endocrine system

physiology

Sheet Slide

number	5
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We finished the topic of the **THYROID GLAND, and in this lecture we will study the **PARATHYROID GLANDS.** But before that**,** check your memory and try to remember the main points and characteristics of the thyroid gland.

THE PARATHYROID GLANDS

*General information about parathyroid glands :-

1- They are normally **four** small glands each one is about 20-50mg in adults. Located behind the thyroid gland. Sometimes in **Thyroidectomy** removal of the parathyroid can mistakenly happen due to the close anatomical relation between both glands(medical mistake).

2- In some pathological conditions the number of these glands can be more than 4.

3- Contain two types of cells**, chief cells** which are responsible for secreting almost all of the parathyroid hormone (PTH) , and **oxyphil cells** which are believed to be modified or depleted chief cells that no longer secrete PTH and some say that they play a role in the metabolism of the parathyroid glands.

*we said that almost all of PTH is synthesized and secreted by chief cells because some other cells secrete another hormone **called parathyroid hormone-related protein** which has the same function of PTH.

4- When PTH binds to its receptors, the response occurs by the activation of **cAMP, IP** & **diacylglycerol** second messengers.

5- PTH is a single chain protein (9600 molecular weight) that contains 84 amino acid. It is first synthesized by ribosome in the form of **preprohormone** which is a polypeptide chain of 110 amino acids, then in the ER and Golgi apparatus preprohormone is cleaved into prohormone of 90 amino acids , and then to the hormone itself with 84 amino acids .

6- The biological activity of PTH is found in the first 34 amino acids which are adjacent **to the N terminus .**

7- Development of these glands occurs at 5-14 weeks of gestation.

8-The half life of PTH is about 25 min. **It also found free in the plasma (doesn't bind to any protein).**

9- PTH is essential for life, without it Ca++ falls in plasma, neuromuscular excitability increases, tetany & death occurs.

*** Some functions of Calcuim :-

1- Skeletal , Cardiac and smooth muscle contraction.
2- Helps in blood clotting .
3- Release of neurotransmitters at the nerve endings.
4- Plays a role as second messenger.
5- Some enzymes need Ca to function.
6- Required for the maintenance of normal sodium permeability in nerves.
7- Constituent of bone.
8- Required for protein secretion.

***Calcuim in our body is distributed as following :**

-98.9% (approximately 99%) in bones // 0.1% in the extracellular fluid // 1% in cells !!

-This 0.1% which is found in the plasma has three forms:

1- 41% of it is combined with plasma protein and this form is nondiffusible through capillaries.

2- 9% is combined with anionic substances such as citrate and phosphate and can diffuse through capillaries.

3- 50% of it is ionized (unbounded) and diffusible .

*The doctor didn't mention the previous informations about Calcium , but i did to make it clear when we come to the next point . (the source of these informations is guyton and hall text book page number 1001).

10- What controls the secretion of PTH(the dominant controller) is the **ionized calcium.**

11- Calcium regulates the **size and number** of parathyroid cells ,but how is that ? the doctor cast down this information without explaining it. But I will do .

The answer : when a slight decrease in calcium concentration occurs PTH secretion increases ,so when this decrease persists for a long period of time the gland undergoes hypertrophy .In contrast , if Calcium concentration increases due to any reason the activity of the gland decreases so that reduces the size of the gland .

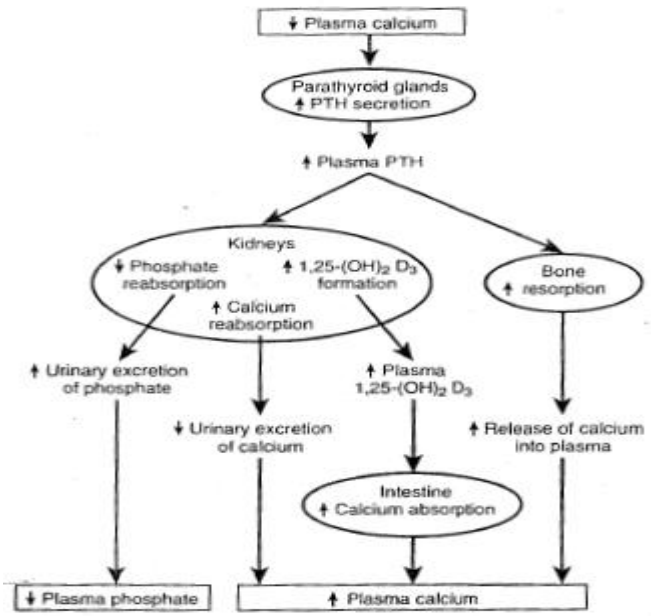
*NOTE : an increase in Calcaium concentration triggers the secretion of a hormone from the thyroid gland called **calcitonin**.(more details in the coming lectures).

