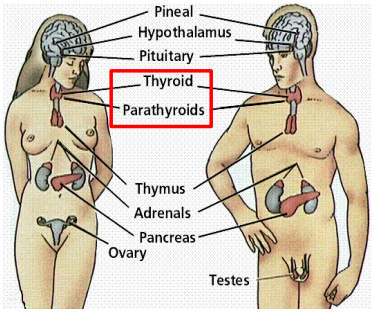
Calcium Homeostasis



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Functions of calcium

- Structural: bone, teeth, connective tissue
- Excitation-contraction coupling (muscles)
- Excitation-secretion coupling (neurotransmitters, hormones)
- Stability of excitable membranes
- Cardiac & smooth muscle potentials
- Enzyme activity
- Blood clotting

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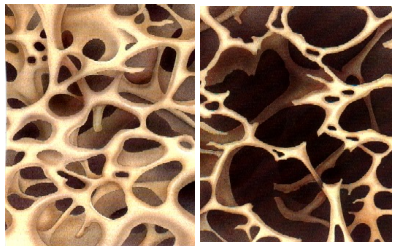
Calcium homeostasis

The issues:

1. Maintaining adequate amounts of calcium in bone. If fails → osteoporosis.

- ↓ bone mineral content & ↓ bone matrix
- Increasing in the Western World
- Risk increases with age
- More common in post-menopausal women than in men
- Oestrogen helps prevent progression of disease



Normal matrix

Severe osteoporotic matrix

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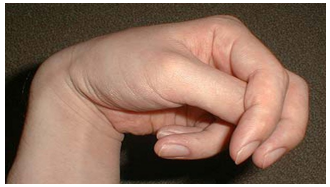
Calcium homeostasis

The issues:

1. Maintaining adequate amounts of calcium in bone. If fails → osteoporosis.
2. Maintenance of a stable concentration of ionized calcium (Ca^{2+}) in the plasma. If fails → tetany, seizures (+ death). Short term.

Tetany: The point at which action potentials are arriving to skeletal muscle rapidly enough in succession to cause a steady contraction, and not just a series of individual twitches.



Larynx: spasm can cause airway obstruction and asphyxia → death

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Distribution of calcium

Total body content is approx 1.3 kg

99% in bone
1% intracellular
0.1% extracellular

Calcium in blood

Normal range: 2.00 – 2.5 mmol/l.

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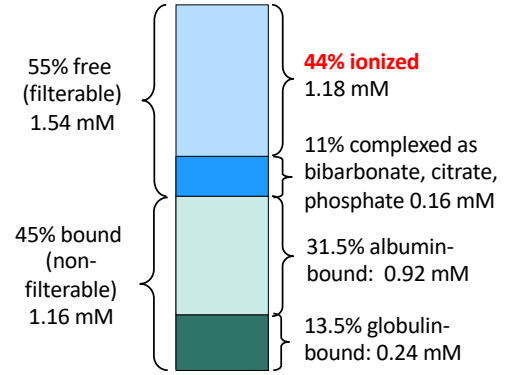
Distribution of calcium in the plasma

- Note: measurements of total serum calcium include both ionised (metabolically active) calcium (Ca^{2+}) and bound calcium.
- When protein (eg. albumin) concentrations fluctuate, total Ca levels may vary whereas Ca^{2+} remains relatively stable.



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Blood pH important

Ionised fraction (Ca2+) depends on blood pH

Protein binding decreases as pH decreases.

Alkalosis:

Less H+

pH 7.45

pH 7.35

More H+

Acidosis:

If H+ decreases (eg hyperventilating)
→↑ calcium binding to protein
→↓ ionised fraction (Ca2+)
→Risk of tetany (if total Ca is <1.5 mmol/l)

If H+ increases
→↓ calcium binding to protein
→↑ ionised fraction (Ca2+)

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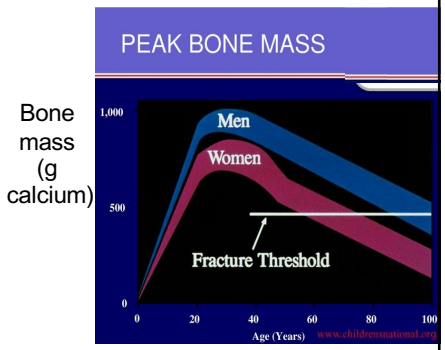
Calcium balance

Normally: intake=loss

Positive balance (intake>loss) in growing young, pregnancy, bone healing.

Negative balance (loss>intake) in old age, prolonged weightlessness, prolonged bed rest.



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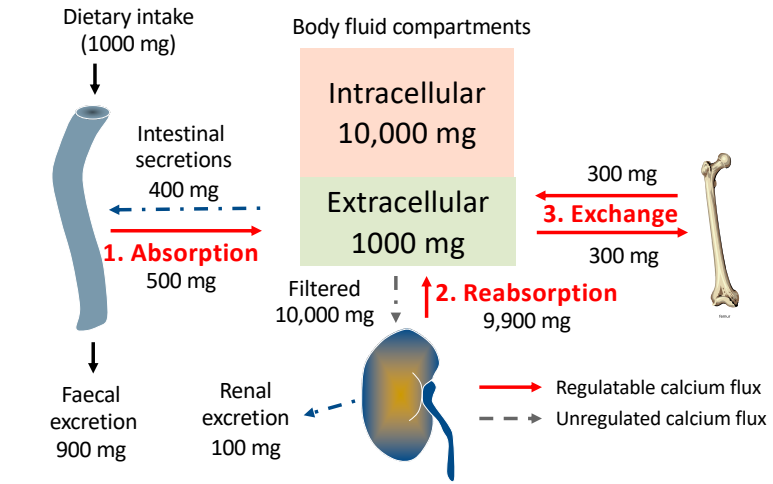
Calcium exchange (per day)



