The Endocrine System

PHYSIOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	8
Subject:	Parathyroid glands, Ca^{+2} and phosphate homeostasis
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Price:	

**** This sheet was written according to the recording that belongs to section 1. Please pay attention that <u>the order of ideas in this sheet is different from that in the recording</u>.**

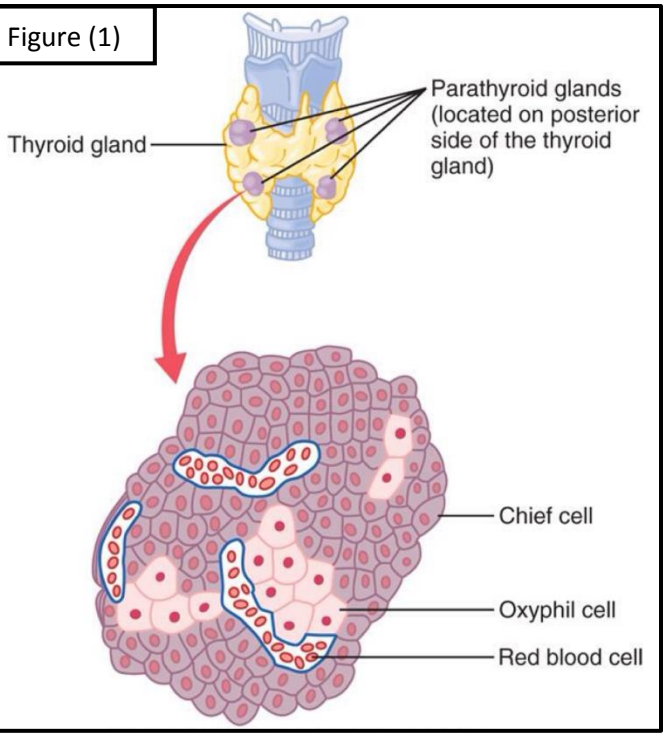
❖ Few notes before we start:

I. The parathyroid glands are located immediately behind the thyroid gland.

The parathyroid gland of the adult human being contains mainly chief cells and a small to moderate number of oxyphil cells. *See figure (1)*

- The **chief cells** are believed to secrete most, if not all, of the Parathyroid Hormone (PTH).
- The function of **oxyphil cell**s is not certain, but the cells are thought to be modified or depleted chief cells that no longer secrete hormone.

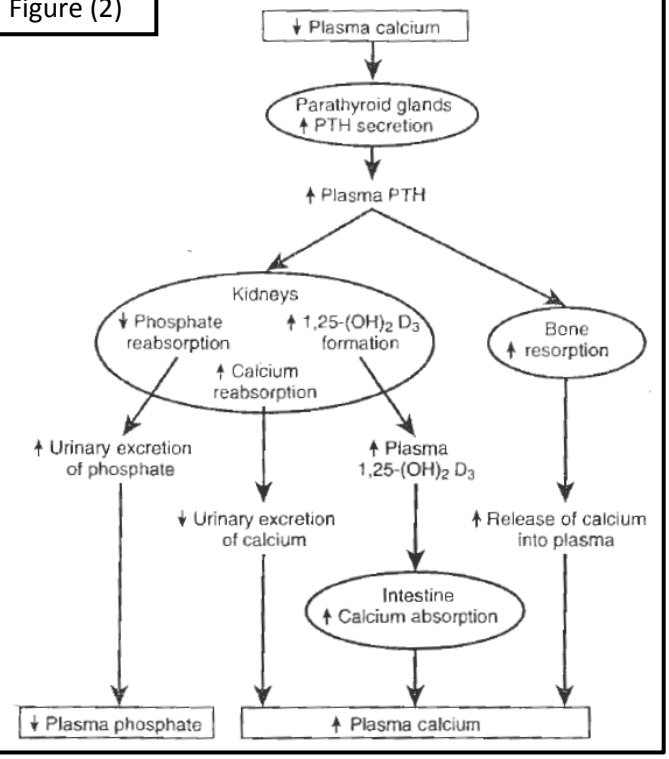
Figure (1)



II. In the previous lecture, Dr. Saleem talked about the PTH, the factors that stimulate its secretion (<u>low plasma Ca^{+2}</u>, <u>hypomagnesemia</u>, <u>elevated plasma phosphate concentration</u>) and factors that reduce its secretion like **<u>1,25(OH)$_2$-D</u>** (the most active form of vitamin D).
He also talked about the effect of PTH on calcium and phosphate metabolism. *See figure (2)*

- It **<u>increases plasma Ca^{+2}</u>** level -to be normal.
- It **<u>decreases plasma phosphate</u>** level -to be normal.

