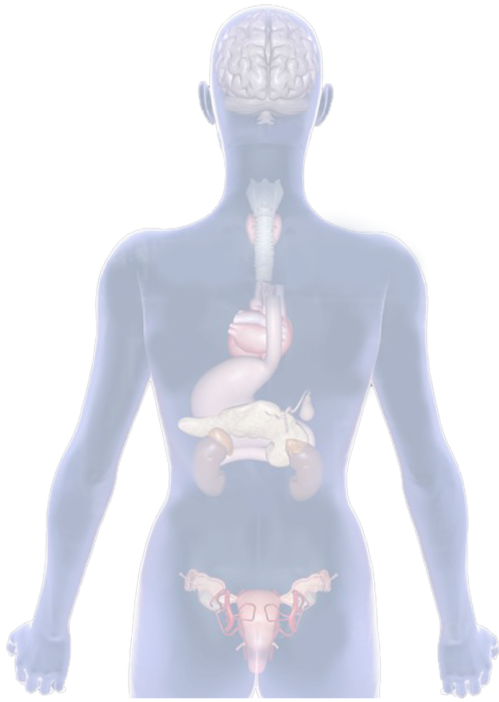
Physiology 435 team

#8&9 Calcium Homeostasis & Hypo\hyper-parathyroidism

Objectives:

- List the functions of calcium
- Describe calcium metabolism
- Describe physiology of bone
- Understand and explain hormonal regulation of calcium metabolism:PTH, Calcitonin&Vitamine D3.
- Understand hypo and hyper-parathyroidism



Important
Male's notes
Female's notes
Extra

Resources: 435 male's & female's slides + guyton
Editing file: click Here

Revised by
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Distribution of Ca in the body

Distribution of ca++ in the body :

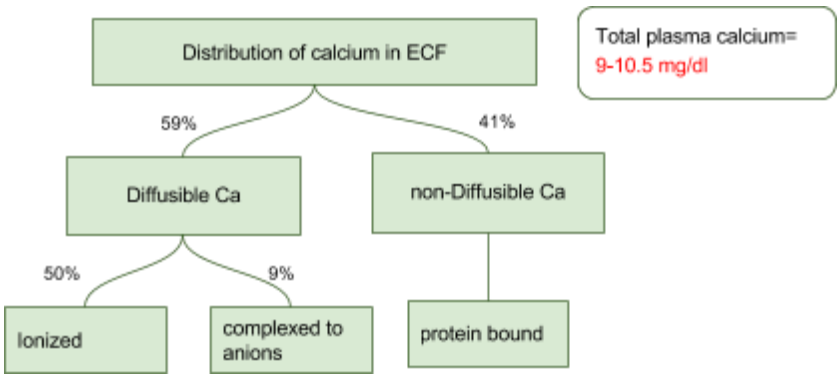
- 0.1% in ECF
- 1% in ICF " endoplasmic reticulum "
- 99% in skeleton and teeth (Bones)

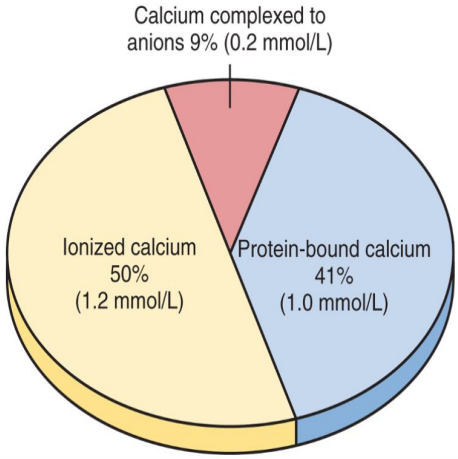
- we are going to talk about the calcium which is exist in the plasma (ECF)
- total plasma calcium is 9-10.5 mg/dl < you can notice that the range is so narrow

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

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

Plasma Calcium:



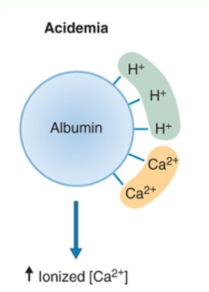
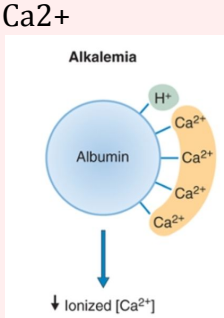


- Ca++ conc. In the ECF is around 2.4 mEq/L and 0.0001 mEq/L in the ICF.
- calcium is distribution in 3 forms:

1 calcium bond to protein 41% (since it's bind to protein it's not diffusible)
2 calcium complexed to anions 9% (diffusible)
3 ionized calcium 50% (free) (responsible for nerve and muscle action potentials).
* any increase in complexed calcium will affect the level of ionized calcium. (ionized calcium will decrease).
* if there is decrease in Ca level this will increase the influx of Na and will cause spontaneous action potentials.

Protein-bound calcium:

- Most of this calcium is bound to **albumin** & much smaller fraction is bound to globulin.
- Binding of calcium to albumin is **pH-dependent** for example: An increase in pH, alkalosis, promotes increased protein binding, which decreases free calcium levels. Acidosis, on the other hand, decreases protein binding, resulting in increased free calcium levels. Thus :**Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level** مهم جدا انتبهولها رجاء

Acidosis: ↑Ionized Ca2+	**Alkalosis**: ↓Ionized Ca2+
	

Calcium Physiology

Physiological importance of Calcium:

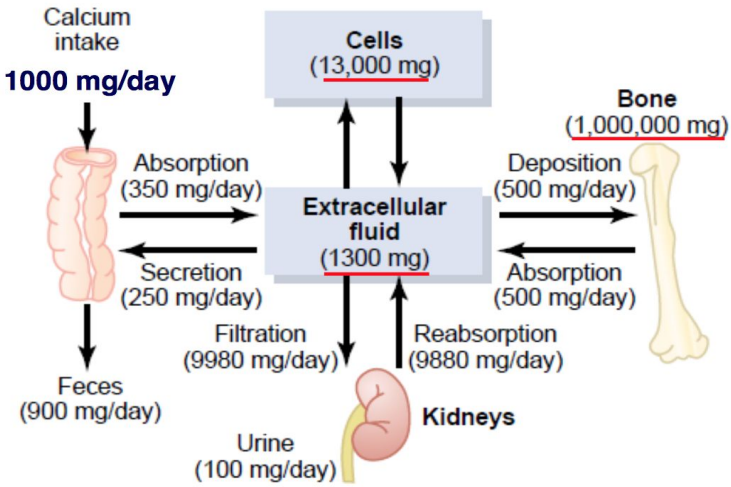
1-Calcium salts in bone provide structural integrity of the skeleton. (support)
2-Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes such as:

- Neuromuscular excitability.
- Hormonal secretion.
- Enzymatic regulation.
- Blood coagulation. When we took a blood sample and put it in a tube it will coagulate but calcium function here is to prevent the coagulation
- Second messenger.
- It helps also in muscle contraction

^ all of these functions are done by ionized calcium

Absorption of calcium	Increased by	Decreased by	Sources of calcium	Daily requirements of calcium
•**Duodenum:** active transport •**small intestine:** concentration gradient	• 1,25 dihydroxycholecalciferol, (active form of Vit.D) •Parathyroid hormone. • Acidic PH. • Lysine and Arginine.	• Phytates • Oxalates • Phosphate • Mg	•Dairy products •Fish •milk	•**Infants & adults:** 12.5 -25 mmol/day •**Pregnancy ,lactation ,after menopause:** 25-35 mmol/day .