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Ways to increase blood calcium

- Ingest/absorb more (GUT)
- Lose less (KIDNEY)
- Release from stores (last defense) (BONE)

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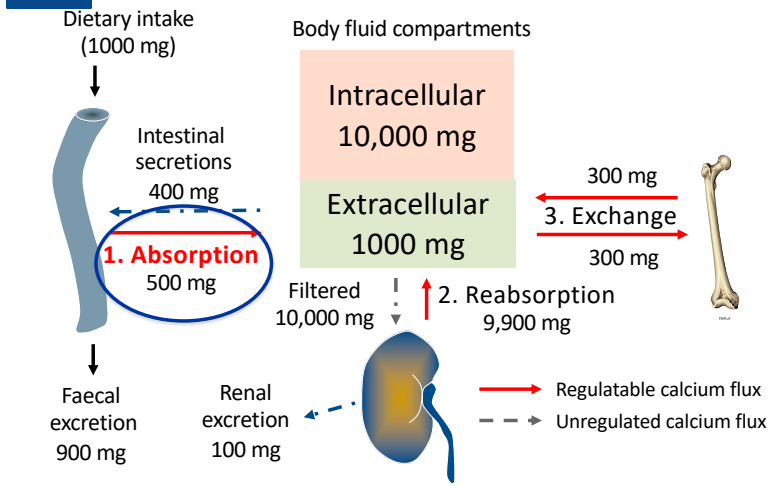
Calcium absorption



Most important hormone is **CALCITRIOL (from Vit D)**

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Calcium absorption by the gut

About 40-50% ingested calcium is absorbed

Duodenum (& upper jejunum)
- Active process regulated by **vitamin D metabolite (CALCITRIOL)**
- Low uptake

Ileum and lower jejunum
- Passive process (ie no hormones involved)
- Uptake higher

Absorption rate also influenced by:
- Acidity of stomach (↑ absorption)
- Fatty acids form insoluble soaps (↓ absorption)

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Calcitriol summary

- Also called 1,25- dihydroxycholecalciferol (1,25-DHCC).
- A steroid hormone derived from vitamin D
- Normal plasma – 0.03 ng/ml
- Nuclear receptors that regulate transcription of RNA. Located in intestine, bone, kidney.
- Action:
  - **DIRECT Primary action: ↑ intestinal absorption of calcium and phosphate.**
  - (Facilitates Ca2+ reabsorption in kidneys)
  - (↑ Synthetic activity of osteoblasts. Required for normal calcification of matrix).
- Deficiency → **rickets** in children; **osteomalaci** in adults

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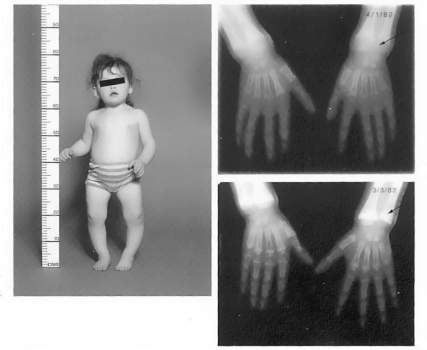
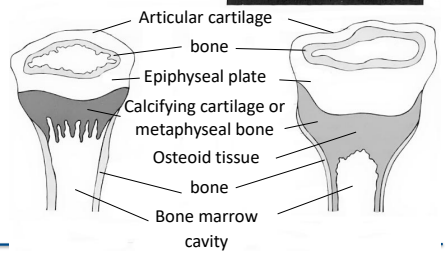
Rickets (vit D deficiency - children)

(in adults vit D deficiency = osteomalacia)

- Soft bones
- Bowing of tibiae
- Cupping of metaphyses
- Epiphyseal cartilage is enlarged.
- Osteoid tissue





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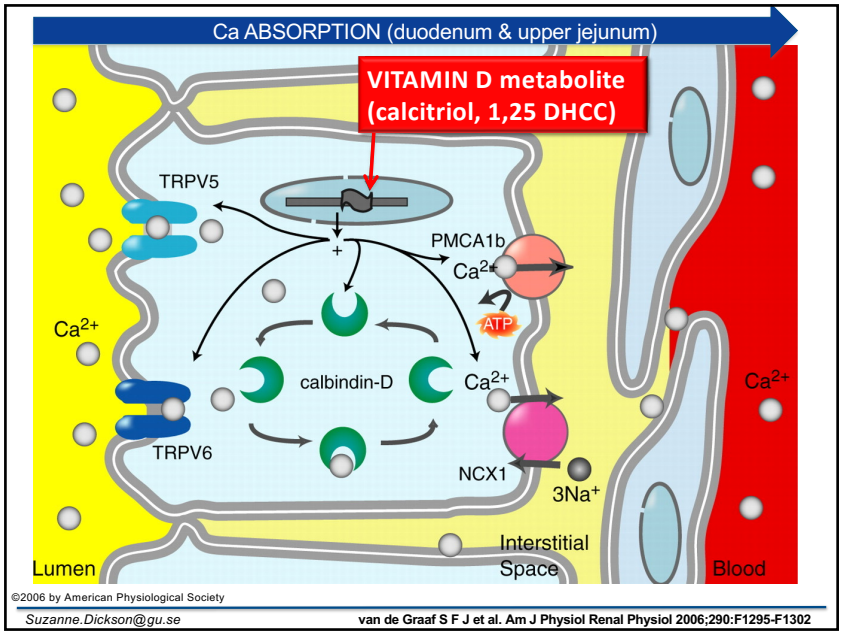

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By what mechanism does calcitriol increase calcium absorption in the duodenum?