Figure (2)



III. Calcium homeostasis and phosphate homeostasis are affected mainly by three hormones:

1. PTH (was discussed in the previous lecture)
2. Vitamin D (also called Hormone D)
3. Calcitonin

Hormone	**Its Effect on plasma Ca^{+2}**	**Its Effect on plasma Phosphate**
PTH	Increase	Decrease
Vitamin D	Increases BOTH	
Calcitonin	Decreases BOTH	

- In this sheet, we will continue the topic by talking about vitamin D and calcitonin among other related topics.

❖ Topics of this lecture:

*Calcium; its functions, distribution in the body, and Calcium homeostasis

*Phosphate; its functions, and homeostasis.

*Vitamin D

*Calcitonin

*Some abnormalities of Calcium homeostasis

❖ <u>Calcium; its functions, distribution in the body, and homeostasis</u>

I. Some of the physiological functions of calcium:

1. Required for the maintenance of normal sodium permeability in nerves. Thus, it is needed for proper neuromuscular activity.
2. Involved in triggering the release of acetylcholine –or other hormones- from nerve endings at the neuromuscular junction. (Acetylcholine release does not occur unless Ca^{+2} entry has occurred).
3. Involved in excitation-contraction coupling in muscle cells, since binding of Calcium ions to troponin C constitutes an important step in the process.
4. Serves as an intracellular signal for some hormones. Ca^{+2} works sometimes as a second messenger.
5. Required by some enzymes for normal activity.one example is DAG (Diacyl Glycerol) that needs Ca^{+2} to function properly.
6. Required for blood clotting to occur normally.
7. Required for protein secretion.
8. Constituent of bone.

Why does tetany occur when calcium is deficient?

Because calcium regulates sodium channels.

Calcium (Ca^{+2}) Deficiency → Na^{+} channels remain open → continuous depolarization → tetany, and death occurs if tetany reaches the respiratory system.

II. Distribution of calcium throughout the body.

- 99% of calcium in the body is found in bones.

Major Inorganic Constituents of bone	
Constituent	**Total body content present in bone (%)**
Calcium	99
Phosphate	85
Carbonate	80
Magnesium	50
Sodium	35
Water	9

- Distribution of calcium in normal human **plasma**:
  a) Diffusible → either ionized or complexed to HCO_3^-, citrate, etc.
  b) Non-diffusible (protein bound) → bound to albumin or to globulin.

Table 21–1. Distribution (mmol/L) of calcium in normal human plasma.

Diffusible		1.34
Ionized (Ca^{2+})	1.18	
Complexed to HCO_3^-, citrate, etc	0.16	
Nondiffusible (protein-bound)		1.16
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		2.50

- Which of the previous forms is the one that stimulates PTH secretion? Diffusible, ionized form (Ca^{+2}).

III. Calcium homeostasis

Factors affecting calcium ions concentration in plasma:

1) **PTH** → increases plasma calcium (its effect was discussed in details last lecture).
2) **Vitamin D** → increases plasma calcium.
3) **Calcitonin** → decreases plasma calcium.
   Note: the detailed effects of vitamin D and calcitonin will be mentioned in the following sections in the sheet.
4) **Blood pH** :
   - pH affects the concentration of Ca^{+2} in plasma. (*Figure* (3))
   - <u>In alkalosis</u>, ionized Ca^{+2} concentration <u>decreases</u>. Note that in alkalosis, more calcium ions are bound to protein. Therefore, the concentration of the diffusible ionized form decreases.
   - <u>In acidosis</u>, ionized Ca^{+2} concentration <u>increases</u>.

Figure (3)

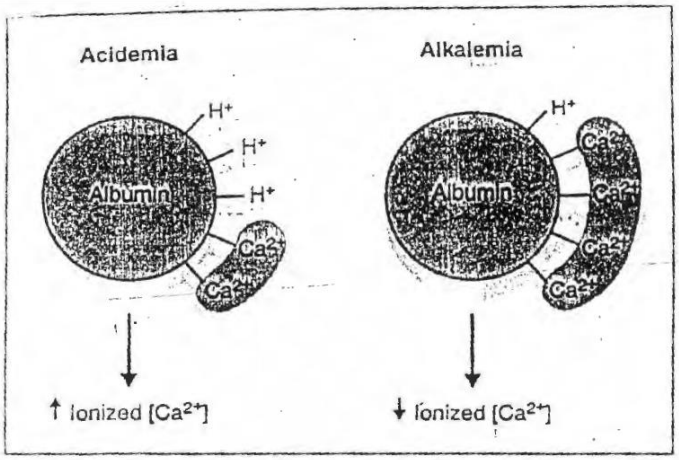


FIGURE 9–32. Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

❖ <u>Phosphate; its functions and homeostasis</u>

85 % of phosphate in the body is found in bones.