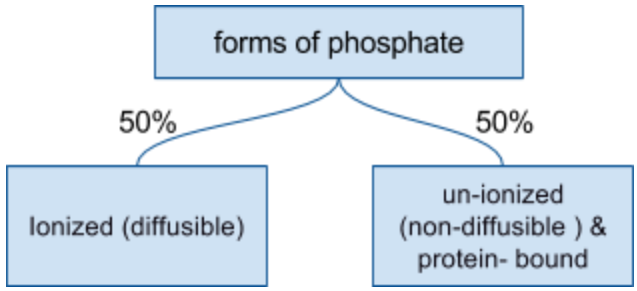
Calcium Metabolism in an adult human:



- Allways calcium metabolism will involve certain organs (intestine, kidneys and bones)
- In normal people calcium intake is 1000 mg/day (تقريبًا لتر كامل) --> 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*
- 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,,(سبحان الله (إِنَّا كُلَّ شَيْءٍ خَلَقْنَاهُ بِقَدَرٍ
- At the level of the bone there will be allways equilibrium between deposition and absorption
- let us say that 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

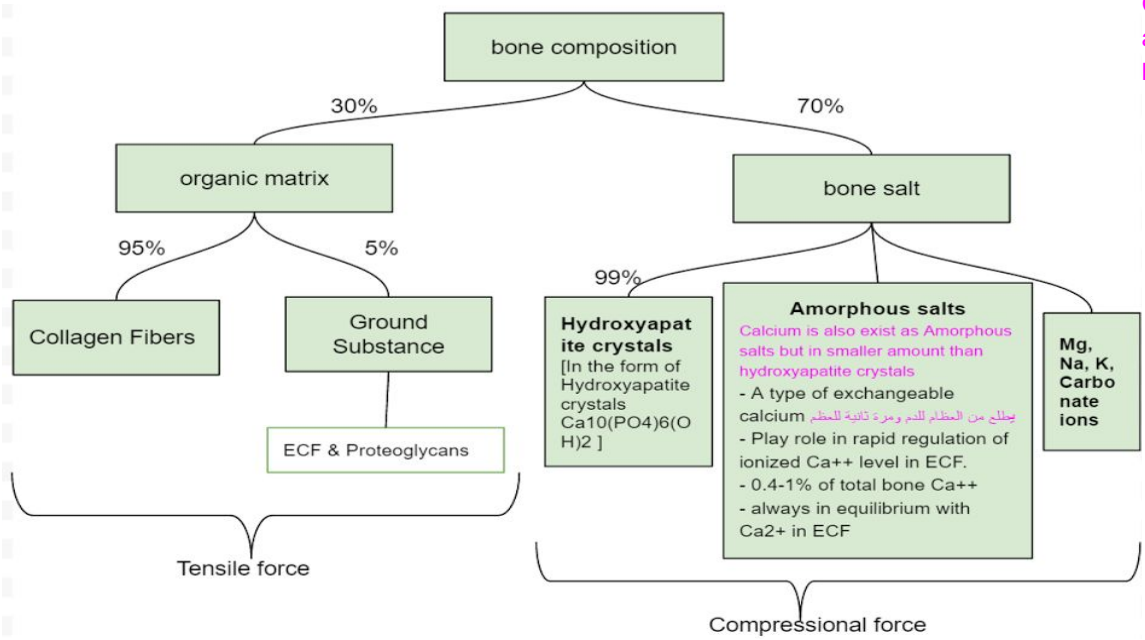
Phosphate

- Phosphorous is an essential mineral necessary: for ATP and cAMP second messenger systems , plasma concentration is around 4 mg/dL.
- Calcium is tightly regulated with Phosphorous in the body.



Physiology of bone

Bone Composition:



Calcium is exist in bone salt as a compound called hydroxyapatite crystals (99%)

اذا كنا نبغى نعرف قوة ال bone salt اعملوا تجربة في البيت وجيبوا عظمة وحطوها في خل؟ حيطلع الكالسيوم برى بعدين خذوا العظمة وحاولوا تثنوها؟ وش بتلاحظون صار؟ حتنعوج (مارح تنكسر بس بتصير مرنة) شايفين اهمية الكالسيوم؟ طيب والكولاجين* الموجود في الاوقانك ماتركس*؟ خذوا عظمة وحطوها في فرن وشغلوه مع الحرارة وش راح يصير؟ راح يتكسر الكولاجين (يتكسر البروتين) وبعدين حاولوا تثنوها؟ راح تنكسر تصير هشه على طول

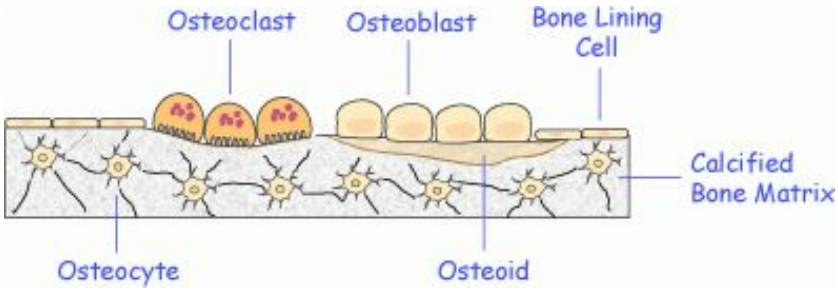
Bone cells :

- Osteoblasts (bone forming cells).
- Osteocytes (osteoblasts surrounded by calcified matrix)

Osteoblast when it's function is over called osteocyte

- Osteoclasts bone eroding Cell (resorbing = reabsorption, remember when we say reabsorption in the GIT we mean that nutrient moves from gut to blood, it's the same here for the calcium but from the bone to the blood)

