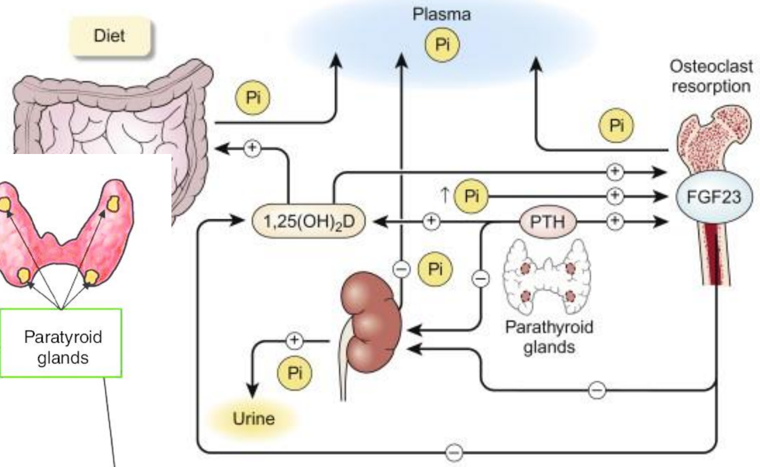


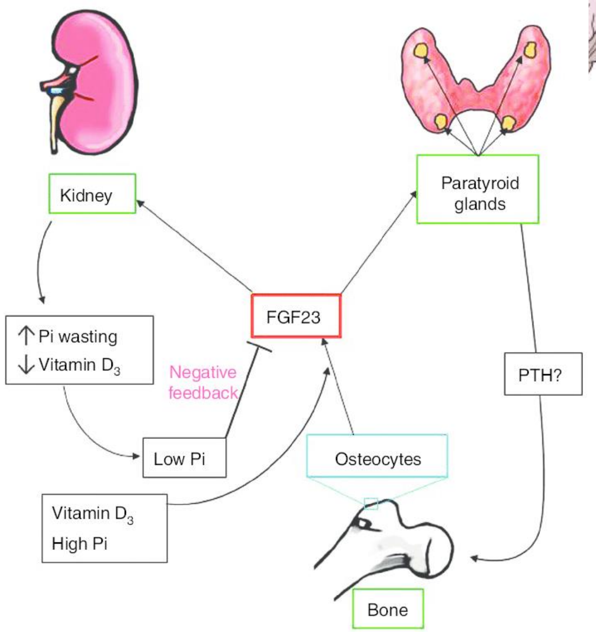
Kidney International
Volume 82, Issue 11, 1 December 2012

Calcium-phosphate equilibrium

- The role of FGF-23
- FGF23 is a hormone
- predominately produced by osteoblasts/osteocytes
- major function – inhibition of renal tubular phosphate reabsorption and suppressing circulating 1,25 (OH)(2)D levels by decreasing Cyp27b1-mediated formation and stimulating Cyp24-mediated catabolism of 1,25(OH)(2)D.







Altered intracellular calcium homeostasis in diseases states

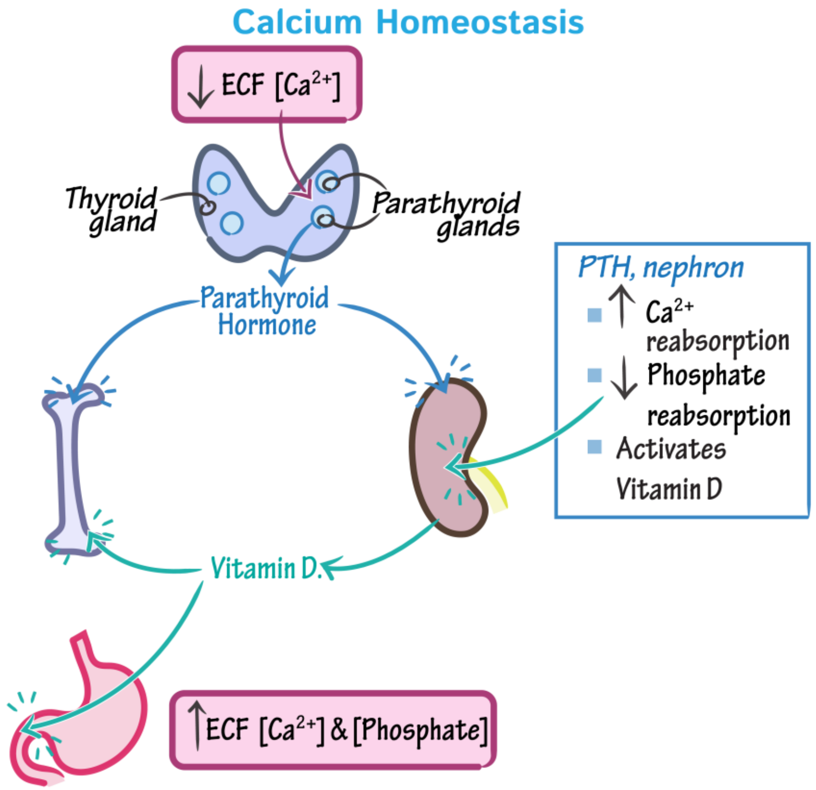
Basal $[Ca^{++}]_i$	$[Ca^{++}]_i$ response to stimulation	Example	Form
Gradually increasing	=/↓	Infarction, toxin-induced cellular death, acute pancreatitis	Acute
Increased, sustained	↑	Hypertension	Chronic
	↓	Idiopathic heart failure	Chronic
Normal, sustained	↑	Alzheimer´s disease	Chronic
	↓	Chronic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

Parathyroid glands

Parathormon (PTH)

raises blood calcium levels in 3 main ways:

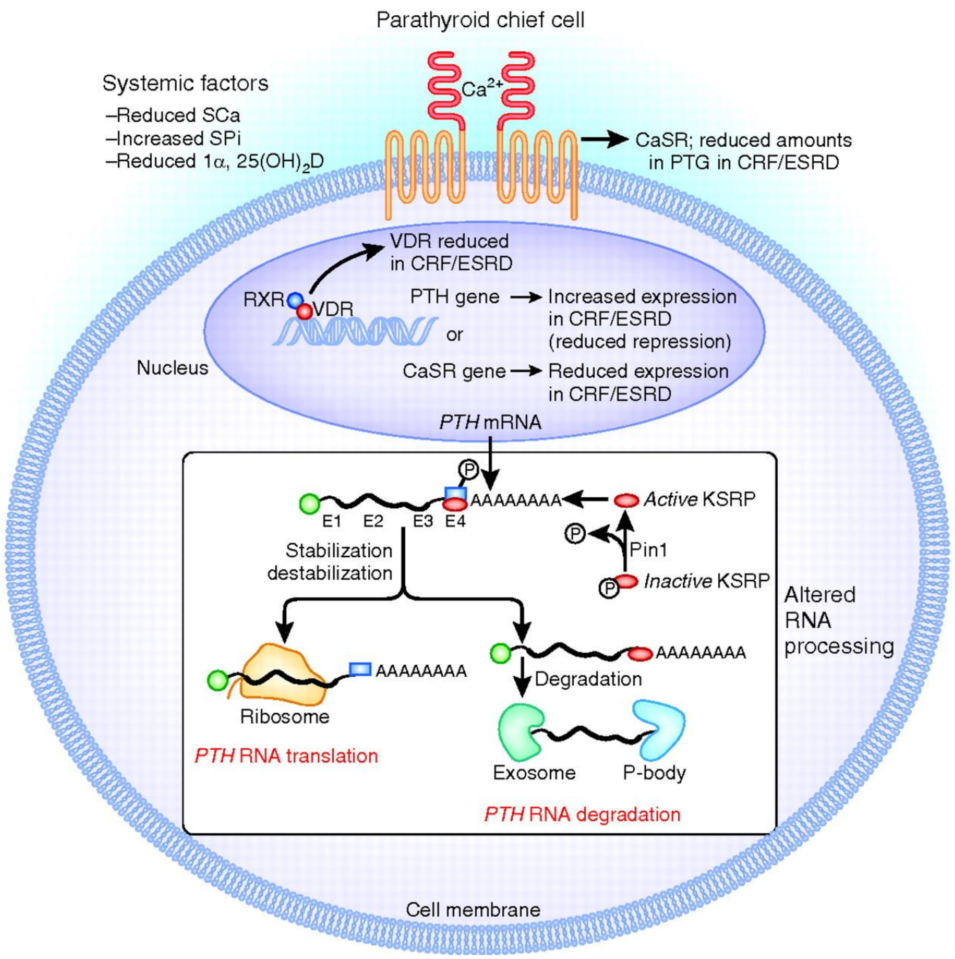
- stimulates the production of the biologically active form of vitamin D by the kidneys.
- supports mobilization of calcium and phosphate from bone. To maintain the calcium phosphate balance, it promotes the excretion of phosphates by the kidney (phosphaturic effect).
- It maximizes tubular reabsorption of calcium in the kidneys, resulting in minimal urinary calcium loss (in healthy kidneys).



