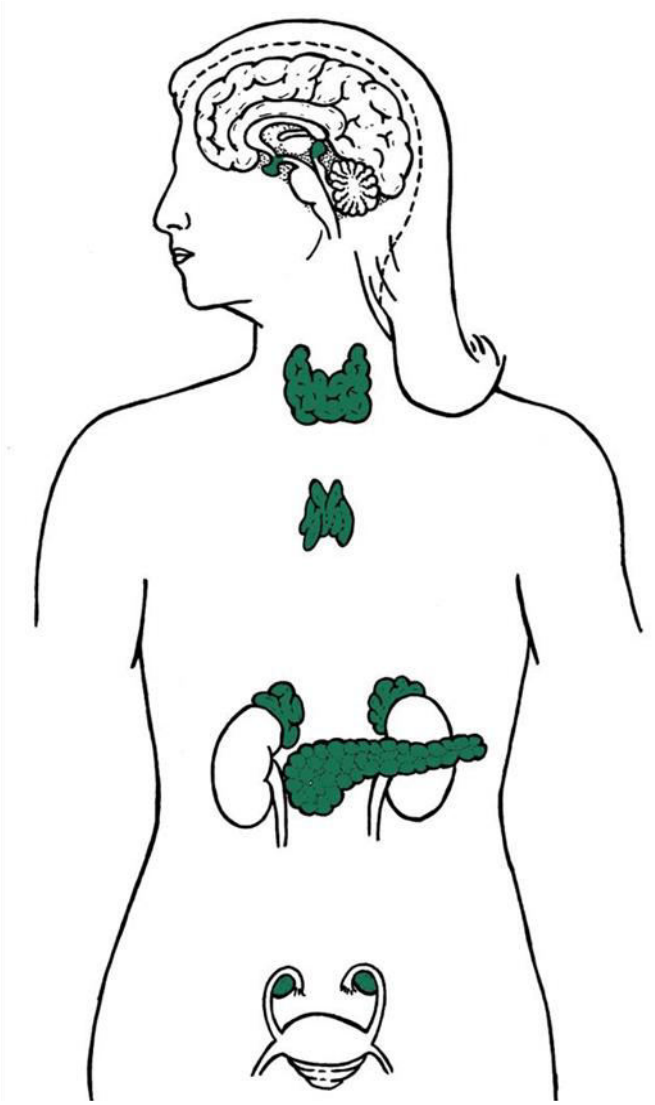
MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري



Physiology Team 436

| | |
|---|---|
| | ▪ Text<br>▪ Only in Females' slide<br>▪ Only in Males' slides<br>▪ Important<br>▪ Numbers<br>▪ Doctor notes<br>▪ Extra Notes |

# Endocrine Block

"إن الله لا يُعطي
أصعب المعارك، إلا
لأقوى جنوده "

# Calcium Homeostasis

By the end of this lecture, students should be able to describe:

1. Identify and describe the primary sources and mechanism of actions in target tissues of the following calcitropic hormones where they exert their major effects:

A. Parathyroid Hormone (PTH),

B. Calcitonin,

C. Vitamin D,

D. Parathyroid hormone related peptide (PTHrP).

2. Identify the actions of calcitropic hormones at bone (osteoblasts and osteoclasts), kidney and intestine.

3. Identify the effect of the following factors on the measurement of free (ionized) calcium and total serum calcium:

A. pH changes

B. Protein abnormalities

Identify and describe calcium homeostasis in pregnancy, lactation and in postmenopausal women (lack of estrogen).

# Bone Composition

- Organic Matrix
  - Collagen Fibers (95%)
  - Ground Substance (5%):
    - ECF
    - Proteoglycans

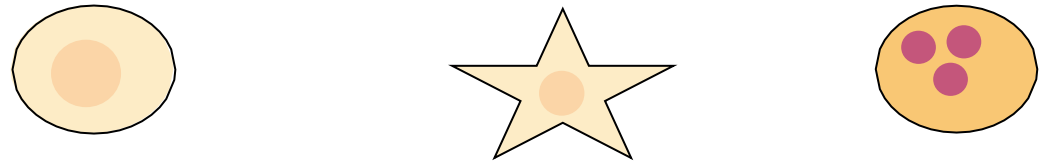
  } Tensile Force

- Bone Salts/ Mineral salts
  - Salts of Ca++ & PO4-

  In the form of:
  - Hydroxyapatite crystals (99%) Ca10(PO4)6 (OH)2
  - Mg, Na, K, Carbonate ions

  } Compressional Force

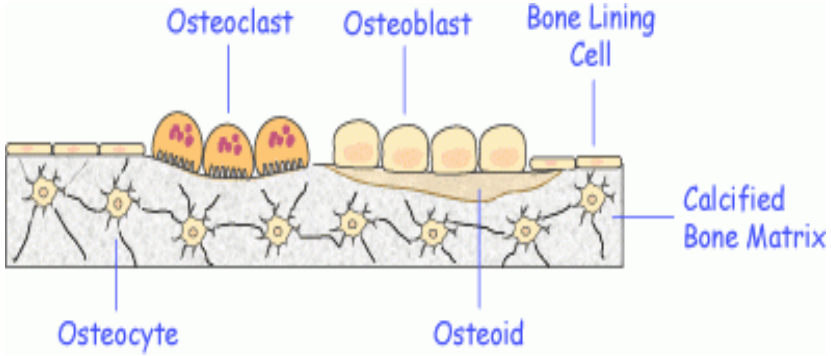
## Bone Cells



**Osteoblasts** (Bone forming cells)

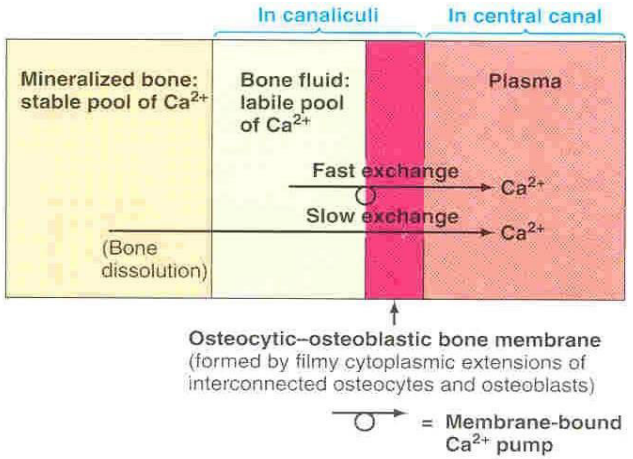
**Osteocytes** (Osteoblasts surrounded by calcified matrix)

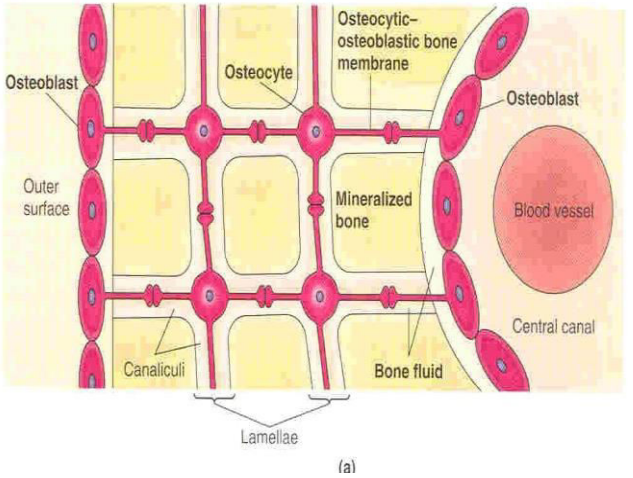
**Osteoclasts** (Bone eroding cell "resorping")