Brush border – uptake into epithelial cell

↑ expression of **TRPV6*** (also TRPV5**), a membrane calcium channel.

Inside epithelial cell

↑ expression of **calbindin-D_{9K}** which binds calcium and acts as a calcium buffer (ie stops it from impacting on the cell function eg excitability etc).

Basolateral membrane – delivery to blood.

↑ expression of **NCX1** (a Na^+/Ca^{2+} exchanger)

↑ expression of **PMCA1b** (a plasma membrane Ca^{2+}-ATPase)

**TRPV = Transient receptor potential cation channel subfamily V*

***TRPV5 More important in kidney*

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Absorption of Calcium (gut)

- When calcium intake is high,
  - active transport mechanism becomes saturated.
  - calcitriol (vit D derivative) levels fall (as plasma Ca levels increase)

Important: Absorption is controllable.

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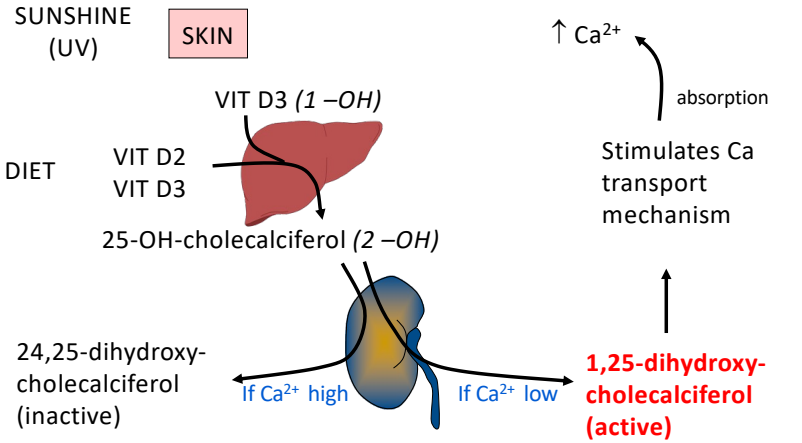
Production of 1,25-DHCC (calcitriol) - only when calcium low



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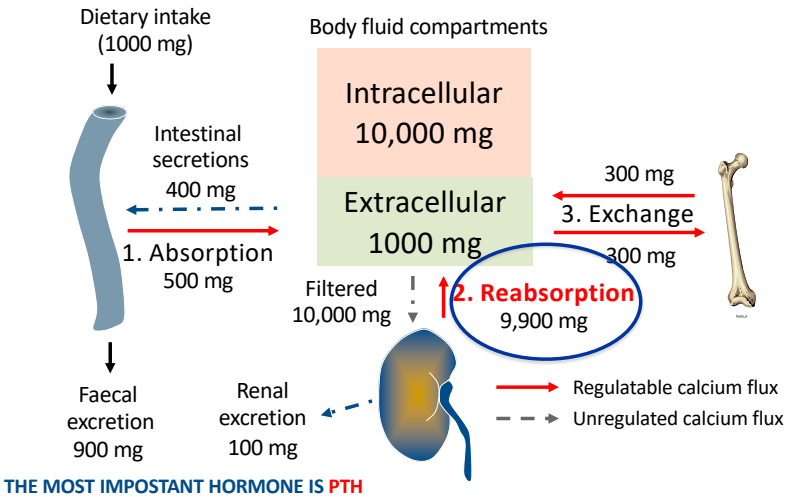
Calcium exchange (per day)



THE MOST IMPOSTANT HORMONE IS PTH

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Renal excretion and reabsorption of calcium

Reabsorption (controllable):

- 98-99% filtered calcium is reabsorbed
- low blood calcium → ↑reabsorption
- 60% occurs in the proximal kidney tubule (an active transport mechanism)
- 25% occurs in the thick ascending limb of the loop of Henle
- 15% occurs in distal tubule and collecting ducts (involves **TRP5** channel). Only this 15% is under **parathyroid hormone (PTH)** control. PTH regulates expression of TRP5 in the distal tubule.

Excretion in glomeruli (unregulated):

Increased by high circulating calcium concentrations.

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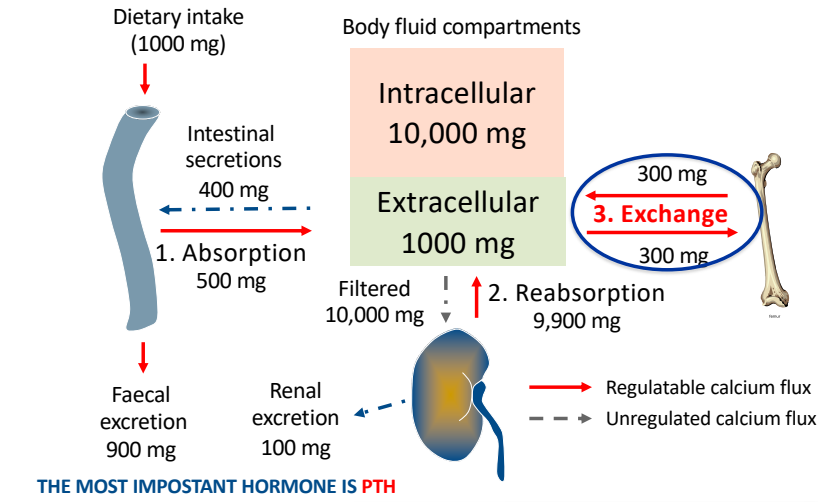
Calcium exchange (per day)



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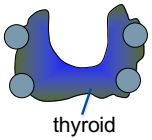
Parathyroid hormone (PTH)

- Secreted by the chief cells of the (usually 4) parathyroid glands.
- Plasma: 10-55 pg/ml; Half-life <10 min.
- Peptide hormone. 84 amino acids.
- Two receptors: PTHR1 and PTHR2.
- Primary physiological role: **↑ blood calcium and ↓ blood phosphate**
- Essential for life.
- Secretion rate increased when blood calcium levels fall.