Parathormon (PTH)

- PTH is a 84 AK peptide whose bioactivity is given by 34 AK at the NH2-terminal end.
- The main regulator of PTH secretion from parathyroidism is the calcium content in **extracellular fluid (ECT)**.
- The relationship between ECT calcium and PTH secretion is controlled by an inverse sigmoidal curve characterized by a maximum secretion rate at low calcium in ECT, a "set point", an ECT calcium value in ECT that lowers PTH to half of maximum, and a minimum secretion rate at high levels of calcium in ECT.

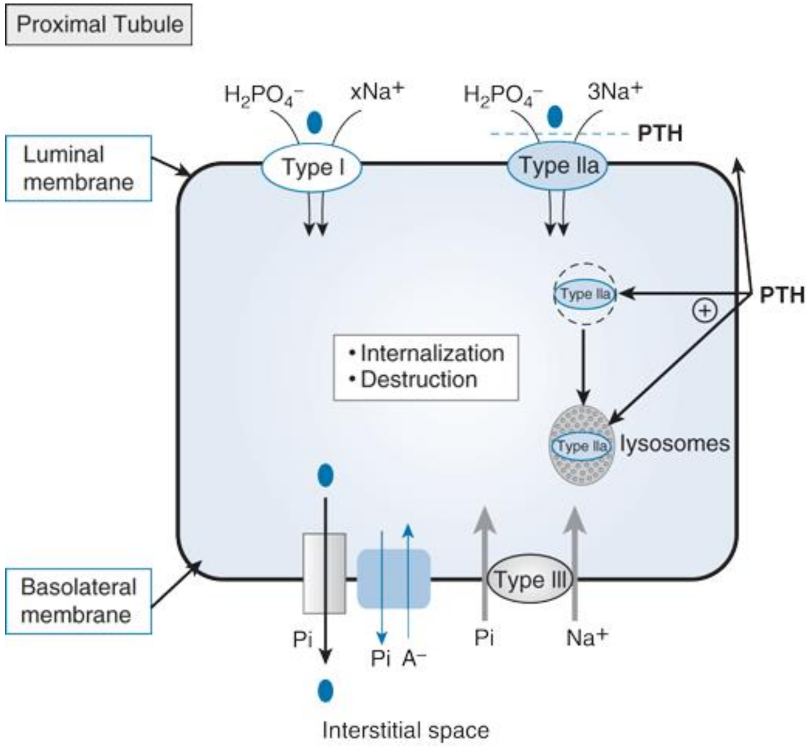
- An increase in calcium increases PTH degradation, a decrease in calcium levels in ECT results in a decrease in intracellular PTH degradation.
- Bioinactive fragments of PTH, which can also be formed in the liver, are digested in the kidney.
- Low levels of calcium in ECF result in increased transcription of the PTH gene and increased mRNA stability for PTH.
- Chronic hypocalcaemia can lead to the proliferation of parathyroid glands and increase its secretory capacity.



JASN February 2011, 22 (2) 216-224

1. Kidney and PTH

- 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**.
- About 20% of filtered calcium is reabsorbed in the cortical thick ascending limb of the loop of Henle (CTAL)
- 15% is reabsorbed in distal tubules, after PTH binding to PTHR, via signal transduction via cAMP.
- In the thick parts of the ascending arms of the Henle loop, the activity of Na / K / 2Cl co-transporter increases, which controls NaCl reabsorption and also stimulates paracellular reabsorption of calcium and magnesium.



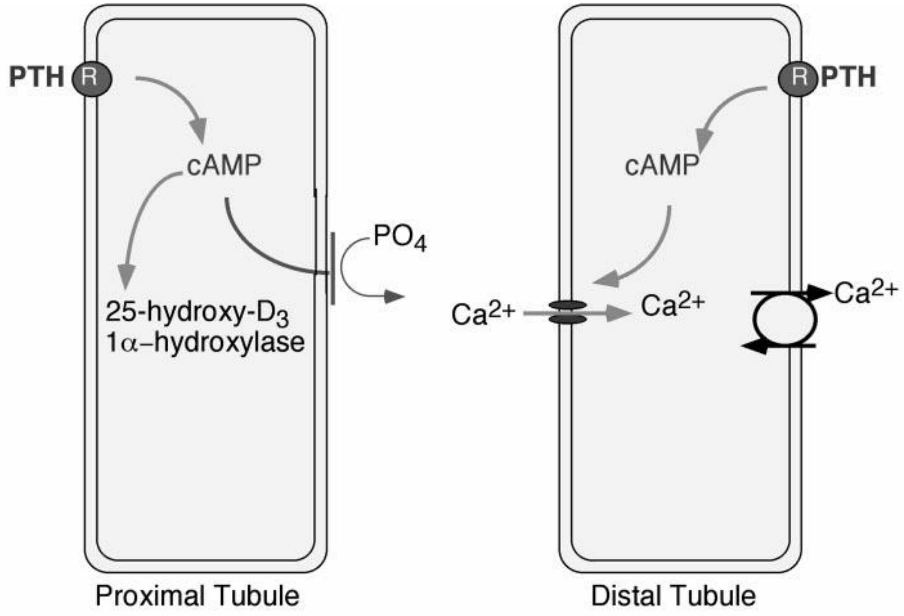
Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com

1. Kidney and PTH

In the distal tubule, PTH affects transcellular calcium transport. This process involves several steps:

- transfer of luminal Ca^{2+} to the renal tubular cell via the transient receptor potential channel (TRPV5)
- translocation of Ca^{2+} across tubular cell from apical to basolateral surface by proteins like calbindine-D28K
- active Ca^{2+} excretion from the tubular cell into the blood via the Na^{+} /Ca^{2+} exchanger (NCX1).

PTH apparently stimulates Ca^{2+} reabsorption in the distal tubule by increasing the activity of NCX1 by a cAMP-dependent mechanism.

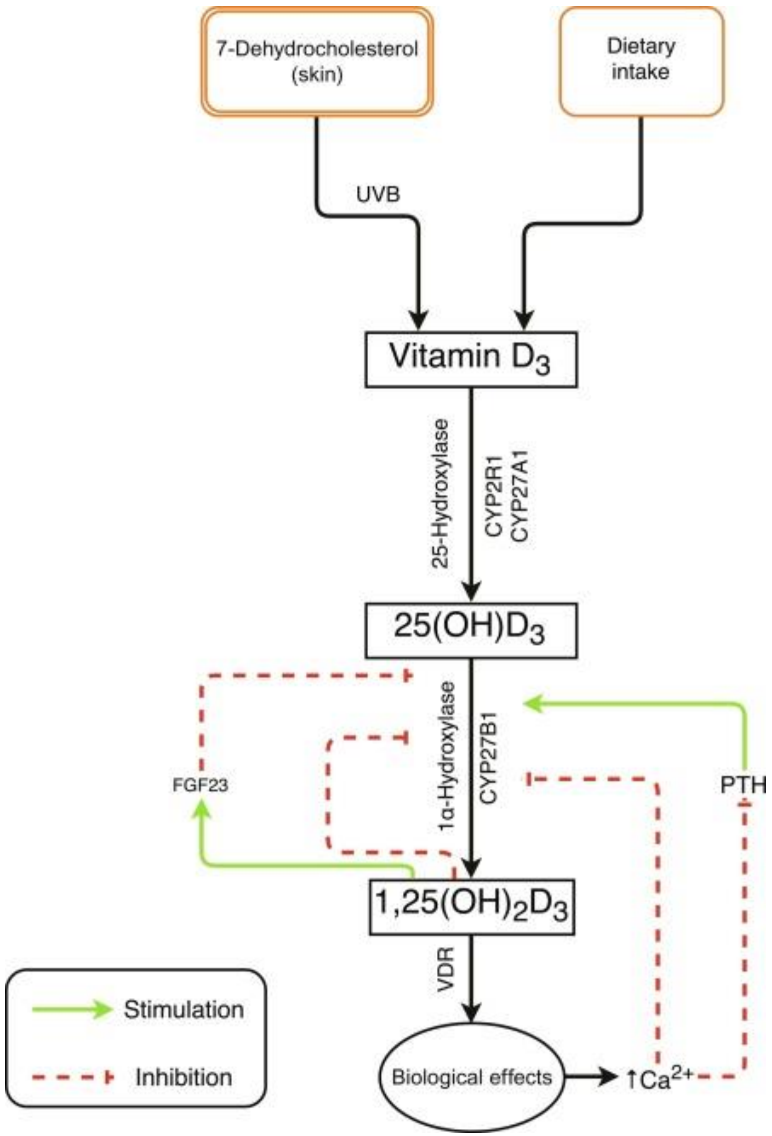


1. Kidney and PTH

- PTH, upon binding to PTHR, can also stimulate 25(OH)D3-1-alpha hydroxylase, resulting in increased synthesis of 1,25(OH)2D3.