# Cont.

- Composition of bones
  - Organic matrix
    - Collagen fibers
    - Ground substances
  - Mineral salts
    - Hydroxyapatite crystals
      - 99% of total Ca++ salt
      - In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$
    - Mg, Na, K, Carbonate ions
    - Amorphous salts
      - A type of exchangeable calcium
        - Play role in rapid regulation of ionized Ca++ level in ECF
        - 0.4-1% of total bone Ca++
        - always in equilibrium with $Ca^{2+}$ in ECF



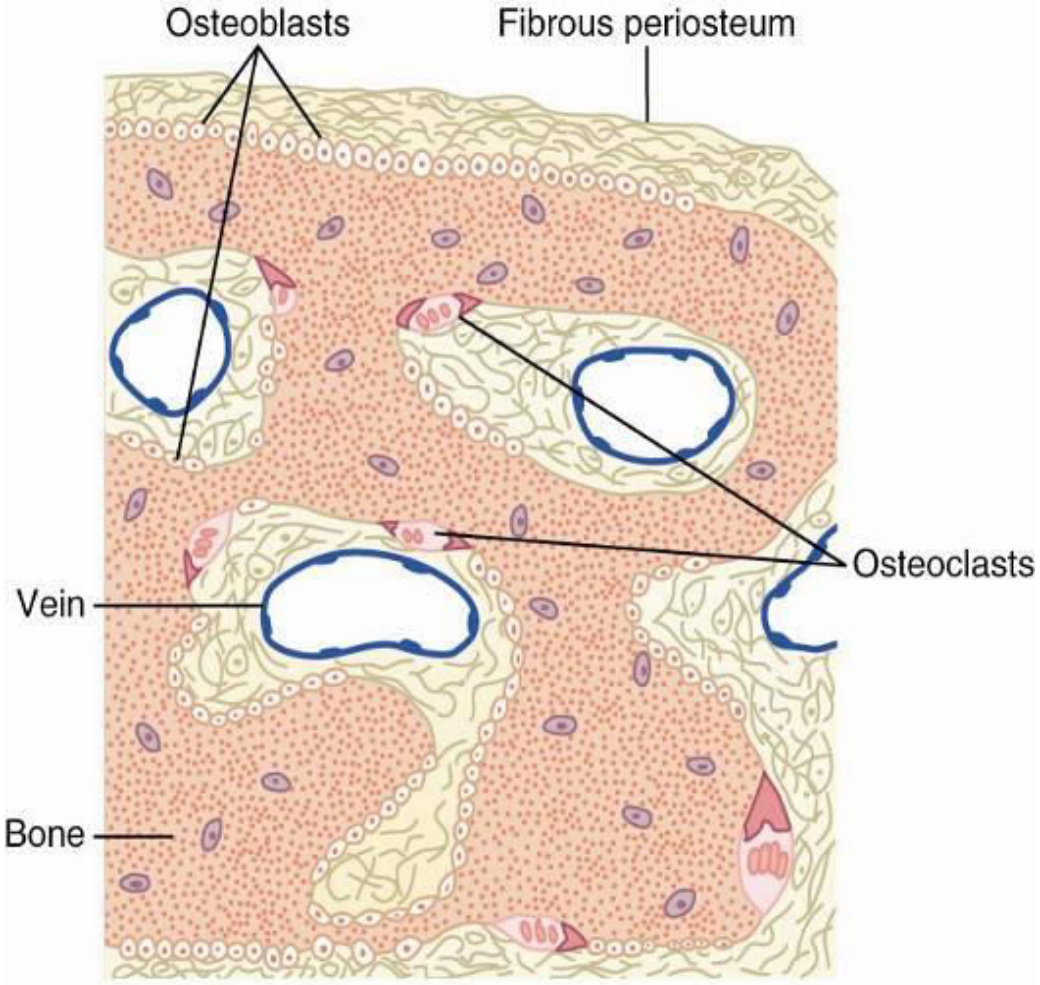

جيبوا عظمة وحطوها في خل، بعد وقت الكالسيوم راح يطلع، جربوا بعدين تكسرونها راح تلقونها مرنة زي الصلصال ما تنكسر بس مو قوية وصلبة (هذه أهمية الكالسيوم).

بعدها خذوا العظمة وحطوها بالفرن، مع الحرارة راح يتكسر الكولاجين، جربوا بعد كذا تكسرون العظمة راح تلقونها علطول انكسرت وهشة جدا (هذه أهمية الكولاجين)

Only in Males' Slides

# Bone Remodeling

- Bone is continually being deposited by osteoblasts, and it is continually being resorbed where osteoclasts are active.
- Cells including:
  1. Osteoblast: form bone.
  2. Osteoclast: resorb bone.
  3. Osteocytes.
- Osteoblast is important to activate osteoclast.
- Balance between formation and resorption is dynamic.



# Calcium

- Calcium is essential for many processes in the body such as bone formation, contraction of muscles, clotting and other cardiac function.
- Source:
  - Milk, dairy products & Fish.
- Daily requirements
  - Infants & adults: 5-25 mmol/day
  - Pregnancy
  - Lactation
  - After menopause

  } 25-35 mmol/day
- Absorption
  - Duodenum: active transport.
  - Small intestine: concentration gradient.


# Cont.

- Distribution of Calcium in Body:
  - Skeleton & Teeth.
  - ICF (Endoplasmic Reticulum).
  - ECF: Total concentration of calcium in ECF = 9-10.5 mg/dl, 5 mEq/L, 2.4 mmol/L

    لاحظوا اختلاف الوحدات

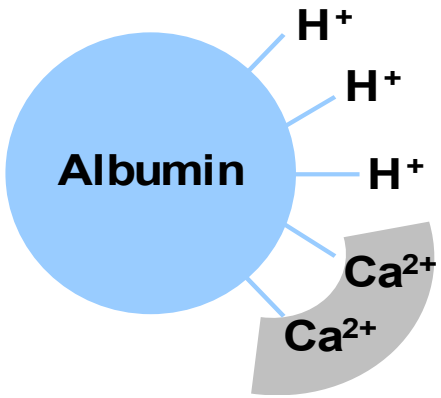
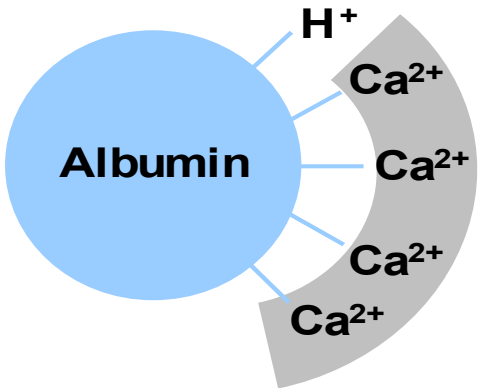
    - Diffusible Calcium 59%
      - Ionized 50%, 1.2 mmol/L "Physiologically Active"
      - Complexed 9%, 0.2 mmol/L
    - Non-Diffusible Calcium 41%, 1.0 mmol/L:
      - Most of this calcium is bound to albumin & much smaller fraction is bound to globulin.
      - Binding of calcium to albumin is pH-dependent.
      - Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level.

- Physiological Importance of calcium: (تكلم عنها دكتور الأولاد اثناء المحاضرة)
  1. Calcium salts in bone provide structural integrity of the skeleton.
  2. Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes:
  - Neuromuscular excitability.
  - Hormonal secretion.
  - Enzymatic regulation.
  - Blood coagulation.
  - Second messenger.