Eroding bone = تطلع الكالسيوم برى



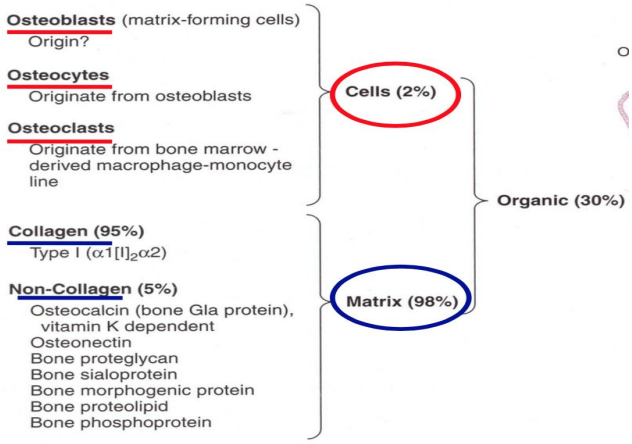
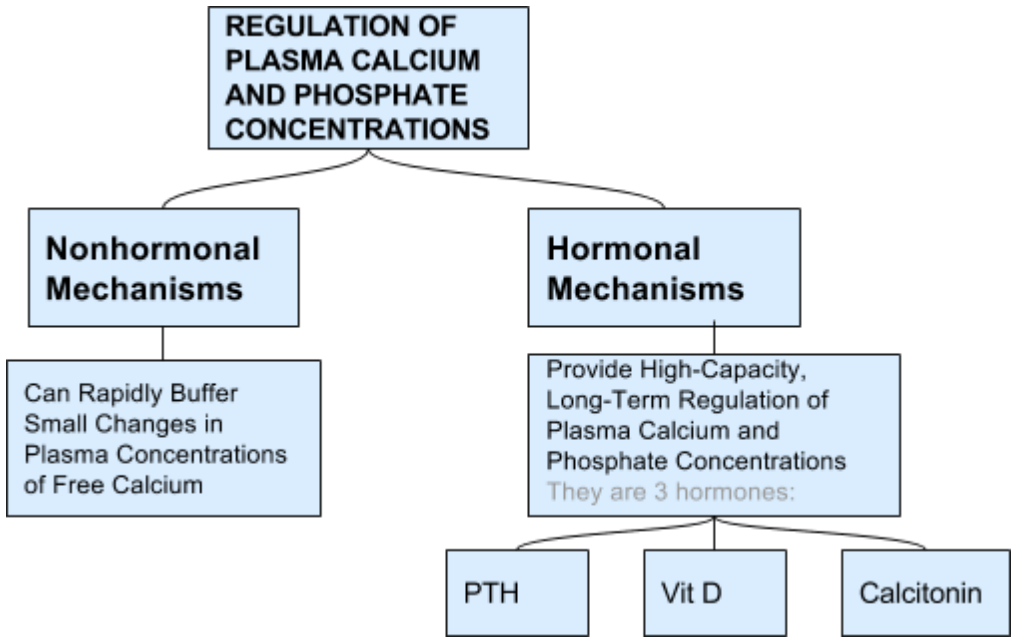


Figure 8.1 The composition of bone.

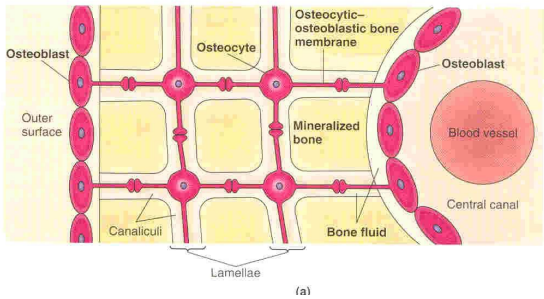
Regulation Of plasma calcium and phosphate concentration

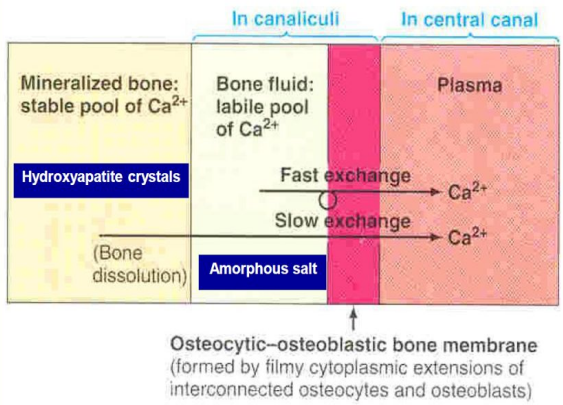
now we said calcium range is narrow, this range should be constant not changeable! and if there is any changing it should be too small. we said the normal level is 9-10.5 any decrease in the range it will cause hypocalcemia and any rise will cause hypercalcemia. there is mechanisms in which turn calcium level to normal if there is any change,
Why is it important to keep calcium level regulated? To prevent several diseases such as tetany, renal stones ..
decrease calcium in ECF leads to excitation of neuromuscular junction which lead to muscle contraction (tetany) and if it involve respiratory muscle it'll lead to death ! And if calcium level in ECF increase that will lead to inhibit neuromuscular junction so the person will develop other problems resulting from decrease muscle contraction → decrease reflexes → in extreme condition it will lead to deposition of calcium in body organs such as heart, lung, kidney and thyroid itself which eventually leads to death within few days.
Do not confuse between intracellular calcium which lead to muscle contraction and extracellular calcium which act on NMJ



1)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.
- **let assume that someone has hypocalcemia (8 mg/dl) what will happen?**
my body should have (fast mechanism) so calcium will excreted from the Amorphous salts since it is the closer and smaller to the ECF. SO, the calcium level will return to normal..... ok, let assume that mechanism is not enough what will happen? calcium will excreted from hydroxyapatite crystals.. BUT this (mechanism is slow) and we need a faster mechanism and here is the role of HORMONS.
If we assume that calcium level is high (12 mg/dl) calcium will start to deposit in the bones
يا بنات انا هنا اشبهه زي اللي عنده فلوس؟ وين يحطها؟ بالبنك،، كل وحدة فيكم عبارة عن بنك وفي عندنا الوديعة طويلة الأمد وعندنا الحساب الجاري،، لو انتِ احتجتي فلوس وش تعملين؟ تاخذين فلوس على طول من الحساب الجاري،،، نفس الشيء هنا احتجتي لكالسيوم لما تكبرين حيطلع لك هنا مخزون نفس الشيء كل ما خزنتي فلوس في حسابك اذا احتجتي بعدين بتلاقين ،، طيب واللي تصرف؟ ما يبقى لها شيء ،، واللي اصلاً ما تخزن؟ حيجي وقت انها تحتاج ومارح تحصل شيء فحتبدأ تطلع الأعراض لذلك كل وحدة فيكم عندها بنك وحساب وانتِ المسؤولة تقللي او تزيدين





2)Hormonal Mechanisms :

- Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations.
- **Ca level regulated HORMONALLY by :**

1- Parathyroid hormone.
2- vit D Although it's vitamin we called it hormone because it has same characteristic as hormone (synthesized inside human body, has target organ & circulate in the blood)
3- calcitonin

Vitamin D [1,25 Dihydroxycholecalciferol]

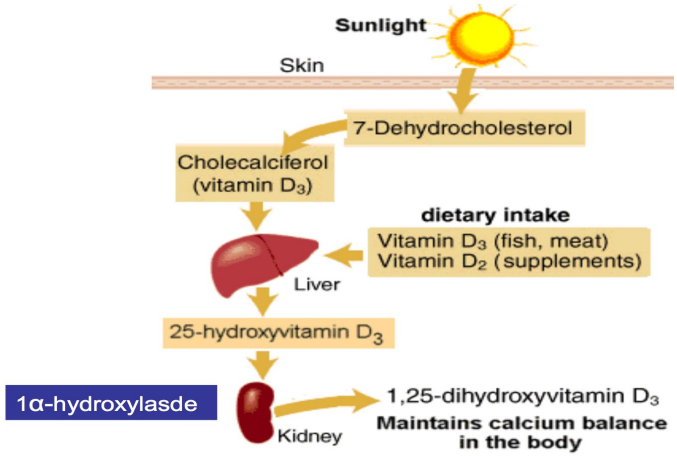
Mechanism of activation of vit D:

Synthesized by the body or taken in food.الفايتامينز اللي ناخذها كمكملات لابد ان تمر في المحطة الأولى وهي الكبد،، ما رح تسوي وظيفتها اذا ما مرت في الكبد وتبعدين تمر في الكلى

1) 7,Dehydrocholestrol (in skin) + Ultraviolet light →Vit. D_3 (inactive form).