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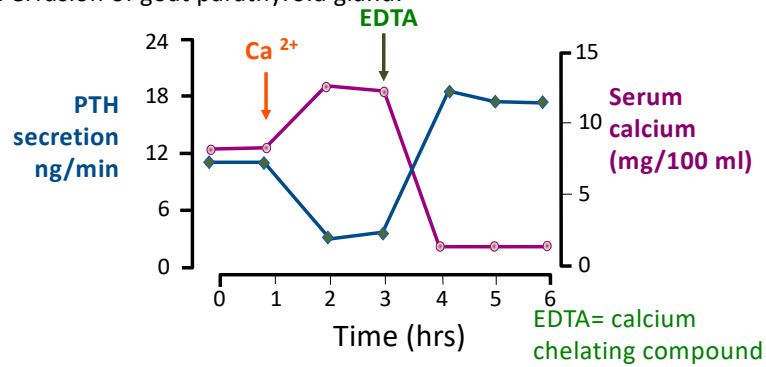
PTH secretion is regulated by blood calcium

The parathyroid glands detect changes in serum calcium levels via calcium sensing receptors.

Perfusion of goat parathyroid gland.



EDTA= calcium chelating compound ie removes calcium

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How does PTH increase blood calcium?

DIRECT EFFECTS

1. Release of calcium from **bone** (↑ resorption).
2. Calcium reabsorption in **kidney**.

INDIRECT EFFECTS

3. ↑ **Gut** calcium absorption by promoting calcitriol formation in kidney. It increases expression of 1 alpha hydroxylase, the enzyme that converts vitamin D into its active form.

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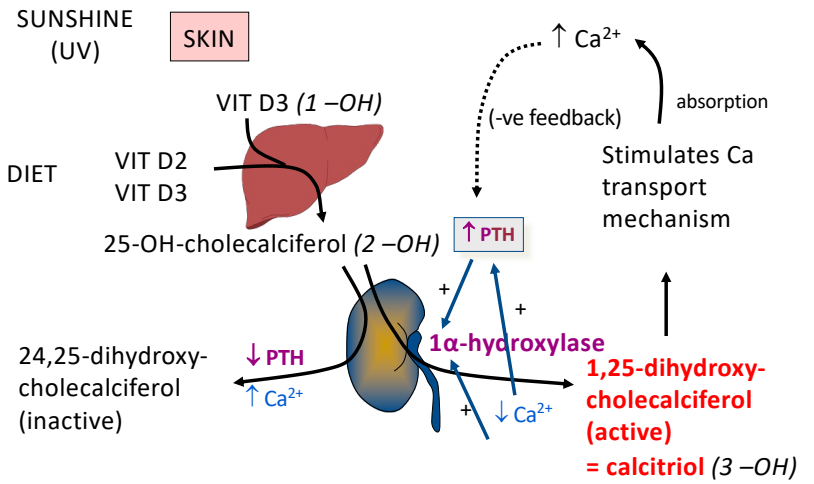
Production of 1,25-DHCC (calcitriol)



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Bone calcium

- 99% of bone calcium is located within the crystal structure (stable, slowly exchangeable).
- There are 2 pools of calcium in bone
  - One that readily releases calcium into blood
  - One dedicated to bone remodelling
- 1% of bone calcium is found as simple calcium phosphate salts - rapidly exchangeable with extracellular calcium pool. (ie provides a buffer for maintaining blood calcium).
- **Key hormone releasing calcium from bone is PTH.**

At low PTH concentrations:
- ◆*remodelling*. (Ca exchange)

At high PTH concentrations
- ◆*demineralization*. (Ca loss)

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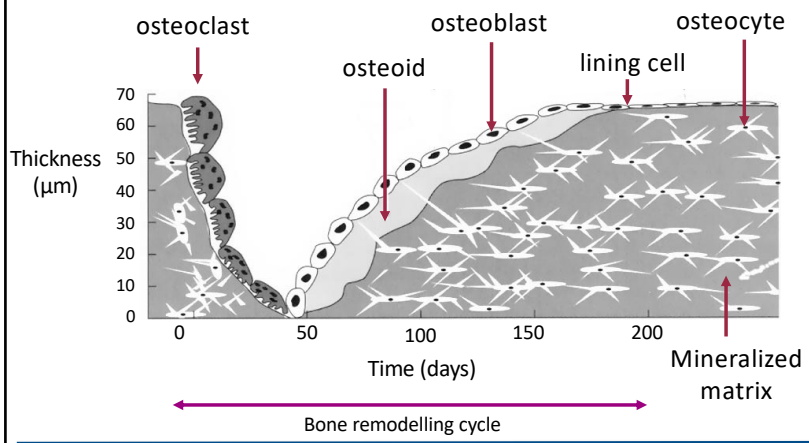
Bone remodelling cycle



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Cell types in bone

Osteoblasts - laying down of bone. They secrete **osteoid** (non-mineralised pre-bone, that has not yet been calcified). Osteoblasts become trapped in the bone as it is being laid down and become **osteocytes**.