12- Hypomagnesemia stimulates PTH secretion such as Ca++ but is less potent.

13- Arise in plasma phosphate concentration **indirectly** causes a transient increase in PTH secretion.

14- 1,25 (OH)2 -D directly reduces PTH secretion.

FUNCTIONS OF PT HORMONE



*PTH has a great role (**its main function**) in controlling the extracellular concentration of calcium and phosphate by regulating :

a- Intestinal absorption: of both calcium and phosphate from the gut by formation of the active form of **VitD** which is (**1,25 (OH)2 –D)** that facilitates the entry of both ions through the epithelium of the gut. SO PTH **indirectly** effect Calcium and Phosphate absorption through (**1,25 (OH)2 –D).**

****PTH in *the kidney* converts 25-hydroxycholecalciferol into 1,25 hydroxycholecalciferol which is the *active and potent* form of VitD needed to allow the entry of both Calcium and Phosphate from the gut into the blood circulation.**

b- Renal excretion: PTH **directly** increases the reabsorption of calcium from kidneys into the blood, **but** decreases the reabsorption and consequently causes excretion of phosphate out of the body.

c- Bone resorption: PTH controls the action of releasing calcium and phosphate from the bone ,so increasing their concentration in plasma, Mechanism :

Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release RANK ligand, also called osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption.

Note: the doctor didn't mention the effects of PTH on phosphate level that happen through gut absorption and bone resorption.

* The overall function of PTH is increasing Calcium concentration in plasma and decreasing Phosphate concentration in the plasma.

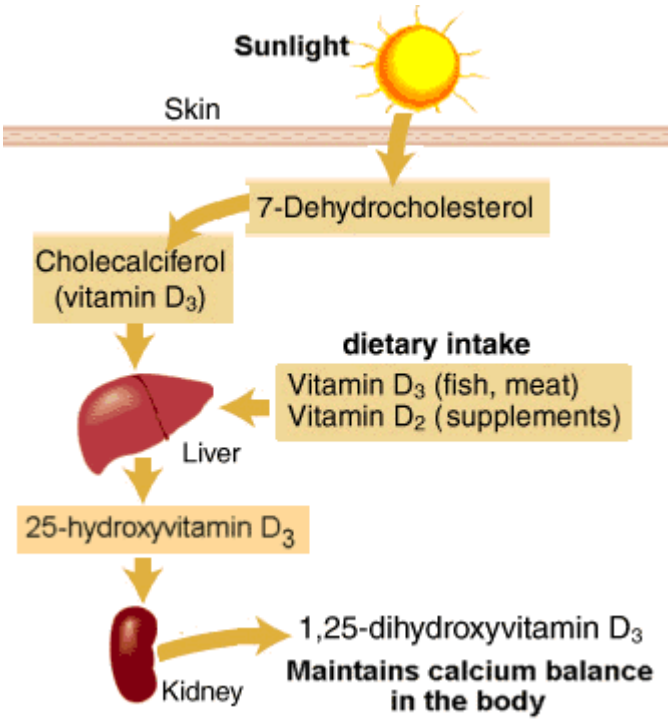
** We said that the normal function of PTH is to reduce phosphate concentration , that's why in point number 13 we said that increased level of phosphate indirectly stimulates the release of PTH.

* Any disease that decreases the release of PTH will affect its functions in the intestine, kidney and bone on the contrary of its normal functions.