2) Hydroxylation of Vit.D first in the liver to 25,hydroxycholicalciferol (inactive form).

3)Second hydroxylation of Vit.D in the kidneys to 1,25 -dihydroxycholicalciferol (active form)this reaction is *stimulated and tightly controlled by PTH*



Functions of vit D:

1- Intestinal tract:	Has a potent effect to increase calcium & phosphate absorption by calcium-binding protein
2- Renal:	Increases Renal calcium and Phosphate absorption
3- Bone:	PTH is the hormone who activate the stimulation of 1 a-hydroxylase enzyme. So, if there is no PTH there won't be 1 a-hydroxylase **1)Vitamin D in smaller quantities:** promotes bone calcification (by ↑ calcium and phosphate absorption from the intestine and enhances the mineralization of bone). **2)The administration of extreme quantities of vitamin D:** causes resorption of bone:by facilitating PTH action on bones leads to Increase number & activity of esteoclasts. So, for effective vit. D what do we need? Sunlight, normal liver & kidneys, skin and PTH
4-immune cell:	Stimulates differentiation of immune cells.

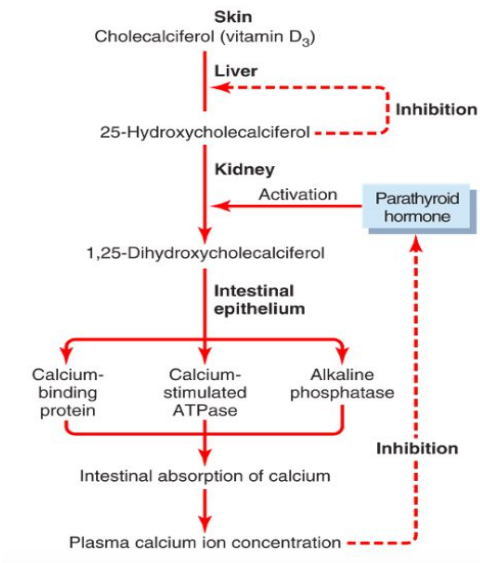
Control of Vit D:

1- low Ca++ ions

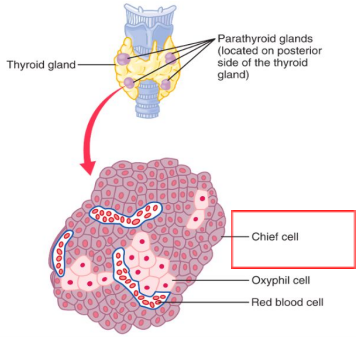
2- Prolactin احنا عارفين ان البرولاكتين مسؤول عن تصنيع الحليب ,فيقوم البرولاكتين يحفز تنشيط الفايتمين ٨.٨ دي عشان يحفز امتصاص الكالسيوم للجسم عشان يدعم حليب الام بالكالسيوم

3- PTH the most powerful

★ All stimulate renal 1,alpha hydroxylase.



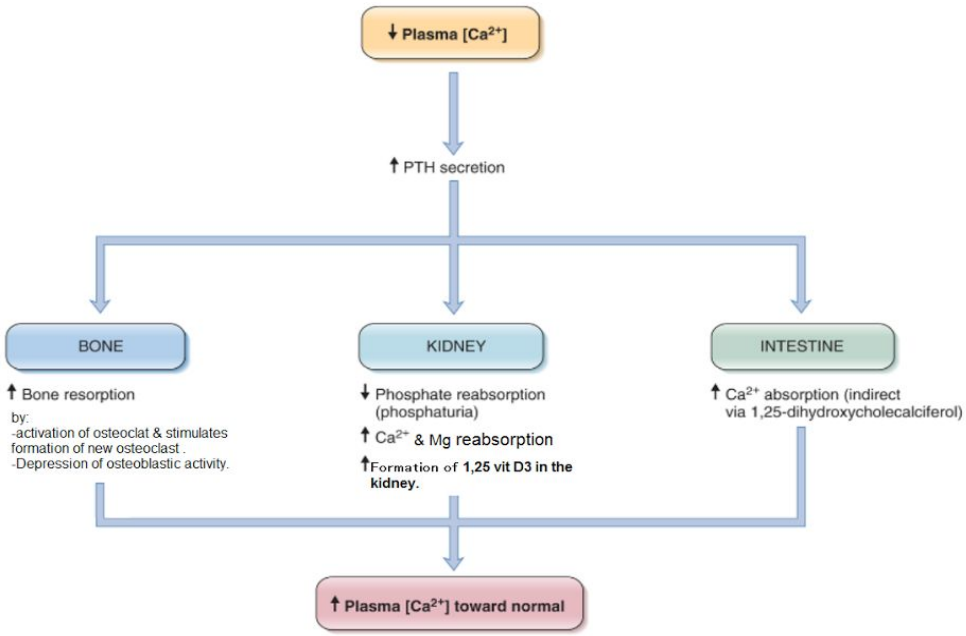
Parathyroid hormone (PTH) (Essential for life!)

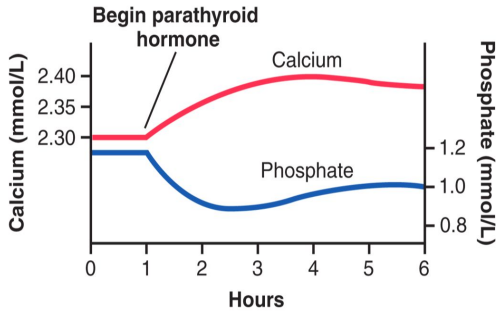


Source: it's Polypeptide hormone (84 AA) secreted from Parathyroid gland

Mechanism of action: acts via **2nd messenger mechanism** utilizing cAMP,gland Half Life: 10 min

Actions (act on): Bone / Kidney / Intestine





عملوا تجربة جابوا حيوان وحقنوه بال PTH ثم قاسوا مستوى الكالسيوم ومستوى الفوسفيت؟ وش صار؟ لاحظوا ارتفاع مستوى الكالسيوم واستمرار ارتفاعه لمدة ساعات اما الفوسفيت شافوا انه قل مستواه (ابيكم تحفظون هالصورة بمخكم!! مو بالارقام بس لما يجيكم سؤال ايش وظيفة الPTH؟ وش تقولون؟ يرفع الكالسيوم ويخفض الفوسفيت)