Very important

فيه سؤال من هنا

# Effects of Acid-Base Disturbance on Ionized Calcium

| Acidosis (Acidemia) | Alkalosis (Alkalemia) |
|---|---|
|  |  |
| More H+ ions are present in the blood, so they will compete with calcium to bind with albumin, so more ionized calcium will be available in the plasma | ✓ Less H+ ions are present in the blood, so more calcium will be bound to albumin which leads to hypocalcemia.<br>✓ Decreased Ca in the blood causes more harm to our body than increased does.<br>✓ Hyperventilation leads to alkalosis and this will decrease Calcium in our blood which causes spasms and many harmful side effects. |
| ↑ Ionized ($Ca^{2+}$) | ↓ Ionized ($Ca^{2+}$) |

الإكسترا من هذه السلايد كانت موجودة بسلايدات الدكتور قبل التعديل، وحرّص على أهميتها أثناء الشرح

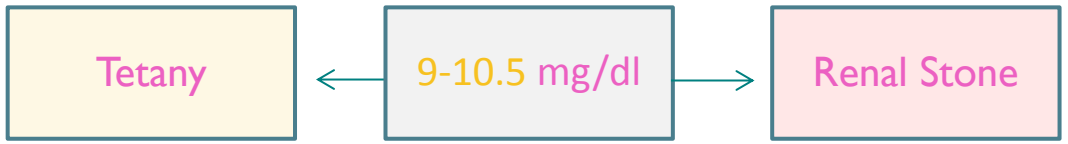
# Plasma Calcium Regulation

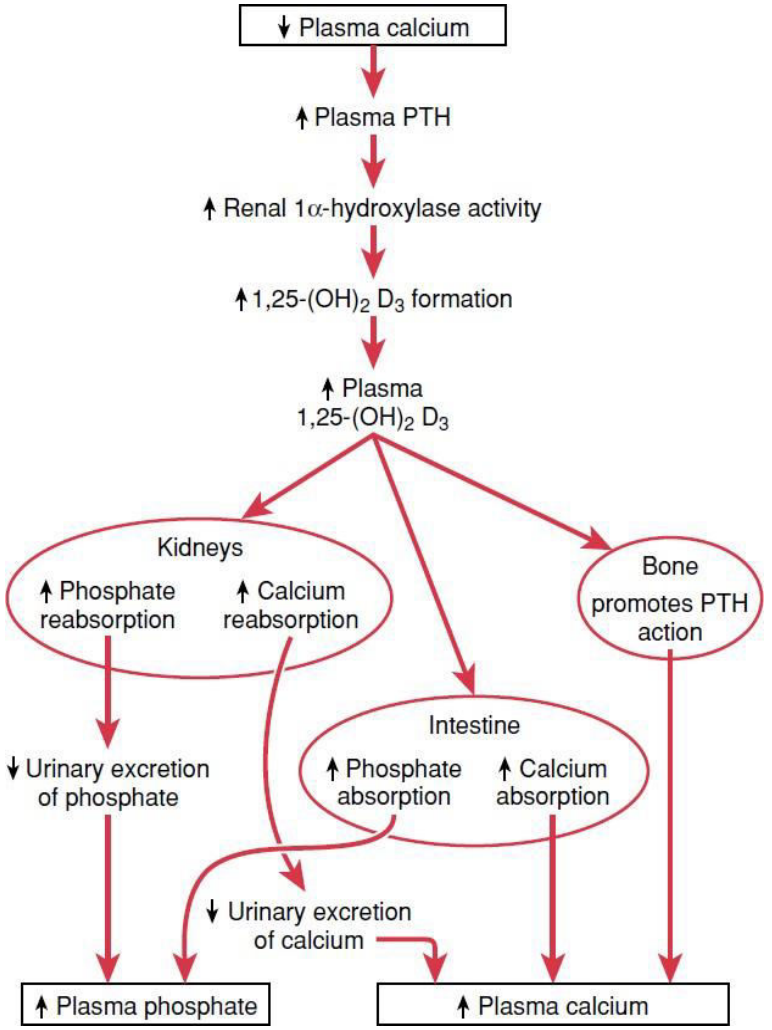
- Free calcium is tightly regulated ±5%
  - Too low = neuronal hyper-excitability (More excitable)
  - Too high = neuronal depression (Less excitable).

  If you have higher calcium outside the cell, the sodium or voltage-gated channels are not easier to open which will make it harder for sodium to enter.

- Control points for calcium
  - Absorption – Via intestines
  - Excretion – Via urine
  - Temporary storage – Via bones. Why its temporary?

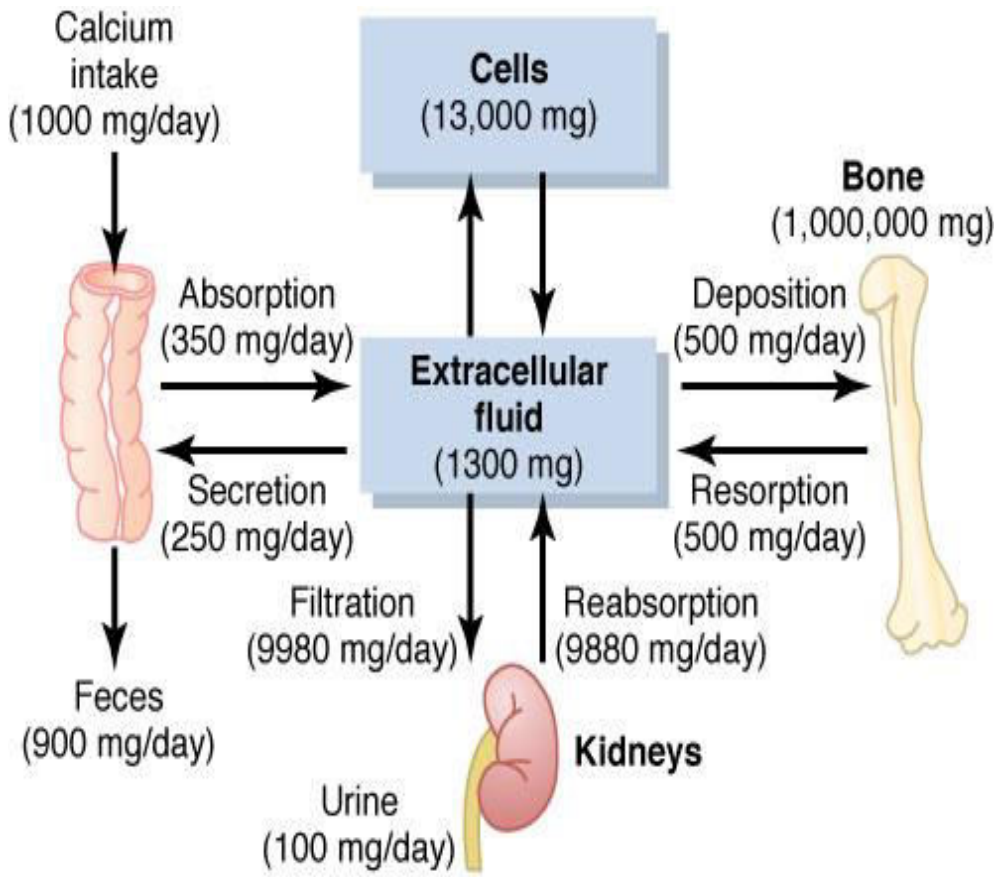
  Because the relation of bone to calcium is similar to the relation of fat for fatty acids and glucose to glycogen in liver… when we eat glucose enter for storage (by insulin) but between meals (we need to consume glucose) so, we need to consume the stored glucose and the hormone glucagon stimulate glucose to get out to the blood.



Important

# Cont.




- ✓ Always calcium metabolism will involve certain organs (intestine, kidneys and bones).
- ✓ In normal people calcium intake is 1000 mg/day (لتر كامل تقريبا).
- ✓ The absorption from it will be 350 mg/day and at the same time there will be secretion from gastric juices of 250 mg/day (1000 - 350 + 250 = 900 which will be secreted in the feces).
- ✓ After entering of the calcium to the ECF at the level of the kidneys (notice that there is diffusible calcium in addition to the 350 mg) there will be filtration of 9980 and reabsorption of 9880 (9980 - 9880= 100) so, approximately 99% of filtered calcium will be reabsorbed again.