PTH can also inhibit the reabsorption of Na^+ and $HC03^-$ in the proximal tubule by inhibition

- Na^+/H^+ apical exchanger typ 3,
- Na^+/K^+-ATPase on basolateral membrane
- Na^+/Pi^--cotransport on the apical side of the proximal tubular cell.



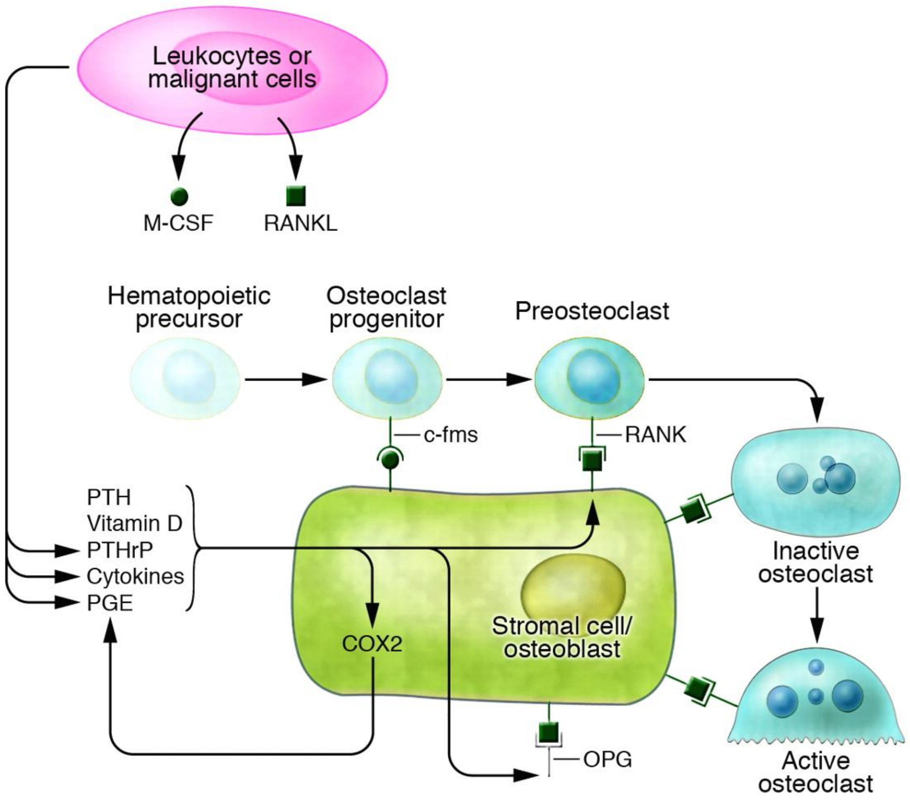
Bioactive Food as Dietary Interventions for Diabetes (Second Edition), 2019

2. Bone and PTH

- 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.

2. Bone and PTH

- 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.



Hyperparathyreoidism - primary

- Parathyroid adenoma – solitary
  - 70 - 80% primary
- Idiopathic primary hyperplasia of PT
- Carcinoma PT - rare
- Familial hyperparathyroidism
  - Multiple Adenomas (MEN)
  - Familial benign hypocalciuric hypercalcemia
  - Severe neonatal primary hyperparathyroidism
    - Inactivation mutations for CaSR - AR

TABLE 3

Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑ →	↑	↓
Secondary	↓ →	↑	↓	↑ or ↓
Tertiary	↑	↑↑	↓	↑

Key: ↑Elevated, ↓decreased, →normal.

Source: Brashers. *Pathophysiology.* 2015.[6]

Hyperparathyreoidism - secondary

- Renal insuficiency
- Hypovitaminosis D
- Malasorption syndromes
  - Celiac disease
  - Disorders of bile and pancreatic secretion

TABLE 3
Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑ →	↑	↓
Secondary	↓ →	↑	↓	↑ or ↓
Tertiary	↑	↑↑	↓	↑

Key: ↑Elevated, ↓decreased, →normal.
Source: Brashers. *Pathophysiology.* 2015.[6]

Hypoparathyreoidism - primary

- Parathyroid damage during thyroid surgery
- Radiation
- Damage in metabolic diseases
  - Wilson's disease - defect of Cu metabolism
  - hemochromatosis - defect of Fe metabolism
- Autoimmune hypoparathyroidism
- Gradual decline in function
- Congenital familial hypoparathyroidism
  - AD, AR and X-linked disorder
- DiGeorg syndrome
  - parathyroid aplasia
- After tumor removal

TABLE 3

Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑ →	↑	↓
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Source: Brashers. *Pathophysiology.* 2015.[6]

Hypoparathyreoidism - seconadry

- Magnesium deficiency/
- hypomagnesaemia - chornic!
- Hypervitaminosis D
  - due to attenuation of PTH secretion due to high Ca levels!
- Increased production of PTHrP
  - the level of PTH alone is low!

TABLE 3

Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑ →	↑	↓
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Tertiary	↑	↑↑	↓	↑

Key: ↑Elevated, ↓decreased, →normal.

Source: Brashers. *Pathophysiology.* 2015.[6]

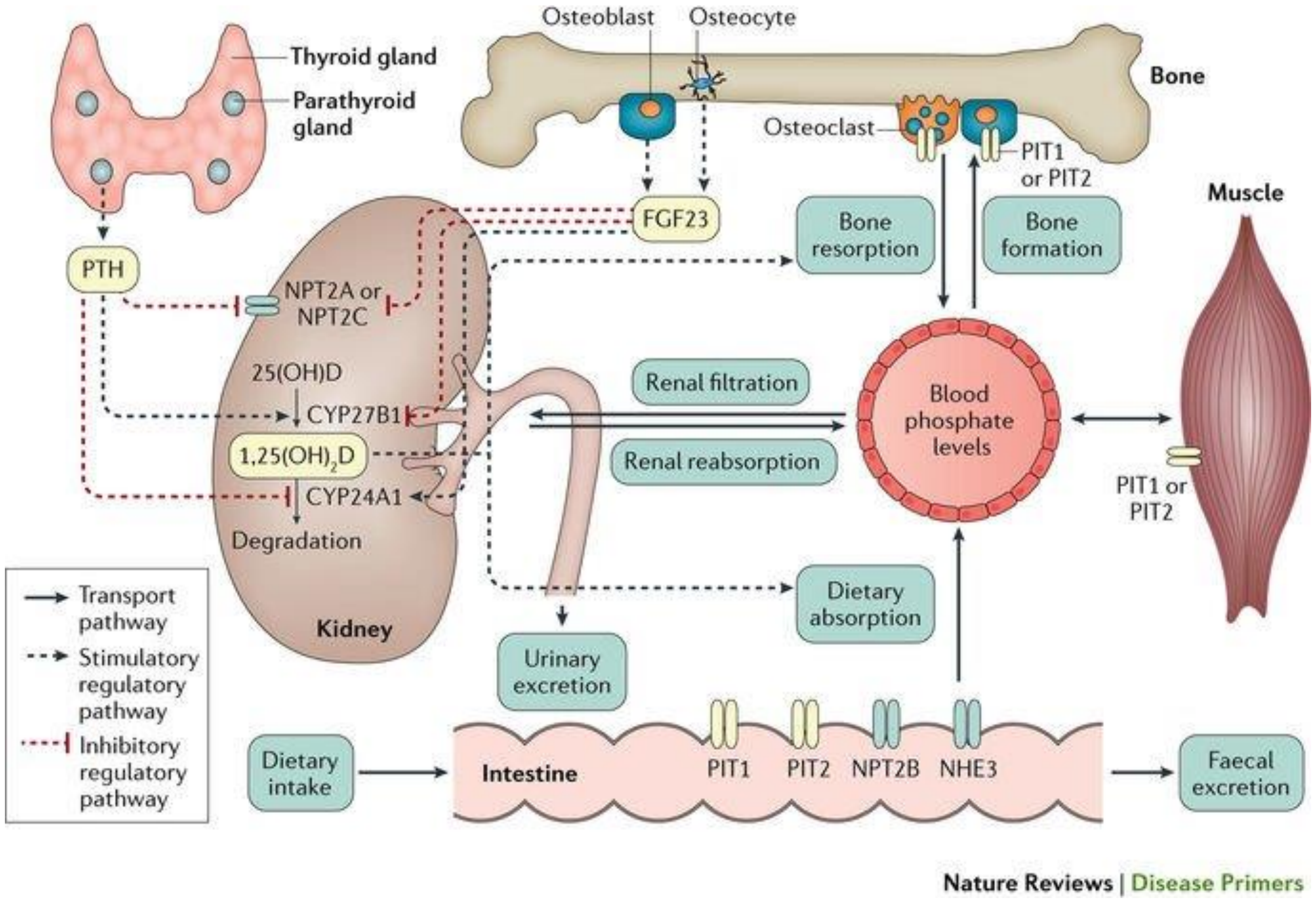
Hypoparathyreoidism

- Decreased PTH

- Hypocalcemia
  - Rise of neuromuscular excitability
    - Parestezia
    - Spazmus and contractions