* When the free ionized Ca++ concentration decreases in the blood, sensors in the the parathyroid gland cell membrane called (**calcium – sensing receptors)** detect this decrease and start to secrete **PTH** to normalize the situation.

*NOTE: increase in **1,25 (OH)2 –D** and **Calcium** concentration **directly** inhibits the release of PTH by negative **feedback inhibition mechanism**, while low concentration of Calcium stimulates the gland to secrete PTH.

*NOTE: VitD3 (cholecalciferol) is produced in the skin by the action of the sun, and then is converted into 25-hydroxycholecalciferol in the liver.After that in kidney with the help of PTH, 25- hydroxycholecalciferol is converted into 1,25- hydroxycholecalciferol the potent and active form of VitD.



*NOTE :Hypomagnesemia stimulates PTH secretion, but less potently than hypocalcemia.

* NOTE : why do we study calcium and phosphate together? Because the homeostasis for both are closely similar and many of the factors that regulate Calcium also regulate phosphate.

UNDERACTIVITY OF PARATHYROIDS

Normal level of Calcium in blood is about 10-11mg/dl , so if PTH level decreases due to any disease, plasma concentration of Calcium will decrease and if it reaches 6mg/dl or less tetany occurs , why ? because Calcium regulates the entry of Na+ to cells ,so when it decreases more Na+ enters the cells because the permeability for Na+ is raised causing continuous contraction of muscles .

Or using guyton's words:

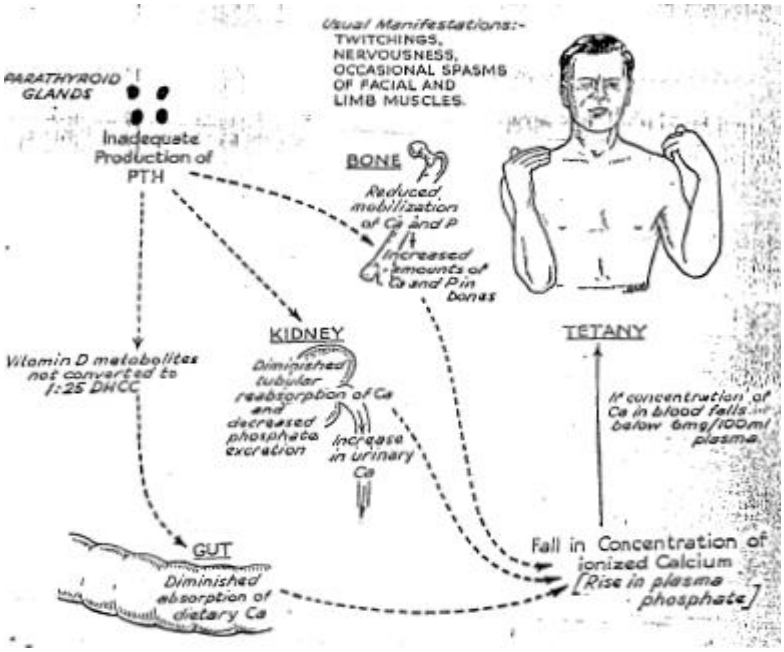
When the extracellular fluid concentration of calcium ions falls below normal, the nervous system becomes progressively more excitable because this phenomenon causes increased neuronal membrane permeability to sodium ions, allowing easy initiation of action potentials. At plasma calcium ion concentrations about 50 percent below normal, the peripheral nerve fibers become so excitable that they begin to discharge spontaneously, initiating trains of nerve impulses that pass to the peripheral skeletal muscles to elicit tetanic muscle contraction. Consequently, hypocalcemiacauses tetany

*NOTE:- hypocalcemia causes tetany while hypercalcemia causes the neurons to become depressed (not excitable).

* When tetanization affects the respiratory system, death will result.

* Heart cannot be affected with tetany, but why? Because the action potential of the heart occupies the mechanical response which means that there is no difference between the electrical and the mechanical response .(the doctor's answer)

The heart cannot be tetanized, or go into sustained involuntary contractions, because of the long refractory period of the muscle, during which it does not respond to stimulus.(another correct answer).