(إنا كل شيءٍ خلقناه بقدر)

- ✓ If you sum the amount of calcium excreted in the feces and the amount excreted in urine 900+100= 1000 it will be equal to normal calcium intake 1000.
- ✓ At the level of the bone there will be always equilibrium between deposition and absorption.
- ✓ If there someone needs more calcium, what will happen? There will be increase in absorption at the level of the intestine and kidneys or decrease excretion of calcium

# Phosphate

- Approximately 85% of the body's phosphate is stored in bones, 14-15% is in the cells (It is the most abundant anion inside the cell).
- Less than 1% is in the extracellular fluid.
- Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.
- Phosphorous is an essential necessary mineral:

  For ATP and cAMP second messenger systems.

  - Phosphate plasma concentration is around 4 mg/dL.
  - Forms:
    - ✓ Ionized (diffusible) around 50% of total.
    - ✓ Un-ionized (non-diffusible) and protein- bound 50%.
  - Calcium is tightly regulated with Phosphorous in the body.

Intracellular:

- ✓ Most abundant negative anion is phosphate.
- ✓ Most abundant positive anion is potassium.

Extracellular:

- ✓ Most abundant negative anion is chloride.
- ✓ Most abundant positive anion is sodium.

Very Important

# Regulation of plasma calcium & phosphate concentration

## Non-hormonal mechanisms:

Non-hormonal mechanisms can rapidly buffer small changes in plasma concentrations of free calcium.

- Bone is divided to units if I take a subunit I'll find { blood vessels (central canal) surrounded by osteoblast } = mineralized bone, osteoblast connected with each other (remember it's function is to give collagen), in between there will be fluid (around blood vessels or in between osteoblast) this fluid called laminae the amorphous salt is located in the laminae.

- If there is someone who has hypocalcemia (8 mg/dl) what will happen?

The body should have (fast mechanism) so calcium will be excreted from the Amorphous salts since it is the closest and smallest to the ECF. SO, the calcium level will return to normal. lets assume that this mechanism is not enough what will happen? calcium will be taken from hydroxyapatite crystals. BUT this (mechanism is slow) and we need a faster mechanism and here is the role of hormones. If we assume that calcium level is high (12 mg/dl) calcium will start to deposit in the bones.

فلنفترض عندنا حسابين بالبنك، حساب نجمع فيه لليوم الأسود وحساب للصرف. صرفك الحالي يحتاج انك تنظمه، وحساب التخزين يحتاج انك تحط فيه عشان لما تكبر تلقى الكمية المناسبة وتستفيد منه. نفس الشيء الكالسيوم، فيه شيء يستعمل بشكل يومي وشيء للتخزين.

طيب اللي يستعلمون كثير جدا ؟ ماراح يبقى لهم شيء وبيخلص.

واللي أصلا ما خزنوا للمستقبل؟ راح يجي وقت يحتاجون وما يلقون شيء بالتالي يمرضون ويتعرضون للمشاكل.

"كل شخص فينا عنده بنك وهو المسؤول بالزيادة والنقصان ومسؤول عن الاحتياج المستقبلي للكالسيوم"

## Hormonal mechanisms:

- Hormonal mechanisms provide high-capacity, long-term regulation of plasma calcium and phosphate concentrations.

- Three hormones that regulates $Ca^{+2}$ level in the plasma:
  - Parathyroid Hormone (Parathyroid Gland).
  - Vitamin D3 (Diet & Sun)
  - Calcitonin (Thyroid Gland)
    (Calcitonin's effect is not very important in adults, normal adult people can live without calcitonin, but it is more important in children and pregnancy)

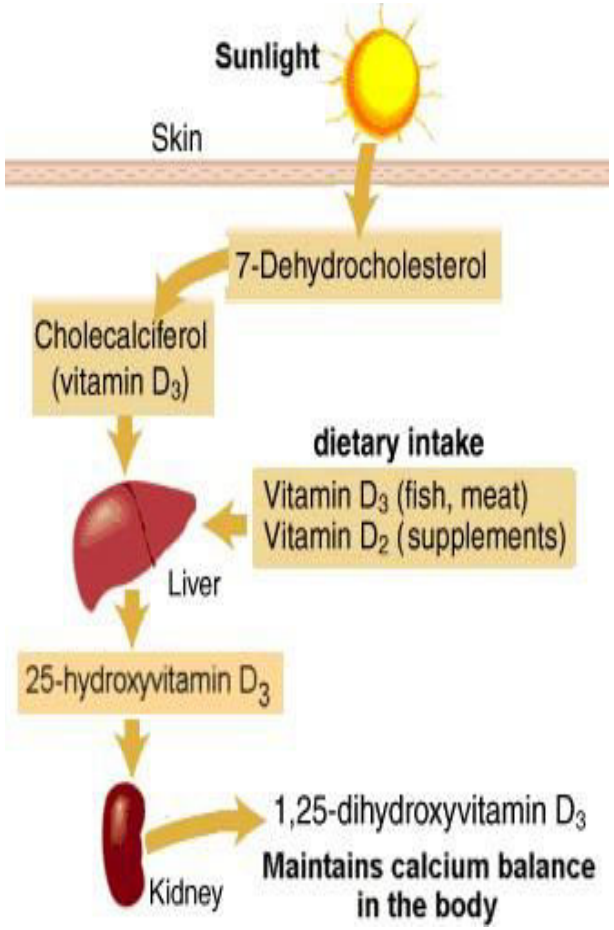
# Vitamin D3

- ✓ Vitamin D is a hormone. It has its own receptors and it does gene alterations to produce actions.
- ✓ Since vit D is fat soluble, it receptors are intracellular.
- ✓ It is derived from Cholesterol. Activates genes involved in Ca absorption from intestine.

- Vitamin D3 (Cholecalciferol) is formed in the skin from (7-dehydrocholesterol).
- Then stored in the liver (Liver form of Vit D has longer half life and activated form has lower so it is better to keep high levels of vit D in our skin and liver).
- Converted in the liver to 25-Hydroxycholecalciferol.
- Feedback control limits concentration (When 25-Hydroxycholecalciferol is decreased, more 7-dehydrocholestrol is formed. Once it is enough, 25 will have negative feedback)
- Converted to active form in kidney: 1,25-dihydroxycholecalciferol (calcitriol) under the feedback control of parathyroid hormone (PTH).
- Vitamin D is a prohormone that must undergo two successive hydroxylation reactions to become the active form known as 1,25-dihydroxyvitamin D or calcitriol
- Stimulates differentiation of immune cells.
- Control of Vit D: controlled by many of the same factors that regulate calcium.

1. Low $Ca^{++}$ ions
2. Prolactin
3. PTH

All stimulate renal 1,alpha hydroxylase




Other Diagram

# Effects of Vitamin D & Its Relation to PTH Activity

- Increases calcium blood level by:
  1. Promotes calcium & phosphate absorption in the intestinal tract (potent effect).
  2. Increases Renal Calcium and Phosphate re-absorption (weak effect) (PTH causes Ca reabsorption but Phosphate excretion).
  3. Causes synthesis of calcium-binding protein and related facilitated transport.
  4. Facilitating PTH to cause calcium absorption from bone.
  5. Takes a couple of days to fully develop response.
  6. Regulate the number & activity of osteoclasts & increase bone resorption.

- Vitamin D in smaller quantities: promotes bone calcification (by ↑ calcium and phosphate absorption from the intestine and enhances the mineralization of bone). (Lack of Vit D causes osteomalacia in adults and Rickets in children)
- Extreme quantities of vitamin D: causes absorption of bone by facilitating PTH action on bones number & activity of osteoclasts.
- Vitamin D also stimulates differentiation of immune cells.