لا تسحبون على صورة الافيكتس تراها مهمه ^^

Parathyroid Hormone related Peptide (PTHrP): Boy's slide only

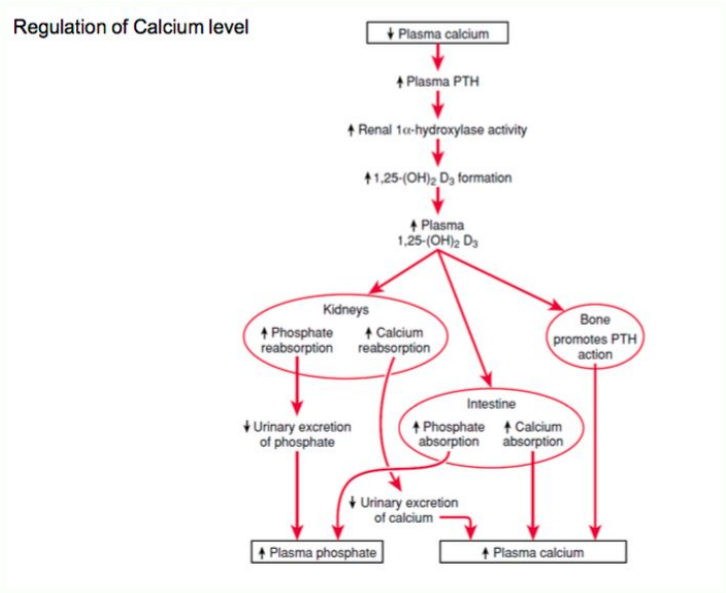
- Can activate the PTH receptor
- Plays a physiological role in lactation, possibly as a hormone for the mobilization and/or transfer of calcium to the milk
- May be important in fetal development
- May play a role in the development of hypercalcemia of malignancy.

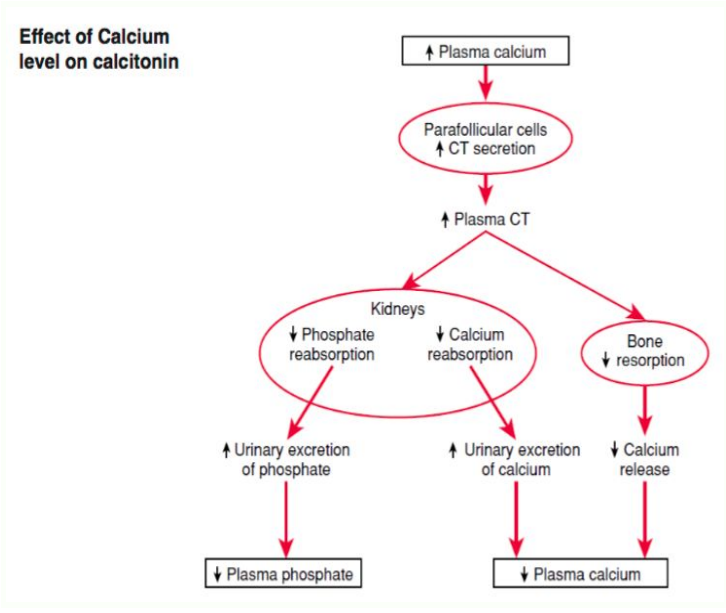
- Some lung cancers are associated with hypercalcemia
- Other cancers can be associated with hypercalcemia

Calcitonin

Source:	Secreted by the parafollicular cells (C cells) of the thyroid gland.
Nature:	32 amino acid peptide.
Stimulus for secretion:	**Increased** plasma calcium concentration.
Function(effects): ابغاكم دائمًا تفرقون بين هالنقطتين في عندي شيء اسمه stimulus وفي stimulus will ال دائمًا effect oppose the effect For example in PTH: stimulus is decreased calcium level but the effect is increase in calcium level	(Opposite effect to PTH)**Decrease** blood Ca++ level very rapidly within minutes. **On the bone:** • [1] ↑ Ca++ deposition of bone • [2] Inhibits Bone resorption: Immediate effect: inhibition of osteoclasts Prolonged Effect: ↓ formation of osteoclasts **On the kidney:** • ↓ ↓ Ca++ reabsorption • ↑ ↑ Ca++ excretion (in addition to phosphate) (phosphate is always in favor of being excreted in the urine)

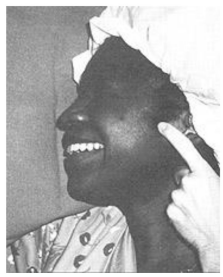
Calcitonin effect is seen in young adult and animals more than older adult





Abnormalities

Rickets (in children) الكساح

Definition:	Rickets is the softening and weakening of bones in children leading to defective calcification of the bone matrix.
Cause:	Lack of vitamin D leading to calcium/ phosphate deficiency in ECF. so there is no mineralization of bone تذكرون تجربة وضع العظمة في الخل؟ نفس الشيء بيصير فبالتالي وزن الانسان نفسه راح يضغط على عظامه مما يؤدي الى الكساح
Occur:	in spring. عشان في الصيف كان يتعرض للشمس فصار عنده فيتامين دال ولما جاء الشتاء ما صار يطلع تحت الشمس بسبب انه يختبئ في البيت من البرد فاستهلك المخزون حقه اذًا على الربيع؟ خلص المخزون وطلعت الأعراض
Feature:	1. Low plasma calcium and phosphate. 2. Weak bones. 3. Tetany. Extreme decrease calcium in ECF leads to excitation of neuromuscular junction which lead to muscle contraction (tetany) and if it involve respiratory muscle it'll lead to death لو صرتي دكتورة اطفال وجاك مريض وشكيتي ان عنده كساح وسألتيه عندك تيتاني وقالك لا؟ وش تسوين تقولين له ارجع البيت مافيك شيء؟ لا طبعًا لأنك دكتورة شاطرة راح تذكري الفيسيولجي فاكيد ال PTH قاعد يشتغل as a compensatory mechanism فانخفاض مستوى الكالسيوم راح يتعوض لكن المريض لسه عنده كساح!! العظام عنده ضعيفة.
Treatment of Rickets:	Supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D. الدكتورة الشاطرة حتعطي كالسيوم وفايتمين دي ليه؟ لان ما عندنا كالسيوم بيندينق بروتين التي يتم تصنيعه بواسطة فيتامين دال (ماعندنا السيارة التي توصل الكالسيوم للعظام)
Tetany in Rickets:	طيب نفترض لو كان فيه دكتورة ماش وشافت مستوى الكالسيوم طبيعي وقالت للاهل ولدكم قاعد يتدلع مافيه شيء ورجعته للبيت؟ ممكن يرجعلها بعد فترة فيه تيتاني او ميت!! ليه؟ لان الكالسيوم خلص من العظام (اقل من ٧) فطلعت له signs of tetany **Early stages:** • No tetany. • PTH stimulate osteoclastic absorption of bone → ECF calcium level is normal. **When the bone finally become exhausted of calcium:** • Calcium level falls rapidly. **Blood level of calcium falls below 7 mg/dl:** • Signs of tetany (positive Chvostek's sign) • Tetanic respiratory spasm → Death. Notice that a very small stimulus cause contraction (Chvostek's sign) فالدكتورة الشاطرة تذكر هالساين وتسويها للمريض positive Chvostek's sign is facial nerve irritability/spasms elicited by tapping the nerve  