- hyperphosphatemia

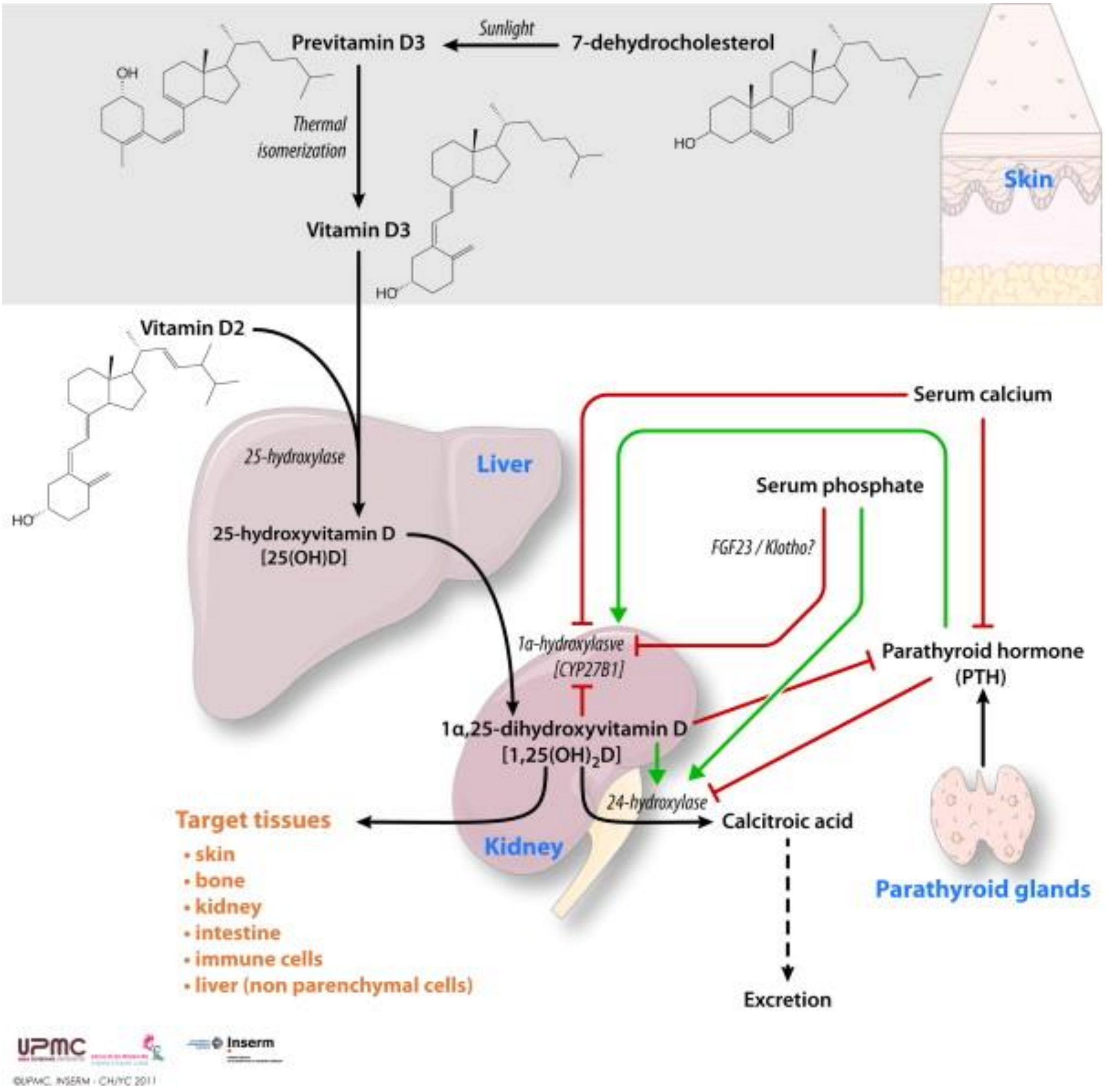
PTH vs FGF 23

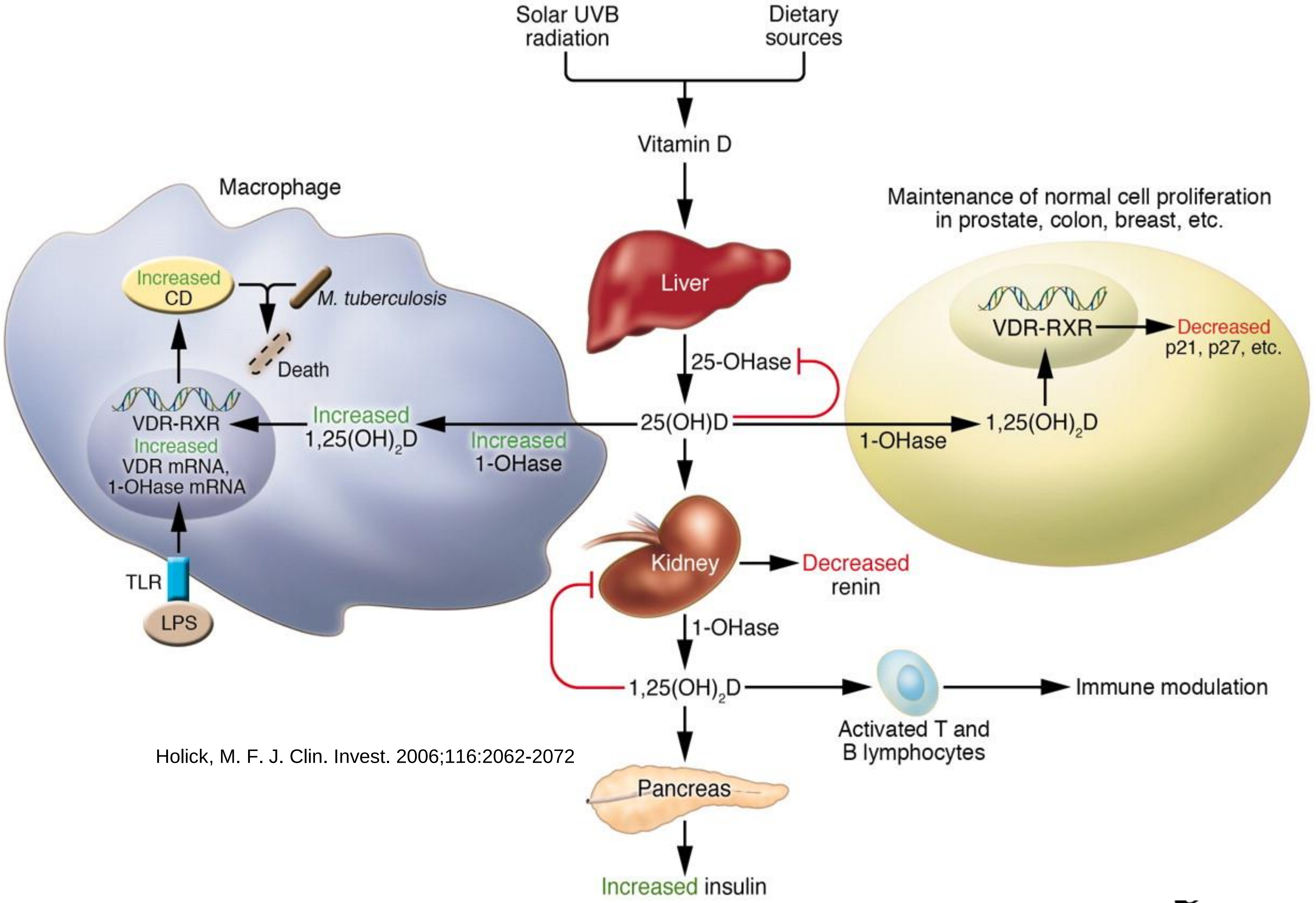

Osteoblast
Osteocyte
Thyroid gland
Parathyroid gland
Bone
Osteoclast
PIT1 or PIT2
FGF23
Bone resorption
Bone formation
Muscle
PTH
NPT2A or NPT2C
25(OH)D
CYP27B1
Renal filtration
Blood phosphate levels
1,25(OH)$_2$D
Renal reabsorption
CYP24A1
PIT1 or PIT2
Degradation
Transport pathway
Stimulatory regulatory pathway
Inhibitory regulatory pathway
Kidney
Dietary absorption
Urinary excretion
Dietary intake
Intestine
PIT1
PIT2
NPT2B
NHE3
Faecal excretion
Nature Reviews | Disease Primers

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

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.