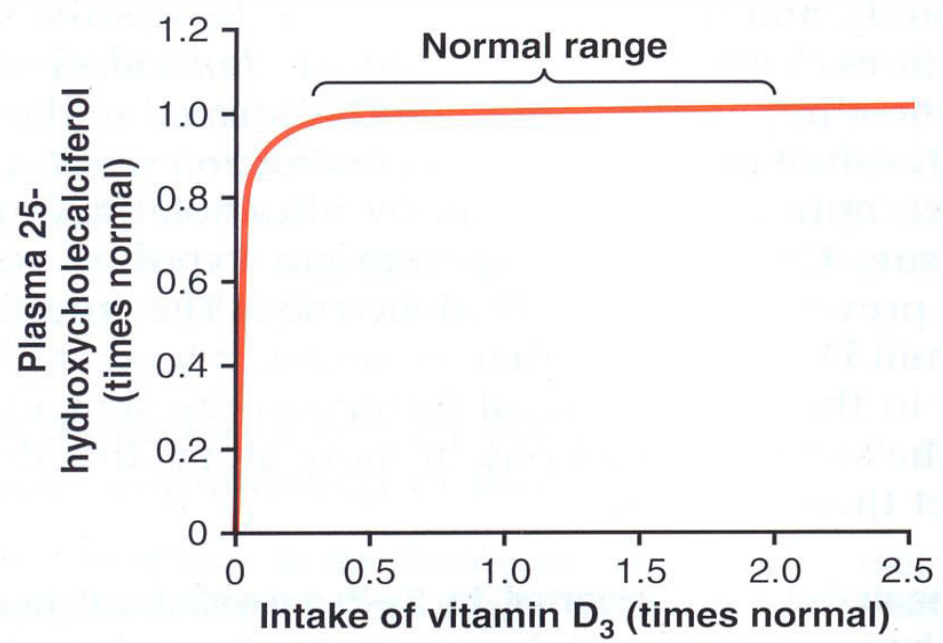
Only in Females' Slides

Only in Males' Slides

الدكتورة شارحة نفس الكلام

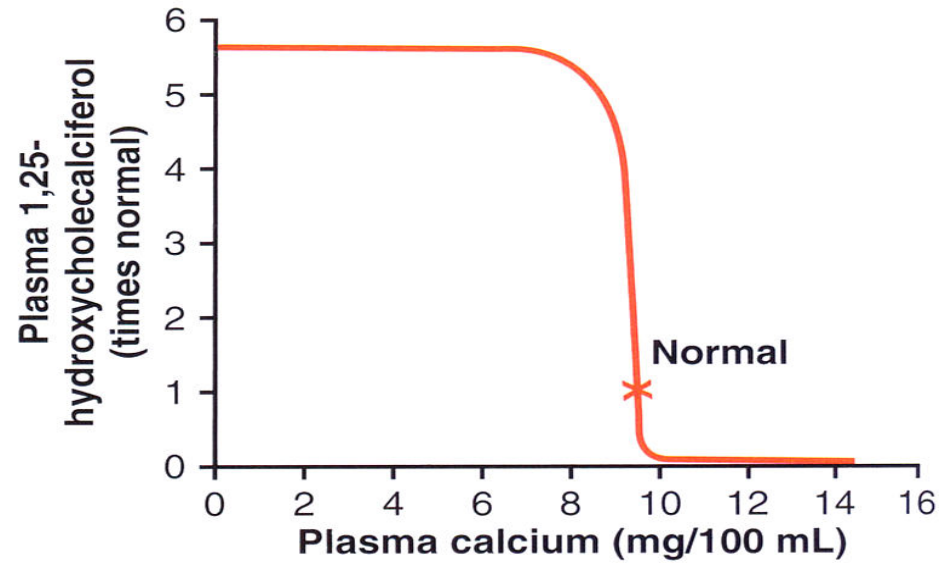
# Regulation of Vitamin D

- Feedback inhibitory effect of 25-hydroxy Vit D3




- ✓ Vitamin D3 (cholecalciferol the stored form in the liver) is converted to 25-cholecalciferol.
- ✓ When 25-cholecalciferol reaches normal levels its levels will remain plateau because no more cholecalciferol is converted to 25-cholecalciferol.

- Calcium Ion Concentration Controls the Formation of 1,25-Dihydroxycholecalciferol



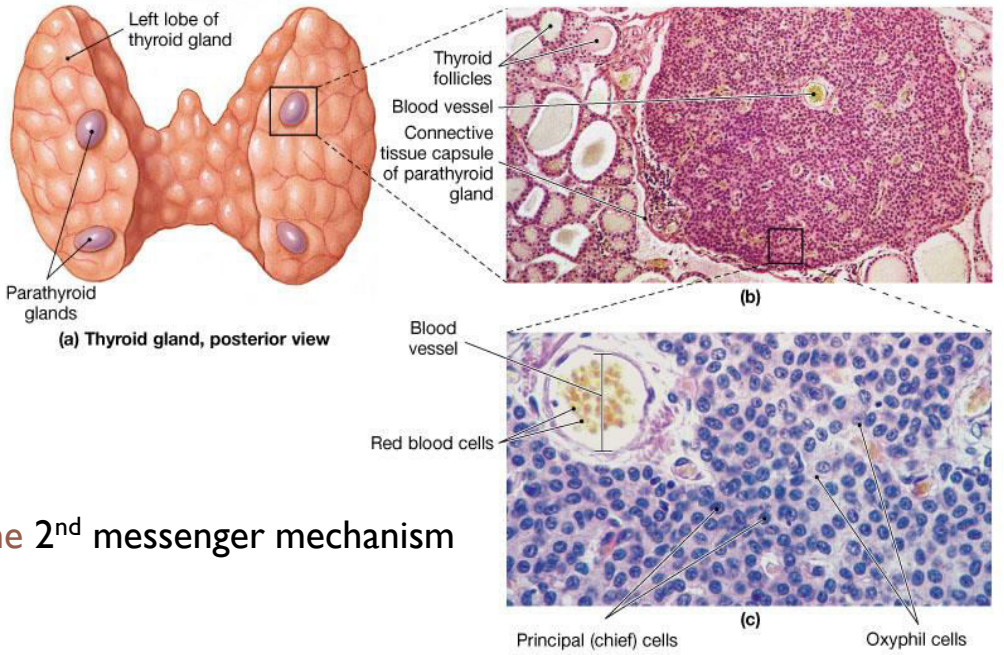

The normal plasma calcium in the blood is 10mg/100 ml, when calcium level exceeds 10 the concentration of the active form of vitamin D3 will drop because the blood contains enough calcium and doesn't need more.

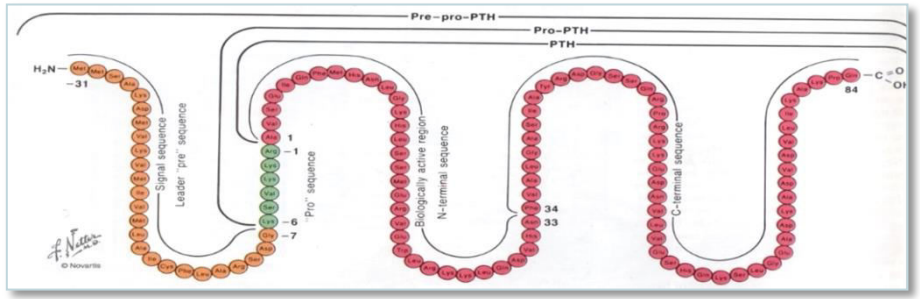
احنا قلنا ان زيادة نسبة الكالسيوم بالبلازما تثبط الباراثايروید هرمون، وبالتالي لما يتثبط الباراثايروید هرمون ما رح يصير في اكتفيشن للفيتامين دي.