Osteoclasts - bone resorption. Release acids and proteolytic enzymes.

Bone lining cells - protect the bone. If they retract, the osteoclasts will get access. Osteoclasts only act where there are no bone lining cells.

Remodelling cycle exists because bone is not intert until we die - it is dynamic - broken down and built up again.

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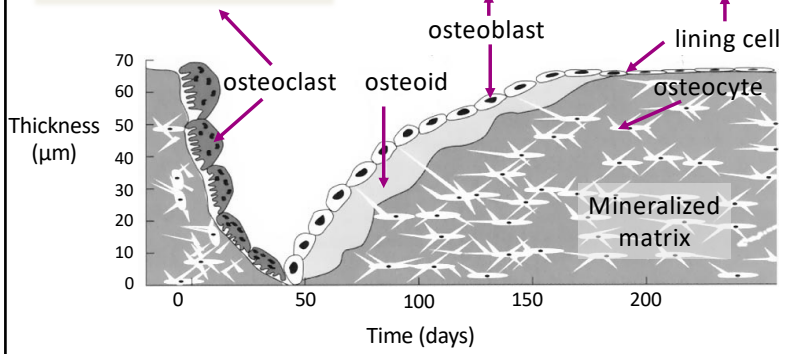
PTH increases osteoclast activity but this is indirect

Indirect actions (no PTH receptors): Increased osteoclast number and activity

↓ cell size, ↓ protein synthesis, ↓ differentiation

Retraction. Osteoclast-stimulating protein



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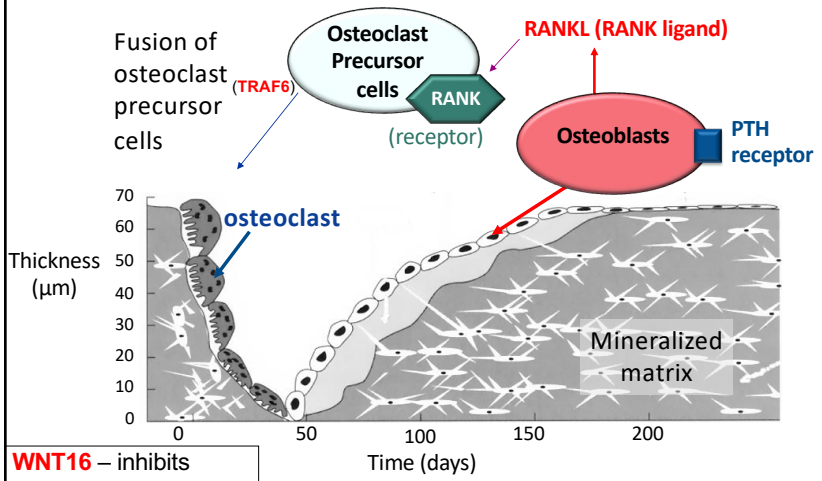
PTH acts on osteoblasts to induce RANK ligand, which aids fusion of osteoclast precursors



WNT16 – inhibits osteoclast formation (bone-saving)

RANK = Receptor activator of nuclear factor kappa-B

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Mechanism of actions of PTH on bone:

Osteoclasts (bone destruction/resorption):

- **indirectly stimulated by PTH.**

1. Osteoblasts (bone creation)

   PTH acts via PTH receptors directly on osteoblasts → production of RANKL (**RANK ligand**)

2. RANKL bind to osteoclast precursors containing **RANK**, a receptor for RANKL.

3. The binding of RANKL to RANK stimulates these precursors to fuse, forming new osteoclasts which ultimately enhances the resorption of bone.

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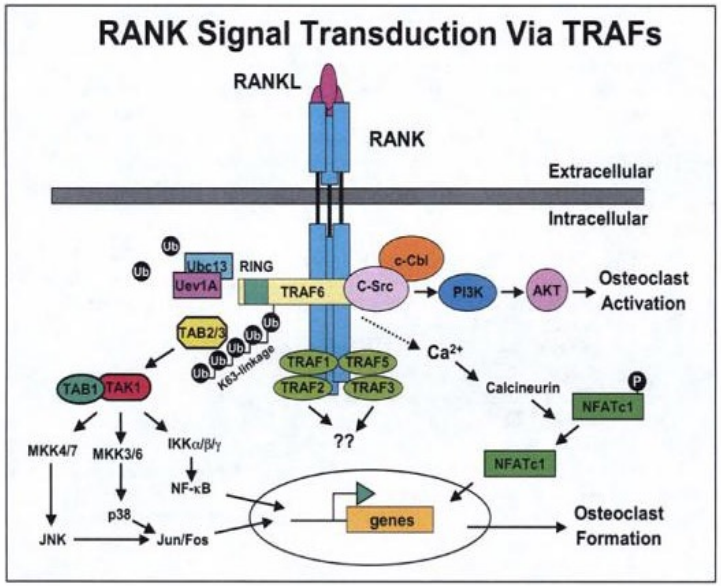