Vitamin D (calcitriol)





Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

Nomenclature

Vitamin D

25-hydroxyvitamin D [25(OH)D]

1,25-dihydroxyvitamin D [$1,25(OH)_2D$]

Vitamin D receptor agonist (synthetic analogues)

Vitamin D receptor agonist prodrugs[a]

Ergocalciferol (vitamin D_2)

Cholecalciferol (vitamin D_3)

Ercalcidiol [$25(OH)D_2$]

Calcidiol [$25(OH)D_3$]

Ercalcitriol [$1,25(OH)_2D_2$]

Calcitriol [$1,25(OH)_2D_3$]

Paricalcitol [$19nor,1,25(OH)_2D_2$]

Maxacalcitol [$22oxa,1,25(OH)_2D_3$]

Doxercalciferol [$1(OH)D_2$]

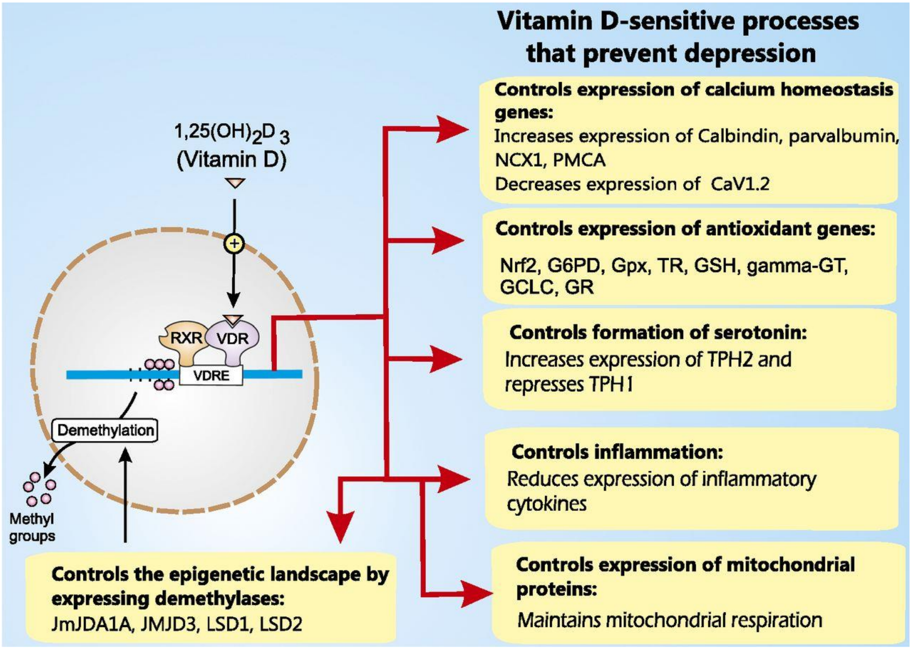
Alfacalcidol [$1(OH)D_3$]

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

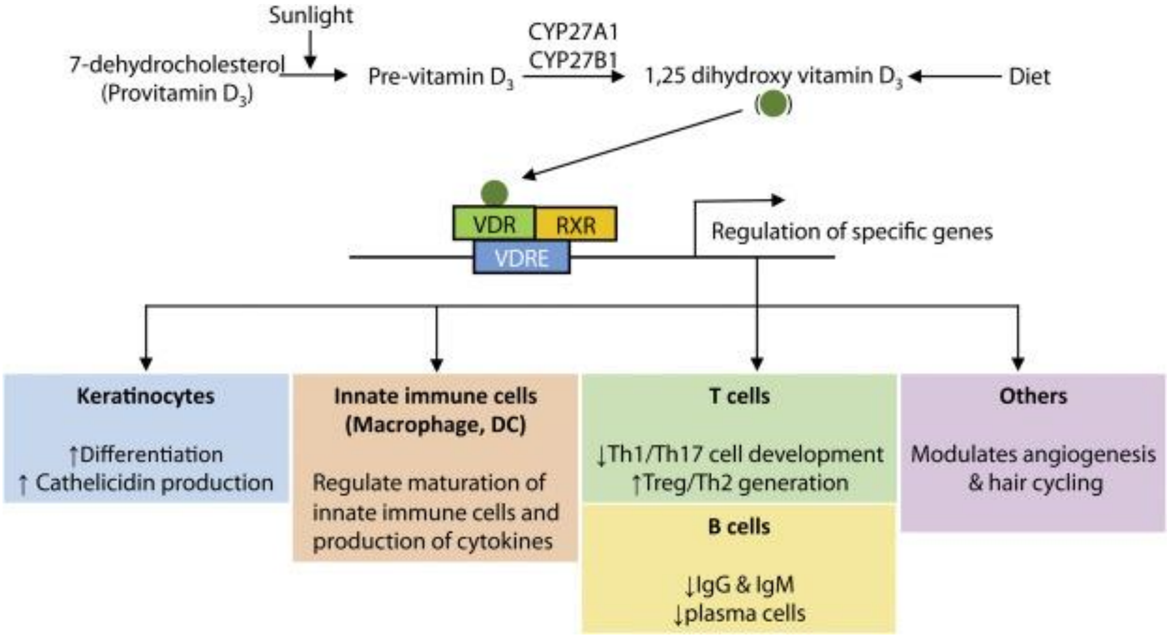
- For calcium, the transcellular transport is ferried by the interaction among a family of proteins that include ***calmodulin, calbindin, integral membrane protein,*** and ***alkaline phosphatase;*** the latter three are vitamin D dependent.
- Cytoskeletal interactions are likely important for transcellular transport as well. Exit from the cell is regulated by membrane structures similar to those that mediate entry.



Pharmacological Reviews April 2017, 69 (2) 80-92;

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

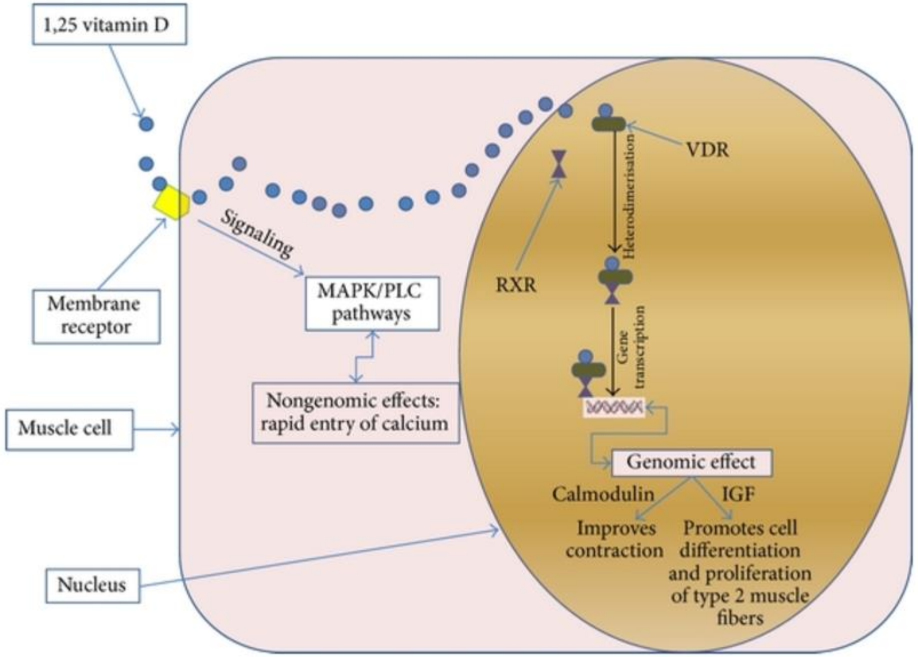
- 1,25(OH)2D enters the target cell and binds to its receptor, VDR.
- The VDR then heterodimerizes with the retinoid X receptor (RXR). This increases the affinity of the VDR/RXR complex for the vitamin D response element (VDRE), a specific sequence of nucleotides in the promoter region of the vitamin 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.