★ Inadequate bone mineralization (the problem is in the bone salt)

Osteomalacia (Adults Rickets)	Osteomalacia (Renal Rickets)
Rare. سابقا كانت نادرة ولكن الان انتشرت بسبب العوامل الغذائية واشياء اخرى •Serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat). •Poor absorption of vitamin D and calcium • Almost never proceeds to the stage of tetany but often is cause of severe bone disability.	•It is a type of Osteomalacia Due to prolonged kidney disease. •Failure of the damaged kidney to form 1,25-dihydroxycholecalciferol. 1 a-hydroxylase enzyme→ no active vit. D → no absorption
★ Inadequate bone mineralization (the problem is in the bone salt)	

Osteoporosis

Definitions:	Osteoporosis is the most common of all bone diseases on adults, especially in old age. Result from equal loss of both organic bone matrix and minerals resulting in loss of total bone mass and strength. لاحظوا الكساح كان فقط في المينرالز اما هنا الماتركس والمينرالز فالوضع بيكون عندهم مختلف هنا composition is normal but the mass is low **The cause of the diminished bone:** •The osteoblastic activity in the bone is usually less than normal so the rate of bone osteoid[1] deposition is depressed. •Excess osteoClastic activity.
Causes of osteoporosis:	1. Lack of physical stress. عملوا تجربة لرجل كسرت قدمه ووضعوا عليها جبيرة فكان ما يستخدمها بعكس الرجل الثانية ثم وجدوا ان الرجل المجبرة التي ما يستعملها فيها osteoprosis والرجل الاخرى كانت طبيعية!! ايضًا الناس الرياضيين وجدوا ان العظام عندهم اثقل؟ ليه؟ لأن physical stress will stimulate mineralization of the bone 2. Malnutrition. Dificincy of protien → collagen decrease 3. Lack of vitamin C. → collagen decrease 4. Postmenopausal lack of estrogen. Estrogen inhibit the activity of osteoclast and decrease the number of osteoclast. So, when estrogen gone the osteoclast will start to do it's function 5. Old age. in which growth hormone and other growth factors diminish greatly, plus the fact that many of the protein anabolic functions also deteriorate with age, so bone matrix cannot be deposited satisfactorily. 6. Cushing syndrome. because massive quantities of glucocorticoids secreted in this disease cause decreased deposition of protein throughout the body and increased catabolism of protein and have the specific effect of depressing osteoblastic activity.
symptoms:	•Typically silent (without symptoms) until it leads to fracture at a minimal trauma. •**Most affected**: - vertebral compression forward posture (may be asymptomatic) - hip fractures (requires surgery in most cases).
★ In adequate bone matrix and minerals. composition is normal but the mass is low	

[1] is the unmineralized, organic portion of the bone matrix that forms prior to the maturation of bone tissue.

Hyperparathyroidism (PTH excess)

Primary Hyperparathyroidism, manifestations:

- Hypercalcemia.
- Hypophosphemia.
- Demineralization of bone forming multiple bone cysts (osteitis fibrosa cystic).
- Broken bones.
- **Increase alkaline phosphatase.** osteoclastic resorption of bone can lead to weakened bones and secondary stimulation of the osteoblasts When the osteoblasts become active, they secrete large quantities of *alkaline phosphatase.* Therefore, one of the important diagnostic findings in hyperparathyroidism is a high level of plasma alkaline phosphatase.
- CNS depressed.
- Peripheral nervous system depressed. *Becuz high Ca in ECF will decrease Na permeability at NMJ.*
- Muscle weakness *Becuz high Ca in ECF will decrease Na permeability at NMJ leading to ms weakness.*
- Constipation. *Due to smth ms weakness*
- Abdominal pain.
- Peptic ulcer. *smth ms weakness*>يتجمع الاكل بالمعده مسببا قرحه
- Decrease appetite.
- Calcium containing stones in kidney.*The reason is that the excess **calcium and phosphate absorbed from the intestines or mobilized from the bones in hyperparathyroidism must eventually be excreted by the kidneys,** causing a proportionate increase in the concentrations of these substances in the urine. As a result, crystals of calcium phosphate tend to precipitate in the kidney, forming calcium phosphate stones.*
- Hypercalciuria.
- **Parathyroid poisoning:** precipitation of calcium in soft tissues occur when Ca> 17 mg/dl leading to death.

اذا استمر مستوى الكالسيوم مرتفع راح يبدا يترسب في الاعضاء زي القلب والرئة ووو،،، اذا وصل الى ١٧ راح يعطينا حالة اسمها parathyroid poisoning وحتؤدي خلال ايام الى الموت

Secondary Hyperparathyroidism ,manifestations: Due to low Ca+2 in ECF → compensatory → Hyperparathyroidism..

In secondary the gland is normal but some other causes lead to hyperparathyroidism such as:

Causes:

- Low calcium diet.
- Pregnancy.
- Lactation because calcium is used for milk formation.
- Rickets.
- Osteomalacia.
- Chronic renal failure. ↓ 1,25 (OH) - D3 synthesis.

Hypoparathyroidism (Rare)

Causes:

1. Autoimmune.
2. Injury to parathyroid glands (surgery).

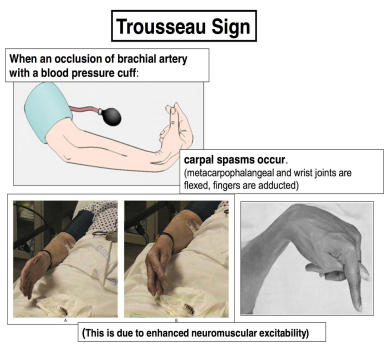
Let assume that someone has a tumor in the thyroid gland and he went to surgery and the surgeon has remove all the thyroid? This of course is wrong (he should keep at least one parathyroid gland) but what will happen? Since he removed the thyroid he took the parathyroid with it and this will lead to decrease in calcium level (hypocalcemia):

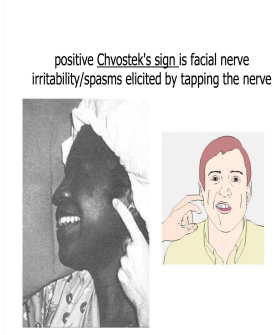
Symptoms: (due to hypocalcaemia)

- Tingling in the lips, fingers, and toes. Due to neural hyperexcitability.
- Dry hair, brittle nail, and dry coarse skin.
- Muscles cramps and pain in the face, hand, legs, and feet. Becuz low Ca in ECF will increase Na permeability at NMJ leading to hyperexcitability & spasm.
- Cataracts of the eyes. No one knows why:(
- Malformation of the teeth, including weakened tooth enamel.بسبب نقص الكالسيوم المكون الاساسي للعظام و الاسنان
- Loss of memory.
- Headaches.