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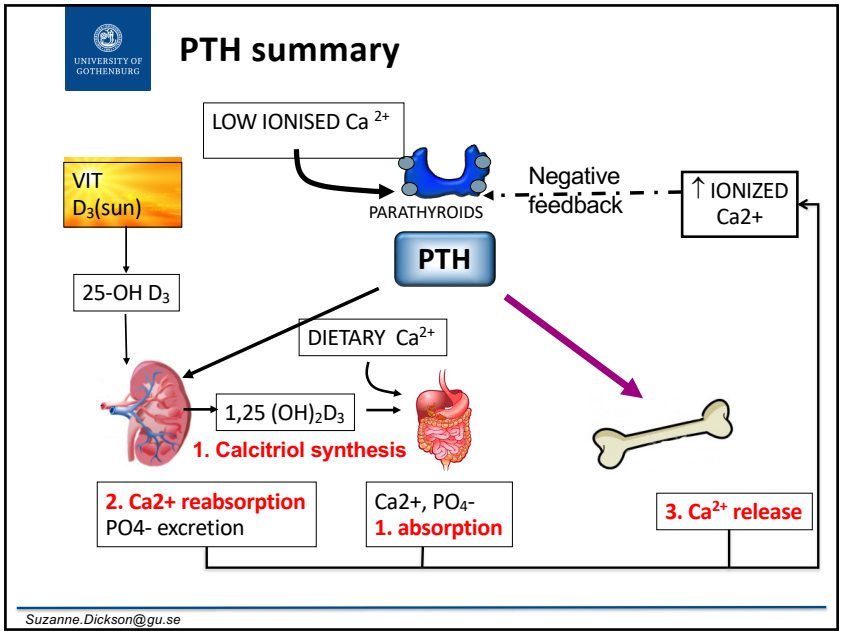
PTH summary
LOW IONISED Ca 2+
VIT D3(sun)
PARATHYROIDS
Negative feedback
↑ IONIZED Ca2+
PTH
25-OH D3
DIETARY Ca2+
1,25 (OH)2D3
1. Calcitriol synthesis
2. Ca2+ reabsorption
PO4- excretion
Ca2+, PO4-
1. absorption
3. Ca2+ release
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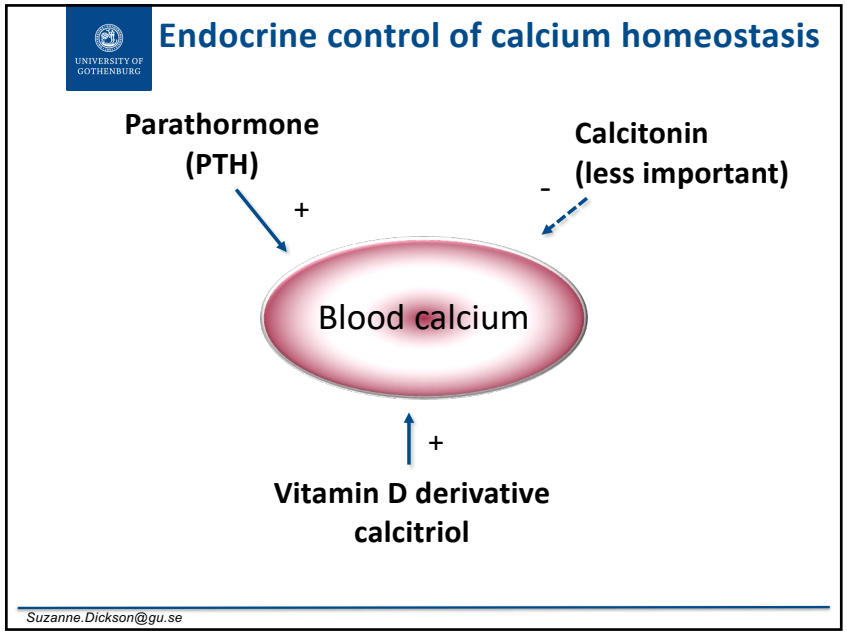
Endocrine control of calcium homeostasis
Parathormone (PTH)
+
Calcitonin (less important)
-
Blood calcium
+
Vitamin D derivative calcitriol
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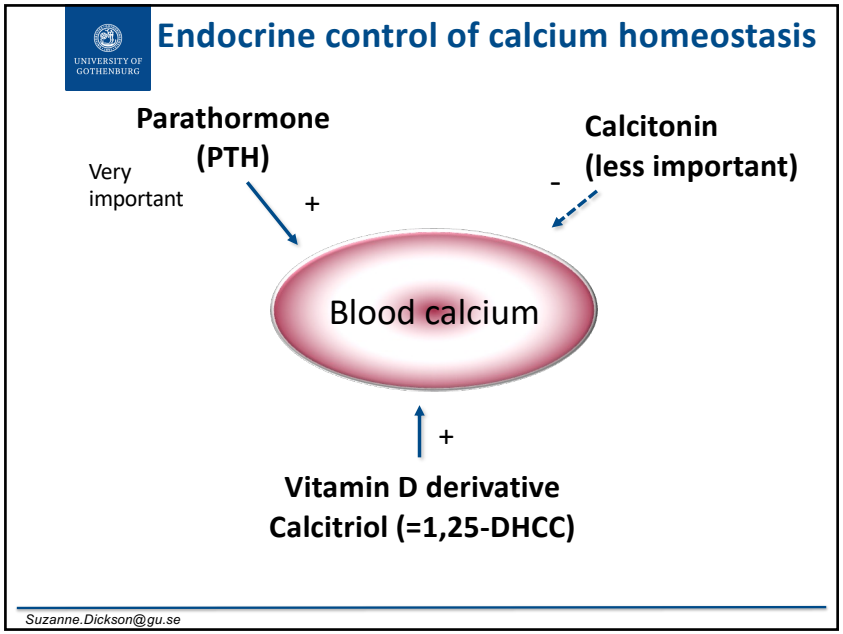
Endocrine control of calcium homeostasis
Parathormone
(PTH)
Very
important
+
Calcitonin
(less important)
-
Blood calcium
+
Vitamin D derivative
Calcitriol (=1,25-DHCC)
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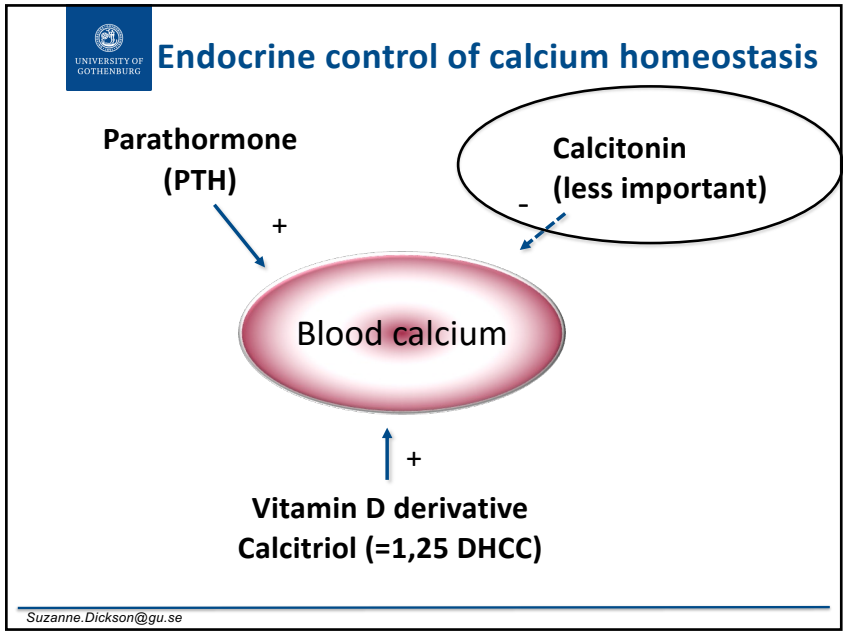
Endocrine control of calcium homeostasis
Parathormone
(PTH)
+
Calcitonin
(less important)
-
Blood calcium
+
Vitamin D derivative
Calcitriol (=1,25 DHCC)
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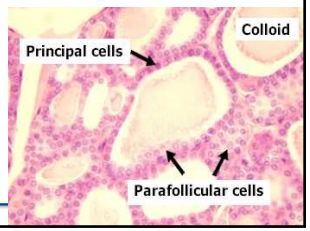
Calcitonin