# Parathyroid Hormone

The primary targets of PTH are bone and the kidneys

- It is essential for life, Rapid response to reduced calcium (minutes).
- Source: Chief (principal) cells of the parathyroid gland.
- Polypeptide hormone: (84 AA)
- Molecular Weight: 9500 Dalton Molecular Weight (M.W)
- Half Life: 10 min.
- Target: The primary targets of PTH are bone and the kidneys.
- Mechanism of action: acts via G-Protein Coupled Receptor (GPCRs.) and the 2nd messenger mechanism is cAMP.
- Action: Decrease Phosphate level and increase plasma calcium level.
- Main regulator for this hormone is Ca levels in the blood. High Vit D levels inhibits it.



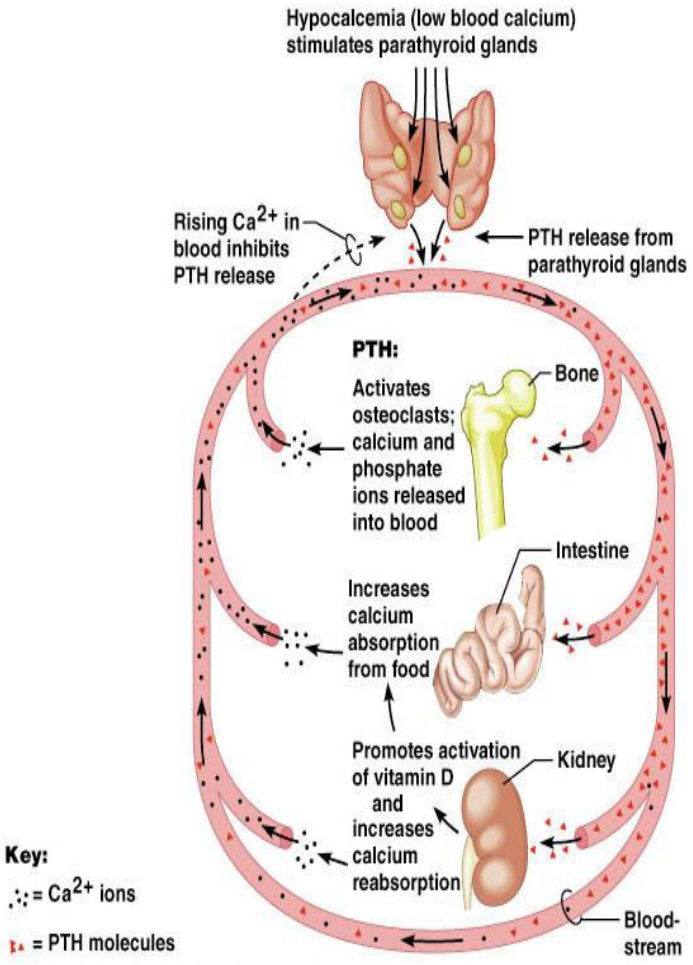




Parathyroid Hormone (PTH ) Synthesis:

DNA Transcription → mRNA Formation → mRNA translation into Pre-Pro-PTH (In Ribosomes) → Pro-PTH (In Endoplasmic Reticulum) → PTH (In Golgi).

# Effect of Parathyroid Hormone

| Effect of Parathyroid Hormone | |
|---|---|
| Intestine | ↑ absorption of calcium and phosphate indirectly through stimulating formation of 1,25 – (OH)2-D3 in kidney. |
| Bone | 1. Increases Calcium and Phosphate Absorption from the Bone.<br>2. Depression of osteoblastic activity.<br>3. Activates and stimulates the formation of new osteoclasts (days to weeks). Stimulated indirectly by osteoblast to digest bone and release calcium and phosphate.<br>4. Existing osteocytes stimulated (minutes to hours) to transport calcium – calcium pumps. |
| Kidney | 1. ↓ phosphate reabsorption from the proximal convoluted tubules (phosphate-uric action). It also increases phosphate absorption from intestine<br>- ↑ Phosphate excretion in the urine.<br>- ↓ plasma phosphate concentration.<br>2. ↑ $Ca^{+2}$ & Mg ions reabsorption from the distal convoluted tubules, collecting ducts and ascending loop of Henle.<br>3. ↑ Formation of 1,25 vit D3 in the kidney. Stimulated indirectly by osteoblasts, osteoblasts express RANKL which binds to RANK on osteoclasts leading to its activation. |



Very Important

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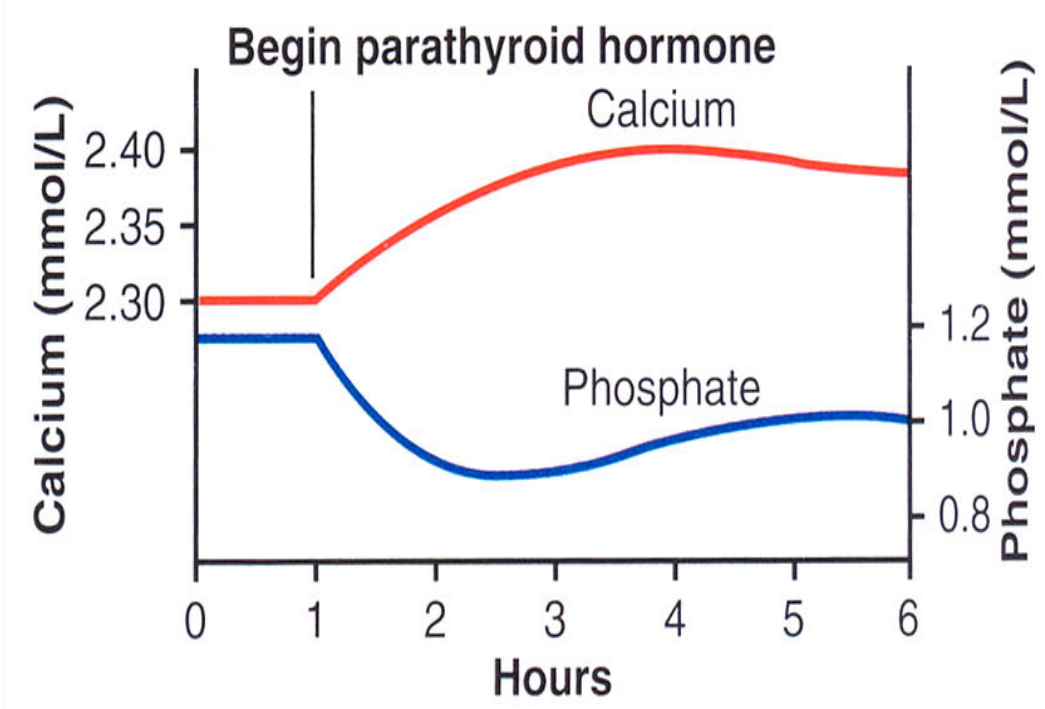