I. Some of the physiological actions of phosphate:

1. Functions as part of the intracellular buffer system (it has a role in pH regulation).
2. Important constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins.
3. Constituent of bone. Mineralization does not occur without phosphate.

II. Integrated phosphate homeostasis

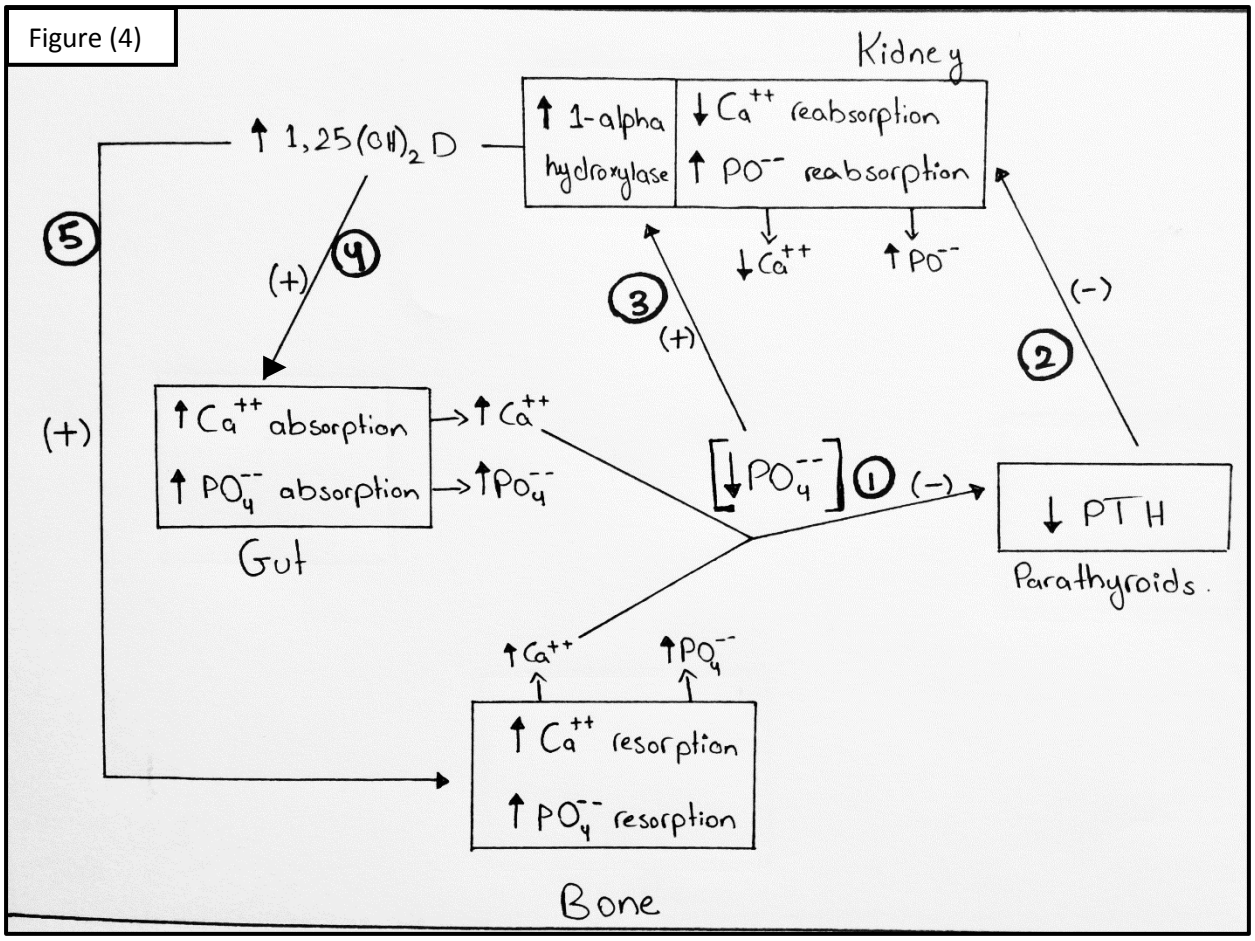
Figure (4) (please follow the numbers in the figure while you read the text so as not to get lost). The figure shows the responses to marked decreases of serum phosphate concentration. -Opposite responses occur to marked increases.
(+ = stimulation, - = inhibition, PTH = Parathyroid hormone).