OVERACTIVITY OF PARATHYROIDS

*Hyperactivity of the parathyroid gland due to the presence of a tumor **(a lot of PTH secretion**) causes more resorption of the calcium and phosphate from the bone , more reabsorption of of calcium in kidney and great loss of phosphate with urine and more absorption of calcium and phosphate from the gut ,and that leads to high concentration of calcium in the plasma and low concentration of phosphate in plasma, as a result many diseases can occur such as :-

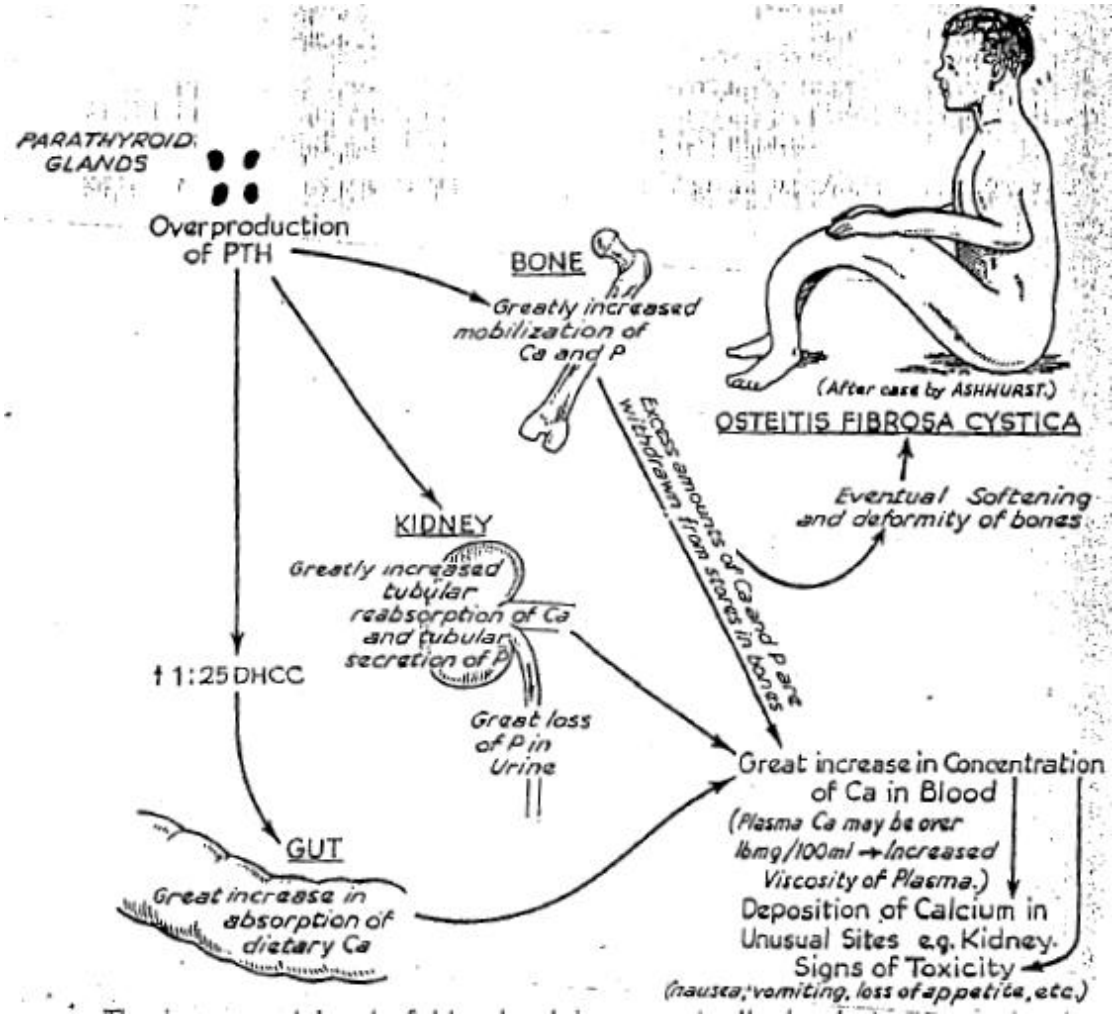
1-OSTEITIS FIBROSA CYSTICA: a disease caused due to persistent secretion of PTH which leads to more relase of Calcium and Phosphate from the bone .