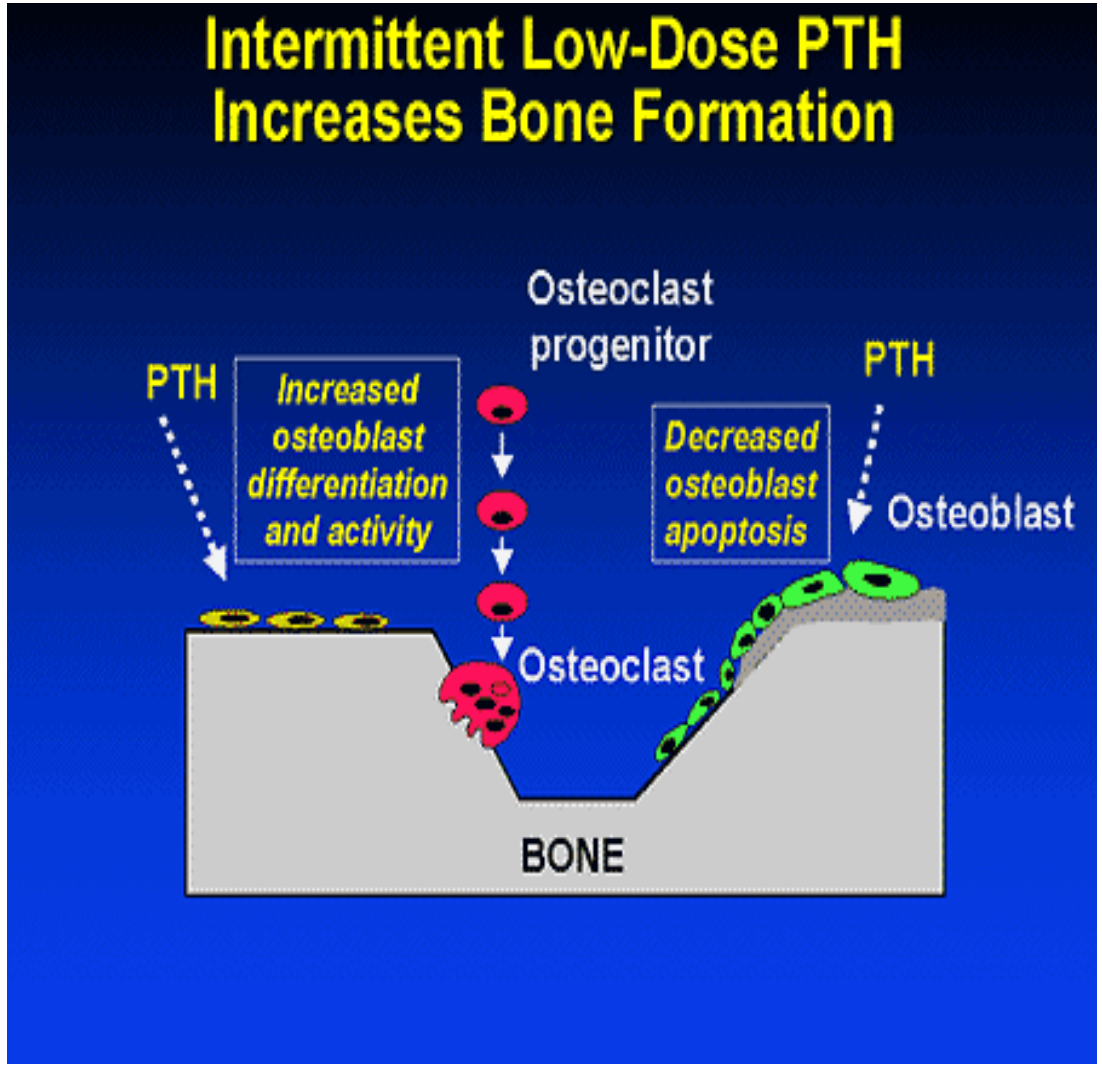

Approximate changes in calcium & phosphate concentrations during the first 5 hours of PTH infusion at moderate rate.

- ✓ PTH will increase Ca & PO4 absorption from bone.
- ✓ PTH will activate Vit D so the absorption of Ca & PO4 will be increased from intestine.
- ✓ PTH will increase Ca reabsorption in kidney and will increase excretion of PO4 in kidney.
- ✓ The Net Result:

Increased Ca level in plasma & Decreased PO4 level in plasma.

- ✓ Remember that 70-90% of calcium is normally re-absorbed by proximal convoluted tubules under NO effect of hormones, while in distal convoluted tubules 8% of calcium is either reabsorbed or excreted depending on the concentration of parathyroid hormone.
- ✓ The amount of phosphate lost by kidney is more than the amount of phosphate absorbed by intestine
- ✓ So, the net effect is decrease in plasma phosphate and increase in plasma calcium when parathyroid hormone is injected.

# Cont.




1. Intermittent Low doses of PTH stimulate formation without stimulating bone resorption

   - It increases osteoblast activity and differentiation and decreases osteoblast apoptosis this is called the anabolic effect of PTH.

2. Continuous high doses of PTH stimulate bone resorption and inhibit bone formation.

✓ The immediate action of PTH is increased osteoblast activity while later on the action is increase osteoclast. How?

There is a communication between osteoblasts and osteoclasts when RANK ligand is formed then it communicates with receptors in osteoclasts and activate it.

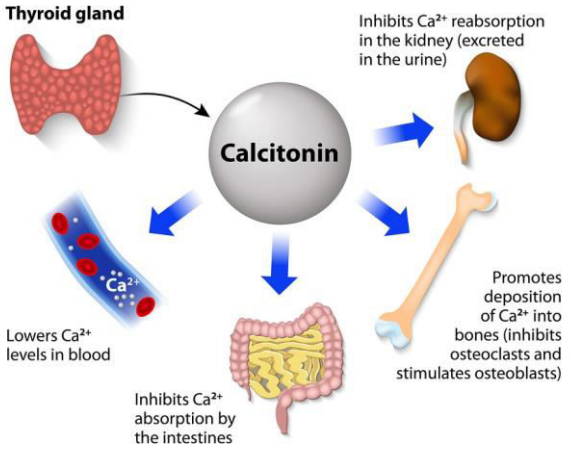
الدكتورة نبهت كثير على أهمية التفريق

هنا بين الـ Stimulus و ال Action.

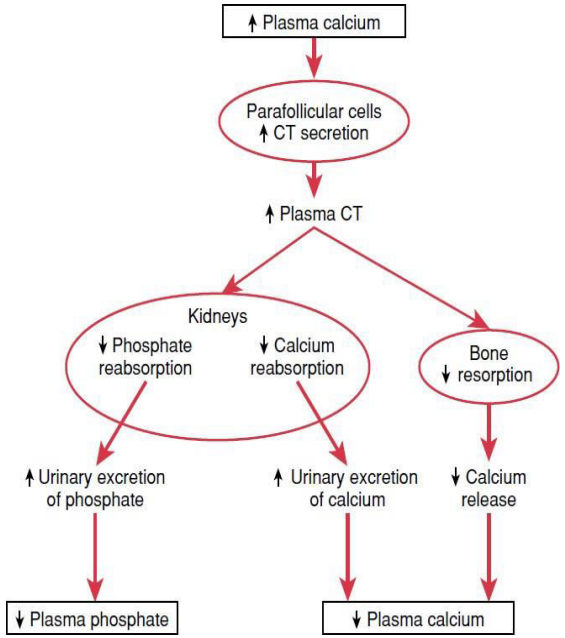
# Calcitonin

- Source: Secreted by the Para-follicular cells (C cells) of the thyroid gland.
- Nature: 32 amino acid peptide hormone.
- Function:
  - Decrease blood $Ca^{+2}$ level very rapidly within minutes.
  - Opposite effect to PTH.
- Stimulus for secretion: Increased plasma calcium concentration → ↓ Ca+2 concentration.

As we said before, Calcitonin's physiological activity is NOT that important in the regulation of calcium levels in normal adult. But its important in children and pregnancy.