Immunity and Inflammation in Health and Disease, 2018

Non-genomic actions of vit D

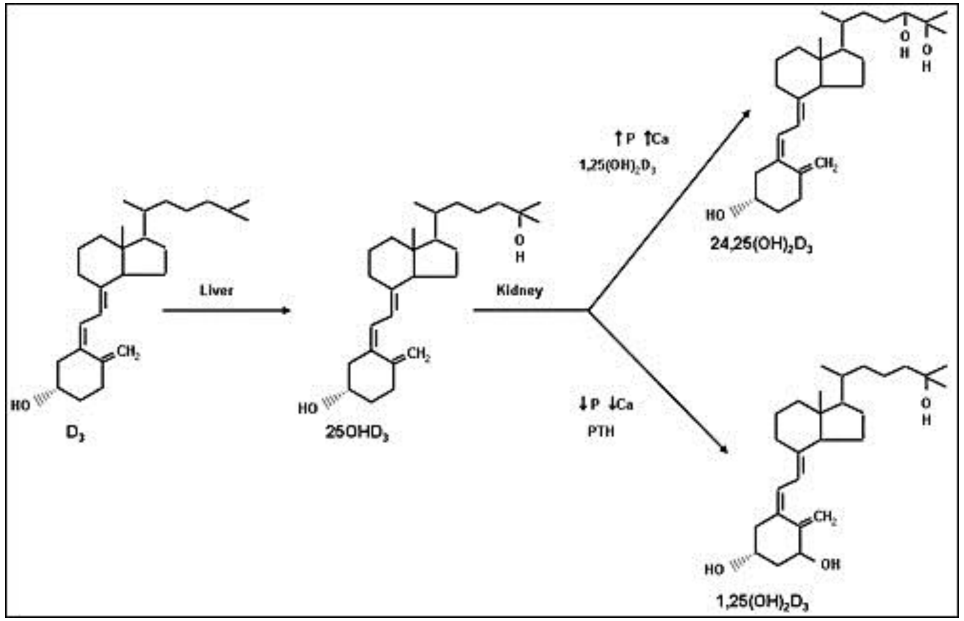
- Besides gene regulation activities, vitamin D also exerts rapid nongenomic actions through cell surface receptors.
- VDR is required for rapid nongenomic effects of 1,25$(OH)_2$ D_3 on chloride and calcium channels in osteoblasts.
- VDR was localized in caveolae-enriched plasma membranes of intestinal, lung, kidney cells and osteoblasts, where it efficiently binds 1,25$(OH)_2$ D_3



BioMed Research International 2015:1-11

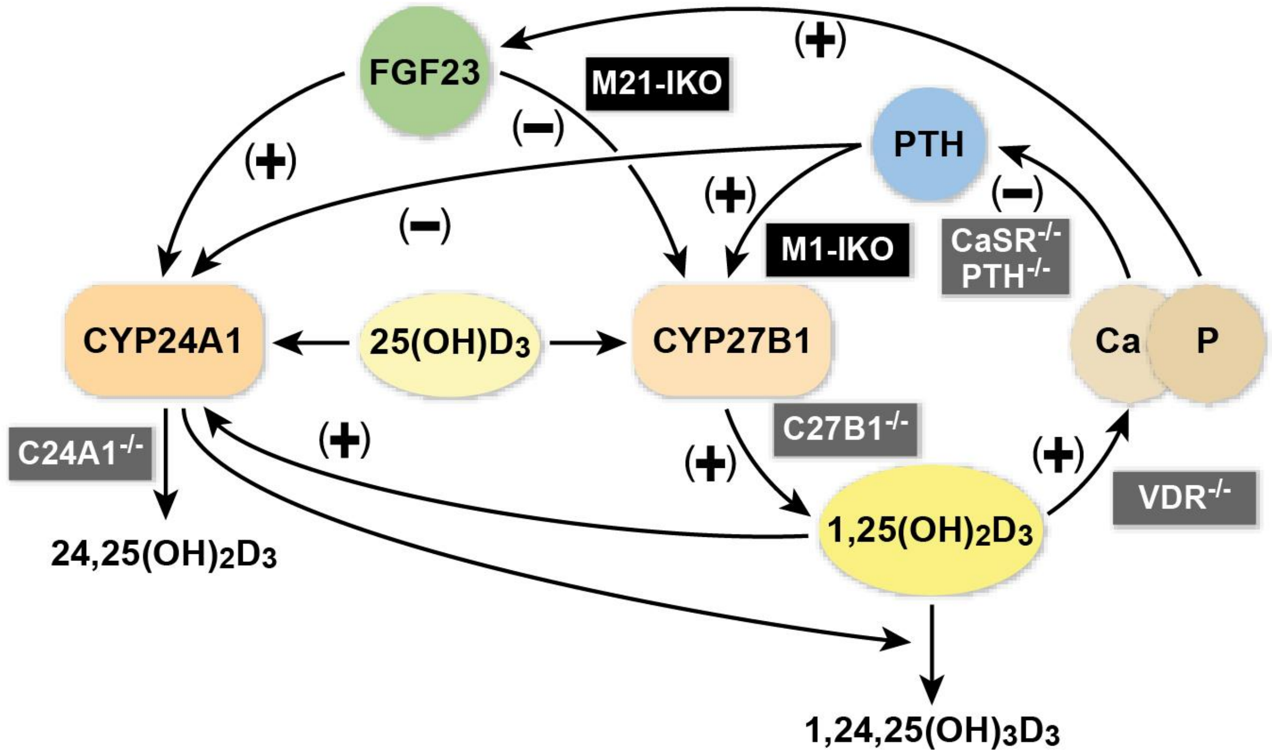
Degradation

- takes place in the kidneys, liver, bones and intestines
- Conjugation with glucuronic acid, sulphation and hydroxylation (in positions 23, 24, 26)
- The products are excreted in urine and bile
- 24-hydroxylase
  - 1,24,25-(OH)3-D - Nonactive metabolite
  - 24,25-(OH)3-D – Active form, in plasma



Regulation of 1-alfa hydroxylase (CYP27B1)

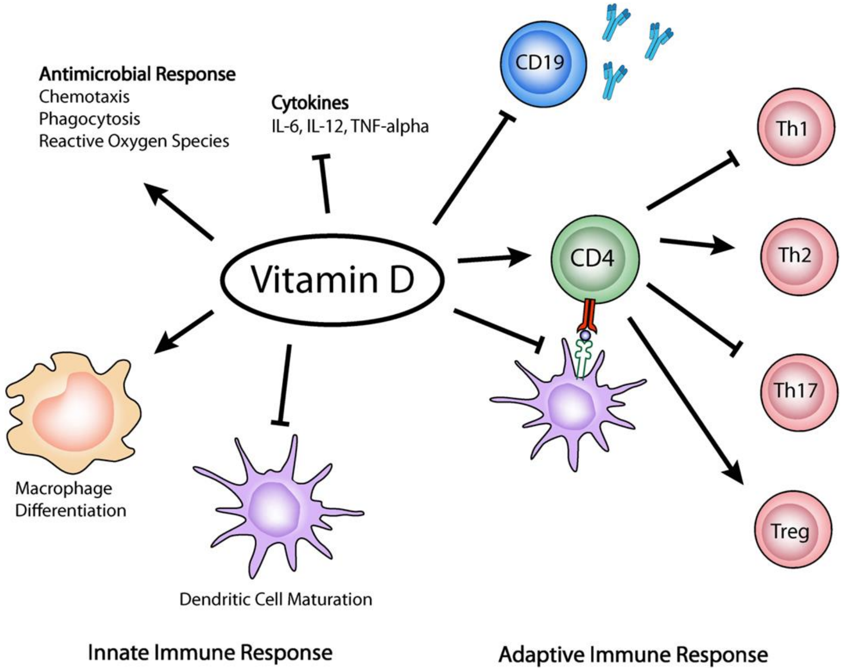
- mainly occurs in the proximal tubule cells of the kidney, and its activity is positively regulated by parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), calcitonin, growth hormone (GH) and insulin-like growth factor I (IGF-I)
- negatively by FGF23 and klotho or minerals - negative regulation by Ca and phosphate levels.