Signs of hypoparathyroidism:

- Tetany can be overt or latent. يعني ممكن يكون واضح شخص يجيك عنده تيتاني واضح وممكن يكون كامن ،، احنا نبغى نكتشف الاشخاص التي عندهم مخفي قبل يوصلون لمرحلة متقدمة ،، طب وش نسوي؟
- **Positive Chvostek's sign (facial muscle twitch):** tapping the facial nerve as it emerge from the parotoid gland in front of the ear causes contraction of facial muscles.
- **Positive Trousseau's sign (carpal spasm):** arresting (stopping) blood flow to the forearm for few minutes (e.g. by sphygmomanometer), causes flexion at the wrist, thumb, and metacarpophalangeal joints. flexion of rest and fingers.





- Delayed cardiac repolarization with prolonged of the QT interval.يعني تزيد انقباض عضلة القلب بسبب قلة الكالسيوم
- Paresthesia.

Treatment:

Calcium carbonate and vitamin D supplements.

Boy's slides only but NOT within the objectives

	Hypercalcemia	Hypocalcemia
causes	**• Hyperparathyroidism** major cause of hypercalcemia. **•adenomas of the parathyroid gland** Single adenomas of the parathyroid gland account for 75% of primary hyperparathyroidism associated with hypercalcemia. **• Malignant neoplasms** major cause of hypercalcemia. **• Neoplasms most frequently associated with hypercalcemia:** Breast cancer, lung cancer and multiple myeloma -Most hypercalcemias in malignancy are caused by humoral hypercalcemia of malignancy (↑ PTHrP)	**• Hypoparathyroid** Post operative , Idiopathic,Post radiation . **• Nonparathyroid:**Vitamin D deficiency, Malabsorption,Liver disease, Kidney disease, Vitamin D resistance. **•PTH Resistance** Pseudo- hypoparathyroidism, Hyperproduction of calcitonin (medullary thyroid cancer). **•Drugs** Furosemide (increases renal excretion). Enzyme induced drugs e.g. Phenytoin (induces hepatic enzymes that inactivate Vit.D).
Clinical features	**• Stones:** Nephrolithiasis, Nephrogenic DI: polydipsia and polyuria, Dehydration, Nephrocalcinosis. **• Bones:** Bone pain, arthralgias, Osteoporosis of cortical bone such as wrist – In primary hyperparathyroidism: Subperiosteal resorption, leading to osteitis fibrosa cystica with bone cysts and brown tumors of the long bones **• Abdominal moans** Nausea,vomiting, Anorexia, weight loss, Constipation, Abdominal pain, Pancreatitis, Peptic ulcer disease **• Psychic groans:** Impaired concentration and memory, Confusion,stupor,coma, Lethargy and Fatigue **• Neuromuscular:** Reduced neuromuscular excitability and muscle weakness **• Cardiovascular:** Shortened QT interval on electrocardiogram, Cardiac arrhythmias, Vascular calcification **• Other:**Itching, Keratitis, Conjunctivitis, Corneal calcification, band kerato pathy, Carpal tunnel syndrome has occasionally been associated with hyperparathyroidism	•Neuromuscular excitability. • Paraesthesia (tingling sensation) around mouth, fingers and toes. • Muscle cramps, carpopedal spasms. • Tetanus → ↑ influx of sodium ions at motor neurons and interneurons → ↑ conduction of impulses → reflex muscle contraction causing: 1- Spasm of larynx and bronchus → asphyxia and death. 2- Muscle cramps. 3- Coronarospasm (cardiotetanus) → angina → infarction • Seizures – focal or generalized. • Cardiac rhythm disturbances (prolonged QT interval). • Chvostek's and Trousseau's signs – latent hypocalcemia.

Boy's slides only but NOT within the objectives

Pseudohypoparathyroidism	
Symptoms and signs	• **Hypocalcemia** • **Hyperphosphatemia** • **Characteristic physical appearance:** short stature,round face, short thick neck, obesity, shortening of the metacarpals • **Autosomal dominant** • **Symptoms begin in children of about 8 years:** –Tetany and seizures. – Hypoplasia of dentin or enamel and delay or absence of eruption occurs in 50% of people with the disorder.
Resistance to parathyroid hormone	• The patient have normal parathyroid glands, but they fail to respond to parathyroid hormone or PTH injections.
Treatment	•Vitamin D and calcium.

SUMMARY

Numbers	
calcium	**Presence** in blood = 9-10.5 mg **Daily requirement** -pregnant, lactating & post-menopause: 30 mmol/day -non-pregnant: 15-25 mmol/day **Pathies** -plasma Ca <9 mg: tetany (muscles involuntary Spasms) -plasma Ca >11 mg: renal stones -lethal deposit of Ca in soft tissues (when blood Ca2 >17 mg)
phasphate	**Plasma conc. 4 mg**
PTH	-plasma Ca < 3.5: more PTH -plasma Ca > 5.5: less PTH

Calcium	
Presence	in blood = 10 mg Plasma ca diffusible: 40% Protein-bound Plasma ca Non-diffusble:10% anion-bound(cmplx) & 50% free(ionized) in organs = 1300 g (99% bones, 1% Intracellular fluid -smooth endoplasmic reticulum , 0.1% interstitial)
Protein binding	-mostly albumin (minute amount to globulin) -highly dependent on pH (the higher pH, the more it binds) Resp. alkalosis causes significant binding of Ca to albumin, dropping the level of ionized form in the blood
Function	-Ca salts: structural block (bones) -Ca ions: essential in IC & EC for: Neuromascular action potential hormones release enzyme regulation Blood coagulation second messengers
Sources	-milk -diaries -fish
Daily requirement	-pregnant, lactating & post-menopause: 30 -non-pregnant: 15-25
Absorption site	-duodenum . (actively) -small intestine (facilitated diffusion “down its normal conc gradiant”)
Pathies	-plasma Ca <9 mg: tetany (muscles involuntary Spasms) -plasma Ca >11 mg: renal stones

Phosphate	
is	a mineral
function	-essential for ATP synthesis & used cAMP 2nd Messenger -highly regulates Ca
plasma conc	4 mg
forms	50% ionized(diffusible) - 50% Protein-bound(non-diffusible)

Bone		
Cells	-osteoblasts: bone formers -osteocytes: osteoblasts trapped in a calcified matrix -osteoclasts: bone destructors (originated from monocytes)	
Ions amount	-Ca(99%) -phosphate -C -Mg -Na -H2O(9%)	
Plasma Ca & phosphate regulation	Non-hormonal	-very Rapid -alters small conc changes using free Ca
	Hormonal	-used for long term regulations or major alters -hormones used: PTH, calcitonin & vit D
	Organic matrix	**salt**
%	30%	70%
ability	tensile (stretch)	Compressional (strength)
blocks	-95% collagen -5% ground (ECF & proteoglycans)	-Mg, Na, K, C (0.1%) -Ca & phosphates (99%) Present as hydroxyapatite crystals -amorphous (1%) Is exchangeable form of Ca. VIP for Rapid regulation of free Ca in ECF "its always equilized with ECF Ca".