- MUCH less important than PTH and calcitriol.
- Role: Moves Ca^{2+} into bone after a meal. Also prevents bone demineralization during pregnancy and lactation.
- Produced by parafollicular (or C-cells) of the thyroid gland
- Action: Lowers blood Ca^{2+} by inhibiting osteoclasts.
- Release: induced by an increase in blood Ca^{2+}, gut hormones (gastrin, CCK, secretin).



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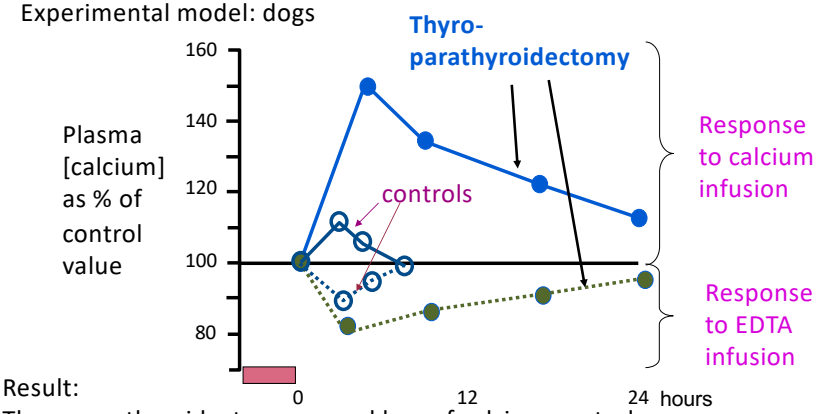
Slow recovery from changes in plasma [Ca2+] after thyro-parathyroidectomy

Experimental model: dogs



Result:
Thyro-parathyroidectomy caused loss of calcium control.
Parathyroidectomy (ie no PTH) → slow recovery when Ca removed
Thyroidectomy (ie no calcitonin)→ slow recovery when calcium infused.

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Hypercalcemia

Cause:

- hyperparathyroidism, malignancy, excessive vitamin D activity.

Symptoms:

- Kidney stones - calcium deposition in soft tissue.
- Impaired renal function –Ca toxicity to kidneys, thirst, large volume of dilute urine.
- CNS: Fatigue, depression
- Muscular aches & pains
- Bone erosion - If too much PTH.
- Gastro-intestinal: nausea, vomiting, constipation

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Hypocalcemia

Cause:

- hypoparathyroidism, (vitamin D deficiency, renal disease)

Symptoms:

- Increased excitability of nervous tissue (pins and needles, tetany, epilepsy, cardiac arrhythmias).
- Chvostek's sign - facial muscles

(http://www.youtube.com/watch?v=XjtHDhNcXEQ)

- Trousseau's sign - wrist spasm

(http://www.youtube.com/watch?v=qHIL3pK_Nao)

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Other hormones in Ca Balance: glucocorticoids

- lower plasma Ca by inhibiting osteoclast formation and activity.
- (longterm) osteoporosis - ↓ bone formation, ↑ bone resorption
- Intestine: ↓ Ca and phosphate absorption
- Kidney: ↑ Ca and phosphate excretion

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Other hormones in Ca Balance: PTH-related peptide

- Structurally related to PTH,
- Similar effects as PTH.
- Produced by almost all cells in the body. ↑ levels in breast milk. Important for cartilage growth in utero.
- Identified as a tumor product that can activate PTH receptors → **hypercalcemia**
- Causes 80% of cancer-related hypercalcemia (paramalignant symptom)
- causes hypercalcemia by increasing bone resorption and renal tubular resorption of calcium.
- Most actions mediated by actions at PTH receptor.