*Normal PTH releases Calcium and Phosphate from the synovial fluid around the bone but in OSTEITIS FIBROSA CYSTICA, Calcium and Phosphate are released from the texture of the bone itself with high rate with the result that the bone becomes fragile and softened.

*Osteitis fibrosa cystica is not osteoporosis, both are different diseases.

2- Increasing **Calcium** concentration rises the blood viscosity and facilitates the deposition of Calcium in unusual sites such as the kidney .As a result of that toxicity occurs (vomiting , nausea , loss of appetite … ect).

3-Increasing Calcium concentration in plasma increases the loss of Calcium with urine (in spite of increased reabrorption) and also water because Calcium pulls water when it is excreted which results in **POLYURIA and THIRST** .



** what is the difference between poliomyelitis and rickets diseases ?

Poliomyelitis >>> caused by viral infection

Rickets >>> caused by a deficiency in vitamine D

VITAMIN D

Genral informations about vitD:-

1-Remember that PTH stimulates the conversion of **25-hydroxycholecalciferol** into **1, 25-hydroxycholecalciferol** in the kidney , which regulates the entry of Calcium and Phosphate from the gut into the plasma.

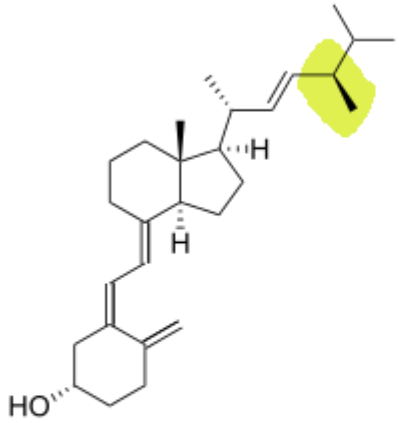
* Vitamin D functions in mineralization of the bone (deposition of Calcium and phosphate) in the bone , so we will see how vitamin D increases the concentration of Calcium and Phosphate.

*Vitamin D, in conjunction with PTH, is the second major regulatory hormone for Ca2+ and phosphate metabolism. The roles of PTH and vitamin D can be distinguished as follows. The role of *PTH* is to maintain the plasma Ca2 + concentration, and its actions are coordinated to increase the ionized Ca2 + concentration toward normal. The role of *vitamin D* is to promote mineralization of new bone, and its actions are coordinated to increase *both* Ca2 + and phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

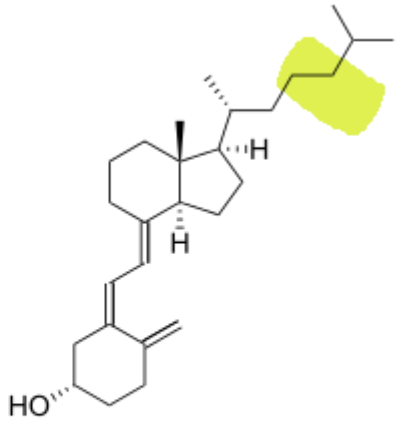
2-It is considered a hormone because it is produced in our cells, and a vitamine because we need it in essential amounts from the diet .

3. Deficiency of vitamin D causes failure of bone mineralization & results in the classic disease of rickets in children & softening of the bones (osteomalacia) in adults.

4-There are two forms of vitamin D (D2 from diet and D3 from our skin) , Once vitamin D enters the circulation from the skin or the gut, it is concentrated in the liver. There it is hydroxylated to 25-0H-D. this molecule is transported to the kidney where it undergoes alternative fates (that produce either 1, 25-hydroxycholecalciferol or 24, 25-hydroxycholecalciferol).