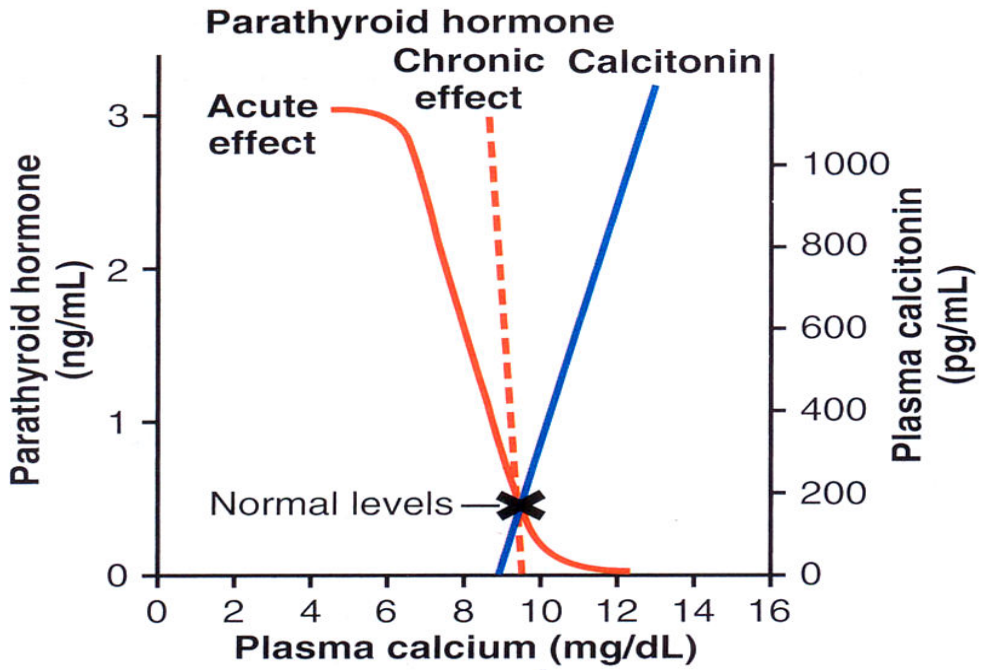

| Actions of Calcitonin | |
|---|---|
| On Bone | 1. ↑ Ca+2 deposition of bone.<br>2. Inhibits Bone resorption: inhibition of osteoclasts, ↓ formation of osteoclasts. The effect to decrease calcium level is transitory<br>3. Causes reduced bone turnover. |
| On Kidney | Has weak effect on kidney and intestine<br>1. ↓ Ca+2 reabsorption.<br>2. ↑ Ca+2 excretion (in addition to phosphate). |




Very Nice Diagram Summary

Only in Males' Slides

# Effects of Plasma Calcium Concentration on PTH & Calcitonin




- ✓ Normal physiological set point of Ca in plasma is 10 and more than that will lead to acute decline in PTH and acute increase in calcitonin, While less than 10 leads to parathyroid is much higher.
- ✓ So, calcium is tightly regulated within its normal range.

- ✓ The graph shows the approximate relation between plasma calcium concentration and plasma PTH concentration.

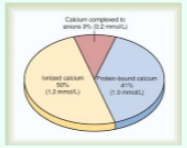
- ✓ **The acute effect:**

The solid red curve shows when the calcium concentration is changed over a period of few hours. This effect shows that even small decreases in calcium concentration from the normal value can double or triple the plasma PTH.

- ✓ **The chronic effect:**

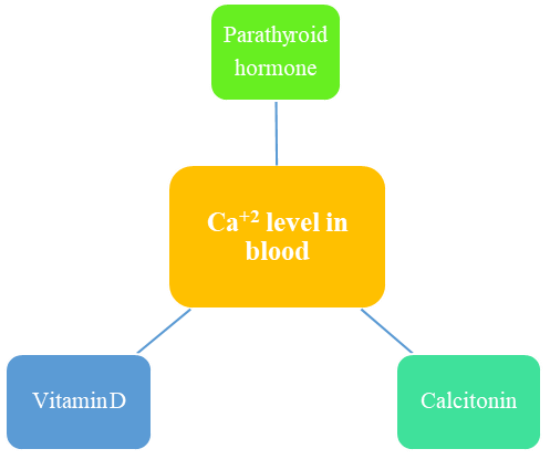
When calcium concentration changes over a period of many weeks, thus allowing time for the glands to hypertrophy greatly, is shown by the dashed red line, which demonstrates that a decrease of only a fraction of a milligram per deciliter in plasma calcium concentration can double PTH secretion. This is the basis of the body's extremely potent feedback system for long-term control of plasma calcium ion concentration.

# Summary

| | | |
|---|---|---|
| **$Ca^{+2}$ level & distribution** | **Plasma Ca+2 level: 9-10.5 mg/dl**  | **Renal stones > 9-10.5 mg/dl > Tetany** |
| trAlkalosis: ↓ ionized $Ca^{+2}$ | Acidosis: ↑ ionized $Ca^{+2}$ | |
| Functions of calcium ions in extracellular fluid | • Neuoromuscular excitability<br>• Hormonal secretion<br>• Enzymatic regulation<br>• Blood coagulation<br>• Second messenger | |
| Sources | • Milk<br>• Dairy products<br>• Fish | |
| Daily requirements in infants & adults | 5-25 mmol/day | |
| Daily requirements in pregnancy, lactation & after menopause | 25-35 mmol/day | |
| Absorption | • Small intestine: concentration gradient<br>• Duodenum: active transport | |
| Bone composition<br>• Organic matrix | Collagen fibers (95%)<br>Ground substance (5%)<br>•ECF<br>•Proteoglycans | Tensile force |
| Bone composition<br>• Bone salts | Salts of $Ca^{+2}$ & $PO4^{-}$ in the form of<br>•Hydroxyapatite crystals (99%)<br>•$Ca_{10}(po_4)_6(oh)_2$<br>•Mg, na, K, carbonate ions | Compressional force |
| Bone cells | •Osteoblasts (Bone forming cells)<br>•Osteocytes (Osteoblasts surrounded by calcified matrix)<br>•Osteoclasts bone eroding cell (resorping) | |

# Summary

| | |
|---|---|
| Bone salts | Hydroxyapatite crystals [In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$ ] |
| | Mg, Na, K, Carbonate ions |
| | Amorphous salts:<br>• A type of exchangeable calcium<br>• Play role in rapid regulation of ionized $Ca^{+2}$ level in ECF<br>• 0.4-1% of total bone $Ca^{+2}$<br>• always in equilibrium with $Ca^{2}+$ in ECF |
| Regulation of plasma calcium and phosphate concentrations | Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium |
| | Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations |




| Vitamin D | | |
|---|---|---|
| Actions | Intestinal tract:<br>• Has a potent effect to increase calcium & phosphate absorption | |
| | Renal:<br>• Increases Renal calcium & Phosphate absorption | |
| | Bone:<br>• Bone absorption | |
| | Stimulates differentiation of immune cells | |
| Control of VitaminD | 1- low Ca++ ions | All stimulate renal 1,alpha hydroxylase |
| | 2- prolactin | |
| | 3- PTH | |
| Effects of Vitamin D on Bone & Its Relation to Parathyroid Hormone Activity. | Vitamin D in smaller quantities :<br>• promotes bone calcification (by increase calcium and phosphate absorption from the intestine and enhances the mineralization of bone | |
| | The administration of extreme quantities of vitamin D causes absorption of bone by:<br>• facilitating PTH action on bones<br>• number & activity of osteoclasts | |

# Thank you for checking our work!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

قادة الفريق:

ليلى مذكور & محمد

خالص الشكر لأعضاء الفريق الكِرام:

| | |
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| دانية الكلابي | حمد الخضيري |
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| بشرى قوقندي | نواف الخضيري |

Please check our editing file to know if there are any additions, changes or corrections.

Examine yourself

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2017-2018 Dr. Khalid Al Regaiey's Lecture& Notes.
Guyton & Hall of Medical Physiology 13th Edition.
Linda S. Costanzo 5th Edition.

Helpful physiology bocks.

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اللهم اني استودعتك ما حفظت وما قرأت وما فهمت، فرده لي وقت حاجتي إليه إنّك على كل شيءٍ قدير.