Handbook of Clinical Neurology, 2014

Vit D and immune reaction

- both VDR and RXR are expressed in several types of cells, e.g., keratinocytes, fibroblasts, monocytes, macrophage, DCs, and T lymphocytes
- modulate other components of innate immunity, such as immune cell proliferation/development and inflammatory cytokine production
- Vitamin D has been shown to inhibit the development and function of Th1 cells, which are mainly involved in activating macrophages and inflammatory responses, and Th17 cells



Front. Immunol., 12 October 2015

Country (health authority)	United States and Canada (IOM)		Europe (EFSA)	Germany, Austria and Switzerland (DACH)	UK (SACN)	Nordic European countries (NORDEN)
DRV/DRI	**EAR**	**RDA**	**AI**	**AI**	**RNI**	**RI**
Target 25(OH)D in nmol/L	**40**	**50**	**50**	**50**	**25**	**50**
Age group	Vitamin D intakes in µg (international units, IU) per day (1 µg = 40 IU)					
0–6 months	10 (400)			10 (400)	8.5–10 (300–400)	
7–12 months	10 (400)		10 (400)	10 (400)	8.5–10 (300–400)	10 (400)
1–3 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
4–6 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
7–8 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
9–10 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
11–14 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
15–17 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
18–69 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
70–74 years	10 (400)	20 (600)	15 (600)	20 (800)	10 (400)	10 (400)
75 years and older	10 (400)	20 (600)	15 (600)	20 (800)	10 (400)	20 (800)
Pregnancy	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
Lactation	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)

Dietary reference values (DRV)/dietary reference intakes (DRI) for vitamin D (reproduced from Pilz *et al*. (81) under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence).
IOM, Institute of Medicine; EFSA, European Food Safety Authority; DACH, Germany, Austria and Switzerland; SACN, Scientific Advisory Committee on Nutrition; EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; AI, Adequate Intake; RNI, Reference; Nutrient Intake; RI, Recommended Intake; 25(OH)D, 25-hydroxyvitamin D.

Vitamin D deficiency

- In children rickets-deformation of long bones due to increased bone softness.
- In adults, osteomalacia.
- Genetic defects in VDR (hereditary resistance syndromes to vitamin D).
- Severe liver and kidney diseases.
- Insufficient exposure to sunlight

Vitamin D deficiency

- Sunscreens (SPF more than 8) effectively block the synthesis of vitamin D in the skin. Usually balanced by quality nutrition.

- Vitamin D Toxicity: Excessive sun exposure does not lead to excessive vitamin D production.

Causes of rickets/osteomalacia

- Lack of calcium and/or phosphates
- Malabsorption of calcium and/or phosphates in GIT
    - Celiac disease, Crohn's disease
    - Absorption-inhibiting substances (eg fiber binding)
- Increased losses of calcium and/or phosphates in the kidneys
- Failure of mineralization process

Vitamin D deficiency rickets

- Vitamin D deficiency in diet
- Insufficient vitamin D absorption in GIT
- Insufficient vitamin D production in the skin

Rickets from disorders of vitamin D activation and effect

- Hepatic or renal failure
- Mutation of gene for 25-hydroxylase (CYP2R1) - rare
- Vitamin D dependent rickets type I
- Mutation of gene for 1-alpha-hydroxylase (CYP27B1) - AR
    - Insufficient conversion of calcidiol to calcitriol
- Vitamin D dependent rickets type II
    - Tissues do not respond to vitamin D
    - AR defect of vitamin D receptor

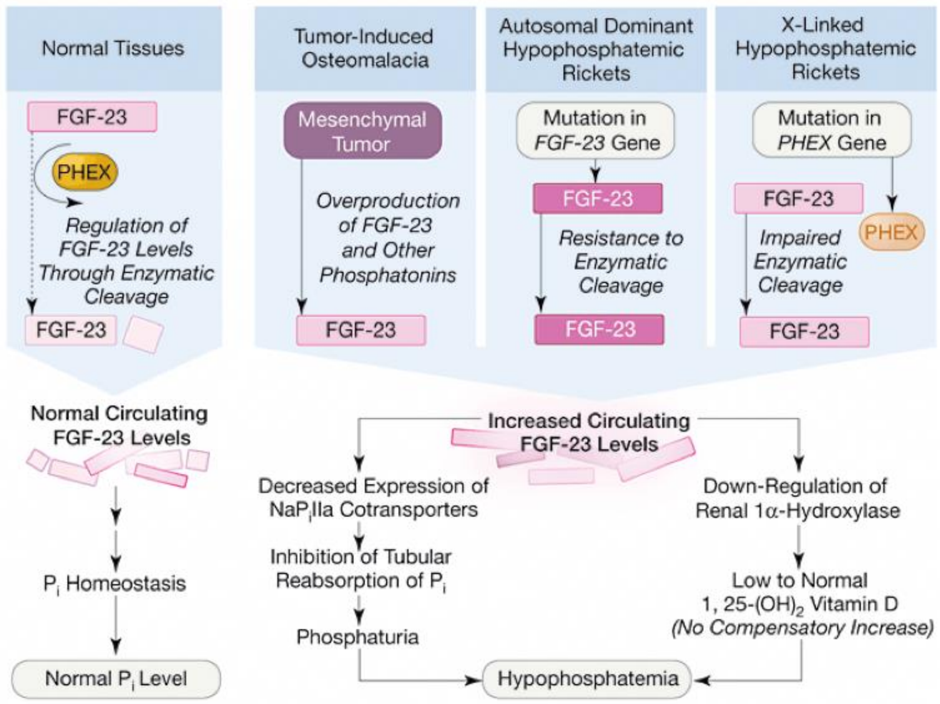
Gene/Chromosome/MIM	Disease
A) Disorder of Vitamin D metabolism	
CYP2Q1/11P15.2/608713	Vitamin D Hydroxylation – deficient Rickets Type 1B (also termed Vitamin D dependent Rickets Type 1B) AR
CYP27B1/12q14.1/609506	25α-HydroxyVitamin D-1α -Hydroxylase defieincey (Vitamin D dependent rickets Type 1A) AR
VDR: Vitamin D receptor/12q13.11/601769	Resistance to calcitriol and Vitamin D–dependent rickets Type 2A, AR
B) Disorder of Phosphate metabolism leading to Rickets	
SLC34A1 (Sodium phosphate cotransporter family 34 member 1/5q35.3/182309	Hypophosphatemic rickets with nephrolithiasis, Type 1, AD, fanconi syndrome Type 2, AR
SLC34A3 Family 34, member 3/9q34/609826	Hypophosphatemic rickets with hypercalciuria,AR
SLC9A3R1/Family member 3/17Q25.1/604990	Hypophosphatemic rickets with nephrolithiasis Type2, AD
CLCN5: Chloride channel 5/XP11.23-p11.22/300008	X-linked recessive hypophosphatemic rickets, hypercalciuria, nephrocalcinosis, XLR
PHEX/XP22.1/300550	X-linked hypophosphatemicrickets, X-linked AD with increase expression of FGF23
DMP1/4Q22.1/600980	AR hypophosphatemic rickets with increase synthesis of FGF23
ENPP1/6q23.2/173335	AR hypophosphatemic rickets with increase expression of FGF23
FGF23/12P13.3/60538	(Gain of function) AD hypophosphatemic rickets associated with decrease degradation of FGF23

Rickets from phosphate loss

- Familial hypophosphatemic rickets
  - Urinary phosphate loss
  - Vitamin D resistant rachitis - do not respond to vitamin D treatment
    - X-linked hypophosphatemic rickets - mutation in PHEX leads to accumulation of FGF23
    - AD hypophosphatemic rickets - mutation in the FGF23 gene
    - AR hypophosphatemic rickets - mutation in gene for DMP1 (nuclear protein of dental and bone tissue) - affecting osteoid mineralization, accumulation of FGF23
    - Tubulopathy with hyperphosphaturia
- Acquired states
  - Diuretics
  - Hyperparathyreoza
  - PTHrP