Ergocalciferol
(Vitamin D2)



Cholecalciferol
(Vitamin D3)

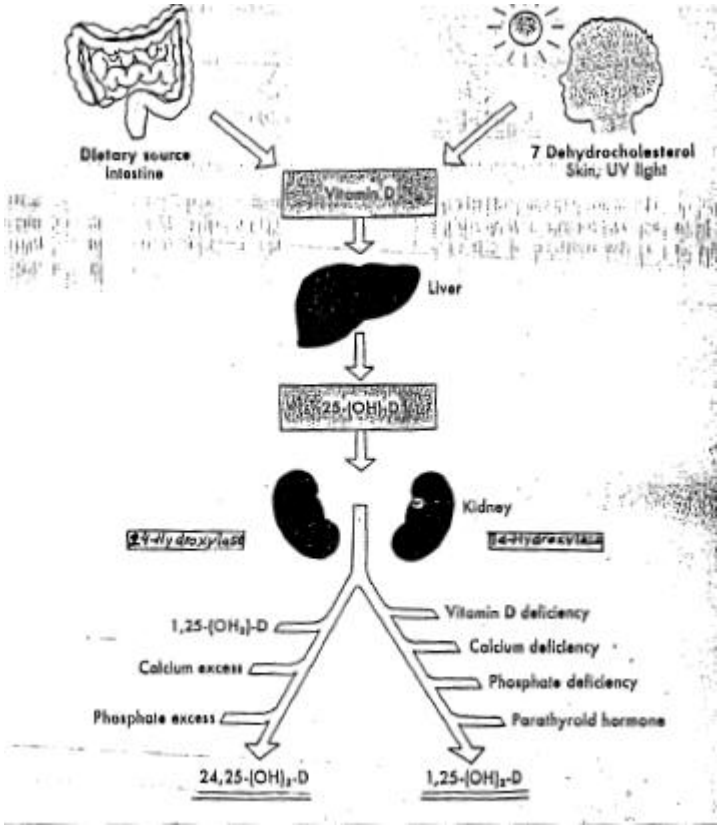
*Pay attention to the name of each form, the structure is not important but you should know that they differ in the structure.

* Vitamins D3 & D2 both are prohormones.

5- 24,25-(0H)2-D is one of vitamin D derivatives which is produced from 25-(0H)2-D by an enzyme.

****NOTE:- Vitamin D metabolism: Whether synthesized In the skin or absorbed from the diet , vitamin D undergoes 25 hydroxylation in the liver . In the kidney, it is further hydroxylated in 1 position when more biological activity is required or in the 24 position when less biological activity Is required.**

*The factors that determine which of the two pathways is mainly used are illustrated in the following figure:



we can see that Vit D deficiency, Calcium deficiency, Phosphate deficiency, and Parathyroid hormone stimulate the pathway that results in the formation of 1,25-(0H)2-D, while 1,25-(0H)2-D, Calcium excess, and phosphate excess stimulate the pathway that results in the formation of 24,25-(0H)2-D.

6- 24,25-(0H)2-D is only 1/20th as potent as 1,25-(0H)2-D & mainly serves to dispose of excess vitamin D.

7- **25-(0H)2-D** , **1,25-(0H)2-D** and **24,25-(0H)2-D** all of them have the same function but with different effectiveness.

8- Vitamin D, 25-(0H)2-D & 1,25-(0H)2D circulate bound to a protein carrier. 1,25-(0H)2D has by far the lowest concentration & the shortiest half-life of the three.

MECHANISM OF ACTION:-

*When vitamin D is low in the plasma this affects the Calcium and Phosphate concentration by leading to low concentration of Calacium and Phosphate in the blood.

* When calcium level is low this promotes the relase of PTH which stimulates an enzyme called 1-alpha-hydroxylase in kidney that stimulates the conversion of 25-(OH)2-D into 1,25-(OH)2-D.

* The produced 1,25-(OH)2-D functions as following :-

1- promotes PTH function in resorption of bone releasing Calcium and Phosphate.

2- inceases the absorption of Calcium and phosphate from the intestine.

3-**In the kidney it increases the reabsorption of both Calcium and Phoshate.**

*The net effect is high Calacium and Phosphate in the plasma.