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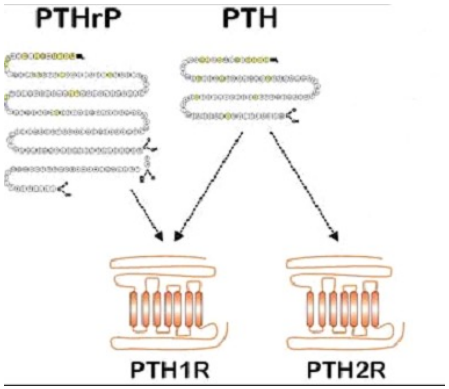
PTH, PTH-rP and their receptors



Bone, Kidney

CNS, pancreas, testis, and placenta

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Other hormones in Ca Balance: oestrogens

- Preserves bone mass in both males (testosterone →estradiol locally) and females
- Reduce bone resorption (Direct effect on osteoclasts),
- Prevent osteoporosis, inhibit the stimulation of osteoclasts by cytokines (e g IL-6).

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Other hormones in Ca Balance: Thyroid hormones

- Hyperthyroidism increases risk of osteoporosis and bone fracture.
- T3 and T4 stimulate the activity of osteoclasts (=the bone resorption).
- They increase the production of RANKL which promotes the differentiation and activity of osteoclasts.
- As a result, osteoclasts break down bone tissue more actively, leading to increased bone resorption.

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Osteoporosis treatment

1. **Bisfosfanate** – binds to hydroxyapatite and inhibits osteoclasts

2. **Denosumab** – monoclonal antibody that binds to RANKL and blocks it.

3. **Teriparatid**. PTH analogue given intermittently.

1 and 2 – anti-resorptive for bone
3 anabolic for bone.

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Phosphate balance

- Total body phosphorus is 500-800 g, 90% of which is in bone (+ continually exchanged).
- Reaborption – kidney – proximal tubule
  - Sodium-dependent Pi cotransporters, NaPi-IIa and NaPi-IIc.
  - **NaPi-IIa** powerfully inhibited by **PTH** → phosphaturea. NaPi-IIa also inhibited by **FGF23** from bone (next slide)
- Absorption – duodenum & small intestine.
  - Involves **NaPi-IIb**
  - Stimulated by **calcitriol**. (Note **FGF23** inhibits formation of calcitriol ie less absorption).

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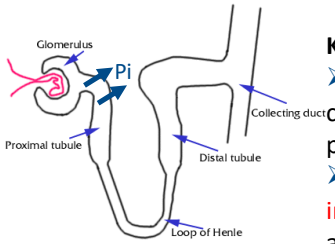
FGF-23 from bone generates a negative phosphate balance



Kidney

- Inhibits the sodium/phosphate cotransporter (NaPi-IIa) → phosphaturea.
- Reduces levels of calcitriol (by inhibiting 1α-hydroxylase). Less gut absorption.

FGF-23 is produced by from skeletal osteocytes and osteoblasts. Also - high production by tumors, that can decrease Ca2+ and phosphate.

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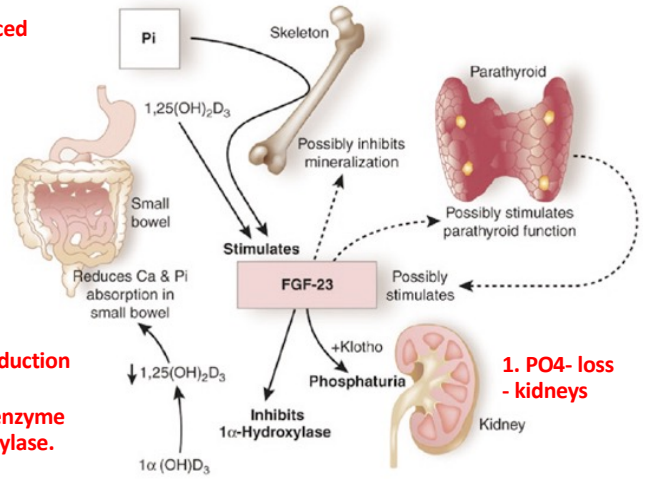
FGF-23 generates a negative phosphate balance

FGF-23 produced by bone



2. Reduces production of calcitriol by inhibiting the enzyme 1-alpha hydroxylase.

1. PO4- loss - kidneys

Suzanne.Dickson@gu.se

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α-Klotho (enhances FGF23 action)

- Klotho = daughter of Zeus who spins the thread of life.
- Anti-aging protein (supposedly).
- Mice that lack it age faster, have decreased bone mineral density, calcifications, high blood calcium.
- Actions:
  Required for stabilizing membrane location of proteins imp for calcium & phosphate (re)absorption.
  Enhances FGF-23 action at its receptor - ie less phosphate (re)absorption

Suzanne.Dickson@gu.se

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