Vit d (1,25 dihydroxycholecalciferol)	
Fun	-Small intestine : increase Ca & phos. Absorption by increasing Ca binding Pr -renal: inc Ca & phos. Reabsorption -bones: stimulate osteoclasts (causes hypercalcemia) -immunity: stimulate differentiation
Intake	-small doses: stimulates Small intestineabsorption & bone mineralization (stronger) -large doses: stimulates PTH action & osteoclasts (weaker bones)
Biochem	sun transforms 7-dehydrocholestrerol under the skin to cholecalciferol(Vit D3), which goes to the liver and it transforms it to 25-hydroxyvitamine D3, which goes to the kidney and it uses **1 alpha hydroxylase** to make 1,25 dihydroxyvitamine D3 which is usable
Regulation	-by: Ca ions, prolactin & PTH All stimulate renal 1-alpha hydroxylase

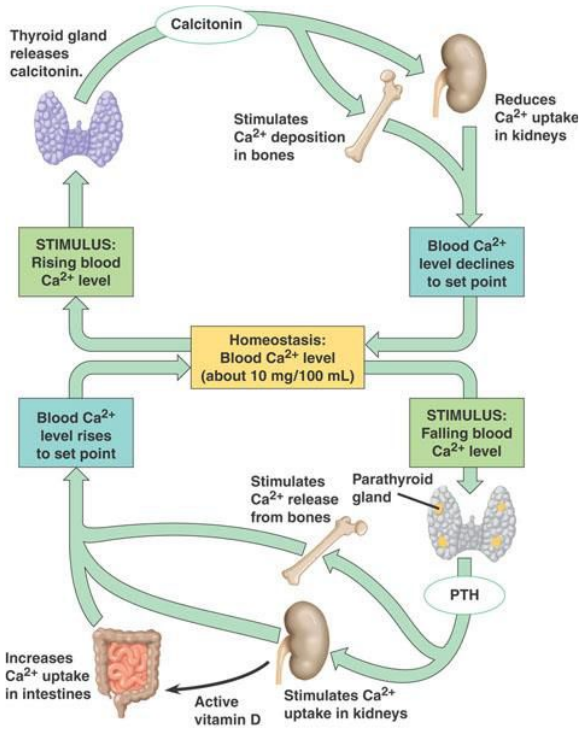
PTH	
Type	Protein
Causes	Hypercalcemia
Regulation	-plasma Ca < 3.5: more PTH -plasma Ca > 5.5: less PTH
Fun MOA	-bone: resorption, causing release of Ca into circulation by activation of clasts & inhibtion of blasts -renal: excretion of phosphate in urine & Ca reabsorption -Small intestine : (indirectly) it converts 25-hydrocholecalciferol to 1,25…ol which is usable form, that stimulate Small intestine Ca reabsorption

Calcitonin	
By	Thyroid parafollicular cells (C cells)
Causes	Hypocalcemia (very rapid action)
Regulation	Hypercalcemia stimulates its secretion
Fun MOA	-bone: oppose resorption, causing Ca deposit into bones by inh of clasts & activation of blasts -renal: decrease Ca reabsorption & increase its excretion along phosphate. (phosphate is always in favor of being excreted in the urine)

Abnormalities

	Normal ricket	Osteomalacia	Renal ricket	Osteoporosis
Epedimoilogy	Children	Adults	-	Elders
Etiology	Vit D def	Steatorrhea	Kidney chronic diseases	-exercise lack -malnutrition -vit C lack -estrogen lack (PostMenopusal) -cushing synd.
Result	-Hypocalcemia -less blood phosphate	-Hypocalcemia -less blood phosphate -vit D def	Failure of kidney to activate 25-hydrocholec…	-active clasts -inh blasts
Symptoms	Weak bones			
Tetany	-early: no tetany cuz PTH will stimulate clasts -falling: when bones are exhausted, blood Ca will drop -death: tetany failing resp.	Nill	Nill	Nill
Bones	Less mineralize (matrix is preserved)			Less mineralize & less matrix

Path: PTH	
(1) hypoparathyroidism	
Etiology	-dysfun paraThyroid -paraThyroid removed during thyroidectomy
Signs	Hypocalcemia (vit D def might be present)
Symptoms	-tetany positive chvostek test (tapping on facial nerve will spasm facial muscles) positive trousseau test (blocking blood flow to forearm for few minutes leads to all hand strong contraction) -CVS: delay repolarization & prolonged QT interval -parasthesia (numbness is more common)
Treatment	Ca carbonates & Vit D supplements
(2) primary hyperparathyroidism	
Etiology	paraT tumors
Signs	-hypercalcemia & hypophosphatemia -hypercalciuria & hyperphoshpaturia -osteitis fibrotic cystica (fibrotic cysts within bones) -renal Ca stones -lethal deposit of Ca in soft tissues (when blood Ca2 >17 mg)
(3) secondary hyperparathyroidism	
Etiology	-low Ca diet -pregnancy & lactation -rickets & osteomalacia & chronic renal failure
MOA	Body compensate to Hypocalcemia by secretion lots of PTH



MCQs

1. A patient with respiratory alkalosis caused by hyperventilation for a long period of time may have:

a. Increased calcium ions
b. Osteomalacia
c. Tetany

2. Which one of the following doesn't have a role in the regulation and metabolism of calcium:

a. PTH
b. Estrogen
c. TSH

3. The majority of calcium in bones is stored as:

a. hydroxyapatite
b. type 1 collagen
c. osteod

4. calcitonin decreases calcium levels in blood by:

a. stimulating osteoclasts.
b. Promoting renal excretion of calcium
c. Increasing the absorption from GI tract

5. Hydroxylation of vitamin D into its active form takes place in:

a. Kidneys
b. Liver
c. Skin

6. Which one of the following decreases the absorption of calcium:

a. PTH
b. Acidic pH
c. Phytates

7. A patient came to the clinic with hypocalcemia, hyperphosphatemia, short stature and round face what is the diagnosis:

a. Hypoparathyroidism
b. Hyperparathyroidism
c. Pseudoparathyroidism

8. A patient came with hypercalcemia, hypophosphatemia and renal stones the diagnosis would be:

a. hyperparathyroidism
b. hypoparathyroidism
c. thyroid gland tumor

9. which one of the following is a symptom of hypercalcemia:

a. shortened QT interval
b. irritability
c. weight gain

10. A patient with chronic muscle pain, frequent falling accidents and high ALP what is the suitable treatment:

a. Calcium supplementation
b. Vitamin D pills
c. Antibiotics

Answer key:

1 (C) | 2 (C) | 3 (A) | 4 (B) | 5 (A) | 6 (C) | 7 (C) | 8 (A) | 9 (A) | 10 (B)

Physiology 435 team

Thanks to this amazing team!

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رغدة القاسم
مي العقيل
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