X-linked hypophosphatemic osteomalacia

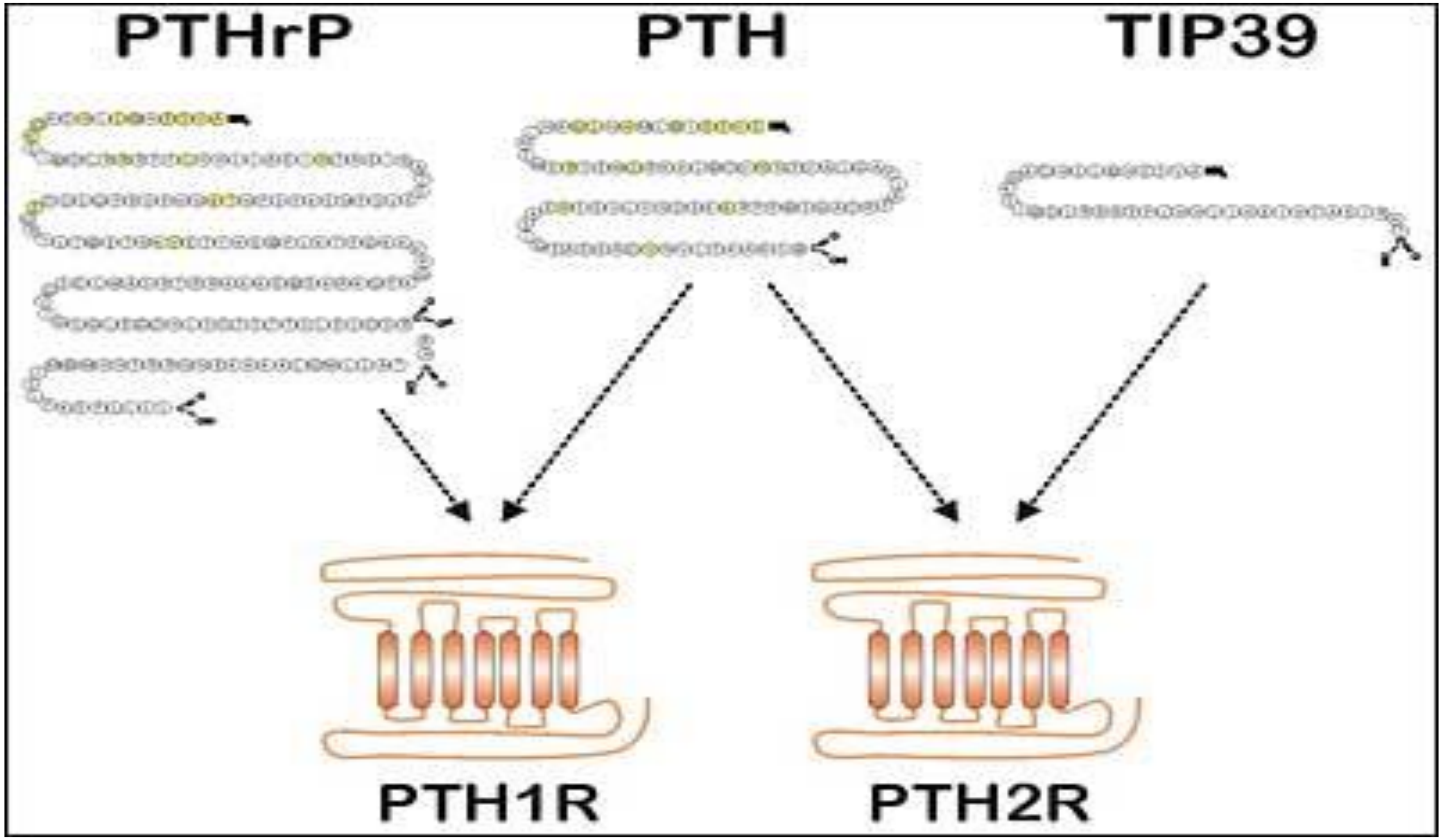
- The condition is characterized by low tubular reabsorption of phosphate in the absence of secondary hyperparathyroidism.
- X-linked hypophosphatemia occurs in about 1 in 25,000 and is considered the most common form of genetically induced rickets.



Jan de Beur, S. M. JAMA 2005;294:1260-1267. With Permission.

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.

Effects of PTHrP

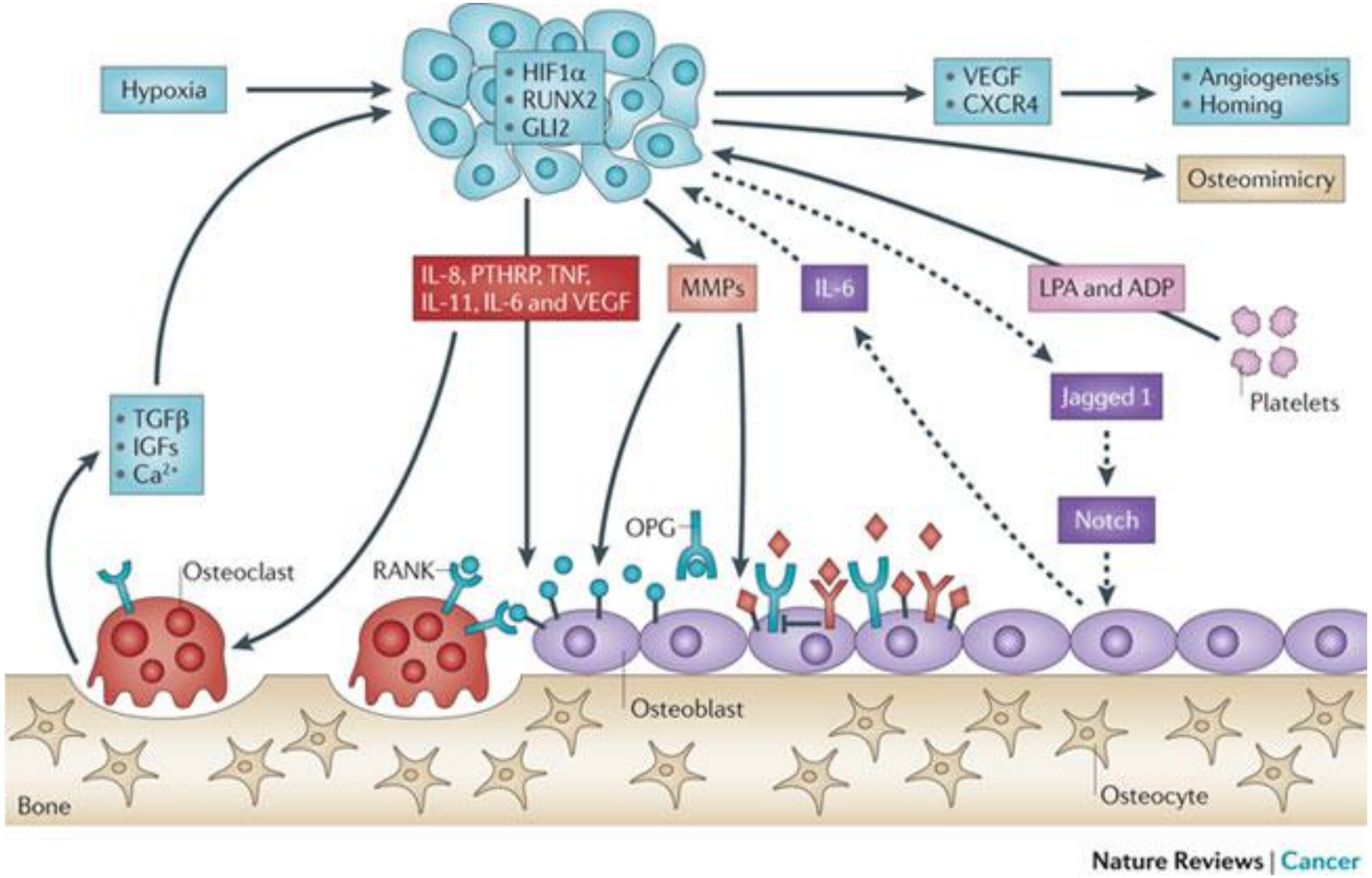
- to ion homeostasis
- to smooth muscle relaxation;
- associated with cell growth, differentiation and apoptosis.
- necessary for normal fetal calcium homeostasis

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.

Effect of PTHrP to

- ***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.

Calcitonin

- The main source in mammals are parafollicular (C) thyroid cells. Furthermore, other tissue - lungs, GIT.
- Peptide of 32 AK.
- Alternative splicing results in the production of a "calcitonin-gene-related peptide" that has functions in the nervous system and circulation.
- The calcitonin receptor is again a member of the 7-transmembrane G protein-coupled receptor family

The most important driving stimulus is the extracellular level of ionized calcium.

Hypo/hypercalcemic disorders summary

Hypercalcemic Disorders

A. Endocrine Disorders Associated with Hypercalcemia

1. Endocrine Disorders with Excess PTH Production
   - Primary Sporadic hyperparathyroidism
   - Primary Familial Hyperparathyroidism
     - MEN I (multiple endocrinal neoplasma)
     - MEN IIA
     - Familial hypocalciuric hypercalcemia - FHH
     - Neonatal severe hyperparathyroidism - 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

Hypercalcemia

Symptoms	Clinical signs	Investigations
Fatigue	Dehydration	Serum calcium >3.0 mmol/l
Nausea and vomiting	Neurological weakness	ECG changes: • bradycardia • prolonged PR interval • short QT interval • widened T waves • arrhythmia
Constipation	Hyporeflexia	
Polyuria	Decreased consciousness	
Psychological disturbance		

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

Thank you for your attention