***PTH increase calcium but reduces the phosphate concentrations .**

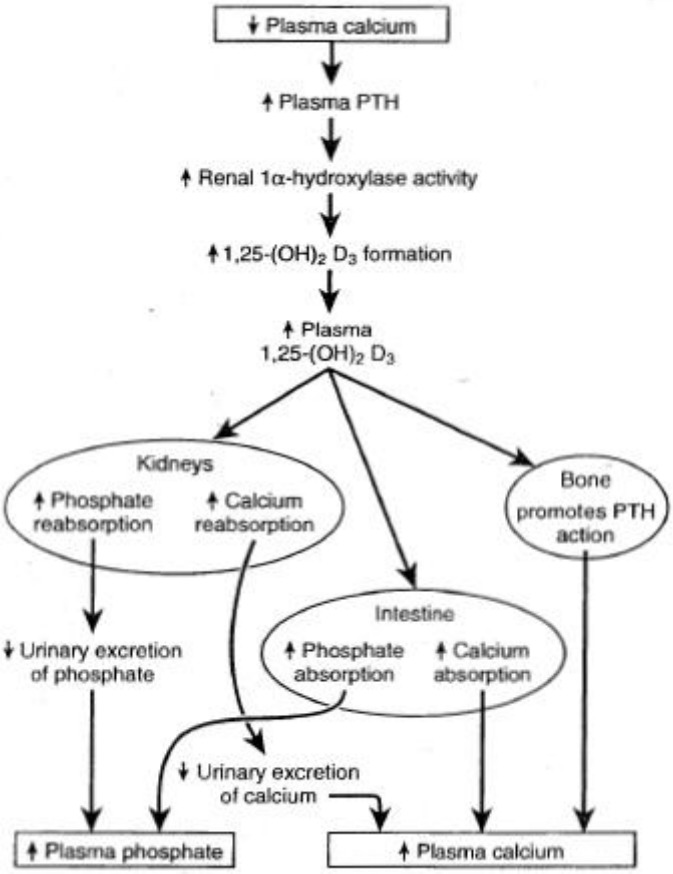
***Vitmine D raises the level of both calcium and phosphate to do its function which is bone mineralization which needs both Calcium and Phosphate.**

*****VERY IMPORTANT NOTE :- Although vitaminD increase the phosphate concentration , it has **a synergistic relation with PTH.**

From the slides: In bone, 1,25-dihydrox-ycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical, since the overall action of 1,25-dihydroxycholecalciferol is to promote bone mineralization. However, mineralized "old" bone is resorbed to provide more Ca2+ and phosphate to ECF so that "new" bone can be mineralized (bone remodeling).

* Depending on the concentration of calcium, 25-(OH)2-D is either converted to 1,25-(OH)2-D or 24,25-(OH)2-D.

*when we need Calcium, 25-(OH)2-D is converted to 1,25-(OH)2-D , but when Calcium level is significant 25-(OH)2-D is converted into 24,25-



(OH)2-D.

-Vit D3 is also available from other natural sources (but it is mainly produced in the skin) such as:-

1-Fish 2- liver 3- Fortified milk 4- eggs

-The source of vitD2 is obtained only from diet and largely from vegetables.

- more details about vitD and its sources will come in biochemistry lectures.

- vitD is fat soluble vitamin stored in the liver and fat tissues of our bodies and only 1-2% of the store is burned each day, therefore several years of very low dietary intake as well as diminished endogenous synthesis is required for deficiency to develop.

- our body needs both VitD3 and VitD2.

* VERY IMPORTANT NOTE:- obese people especially teenagers have a type of fat in their abdomen which captures vitD and does not allow it to be released so they suffer from problems effecting their bone and hearts.

* But why hearts ? we know that VitD increases the level of calcium so helping the heart to function well .

*In addition to the three vitD metabolites there are 15 other metabolites of VitD found in the blood ! but their physiological function is unclear yet.

* Potency of the known VitD metabolites:-

1- 1,25-(OH)2-D is the most potent one

2- then 24,25-(OH)2-D

3-then 25-(OH)2-D