- **(1) → Decreased plasma phosphate** concentration inhibits the secretion of PTH. Consequently, **(2)** → the action of PTH on the kidneys will be inhibited. As a result, the concentration of plasma phosphate will rise again.

- **(3)** → **Decreased plasma phosphate** concentration stimulates 1-alpha hydroxylase in the kidney to produce 1,25 $(OH)_2$-D
- **(4) & (5)** → 1,25 $(OH)_2$-D acts on the:
  - Intestines, to increase absorption of both, Ca^{+2} and phosphate.
  - Bone, to increase the resorption of both, Ca^{+2} and phosphate.

→As a result, the concentration of plasma phosphate will rise.

Figure (4)



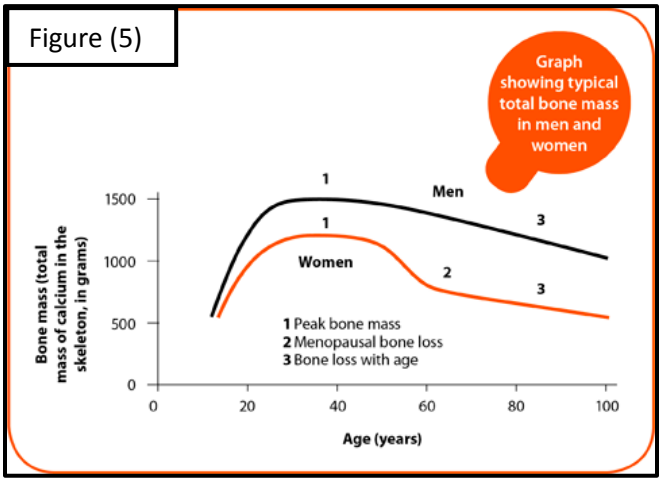
***Bone mass in men and women

Figure (5)

Why do women have smaller bone mass compared to men?

Because **androgens** of the male affect the accumulation of organic matrix -in addition to Ca^{+2} - in the bone in a positive way.

Figure (5)



***Few notes

- Homeostasis of Ca^{+2}, phosphate (PO_4^{-3}), Mg^{+2}, is essential for health and life.
- A complex system acts to maintain normal healthy concentrations of these minerals in the ECF and the whole body in the face of environmental and internal changes.
- The major elements in this system are:
  - PTH
  - Vitamin D
  - Calcitonin
  - Other hormones (like; Growth Hormone, Insulin, and Prolactin)
- The GIT, kidneys, skeleton, skin, and the liver are all involved in the homeostasis of the previously mentioned three minerals.

❖ Vitamin D

I. About vitamin D,

Vitamin D is responsible for mineralization of bone.
There are three derivatives of vitamin D,

- 25 (OH)-D
- 24, 25 $(OH)_2$-D
- 1, 25 $(OH)_2$ –D
- ➔ All of them can act, but the most potent is (1, 25), followed by (24, 25), and (25) comes at last.

25 (OH)-D is processed in the liver and then transferred to the kidney to produce 1, 25$(OH)_2$-D. If the body does not need too much vitamin D, 24,25 $(OH)_2$-D will be produced instead.

Note: we said last time that vitamin D is stored in lipids. Lipids in the abdomen do not release vitamin D easily. Therefore, obese individuals with high content of lipids in the abdomen are exposed to many problems including heart diseases, high blood pressure, high cholesterol, and other problems.

II. Actions (or effects) of vitamin D *(figure (6))*

On the bone: it promotes PTH action
On the intestines: it increases the absorption of calcium and phosphate.
On the kidneys: it increases the reabsorption of calcium and phosphate.

Final effects:

1) Vitamin D **increases Ca^{+2}** concentration in plasma.
2) Vitamin D **increases phosphate** concentration in plasma, (through intestines and kidneys).

What is the difference between the action of PTH and vitamin D?
PTH decreases plasma phosphate, while vitamin D increases it. *(Refer to the table in page 2).*

Since both, PTH and vitamin D, increase Ca^{+2} concentration in plasma, what would be the type of hormonal interaction?
Synergism

Note: We can say that vitamin D is responsible for mineralization of bone, and PTH is responsible for other uses that need Ca^{+2} in the body.

Figure (6)

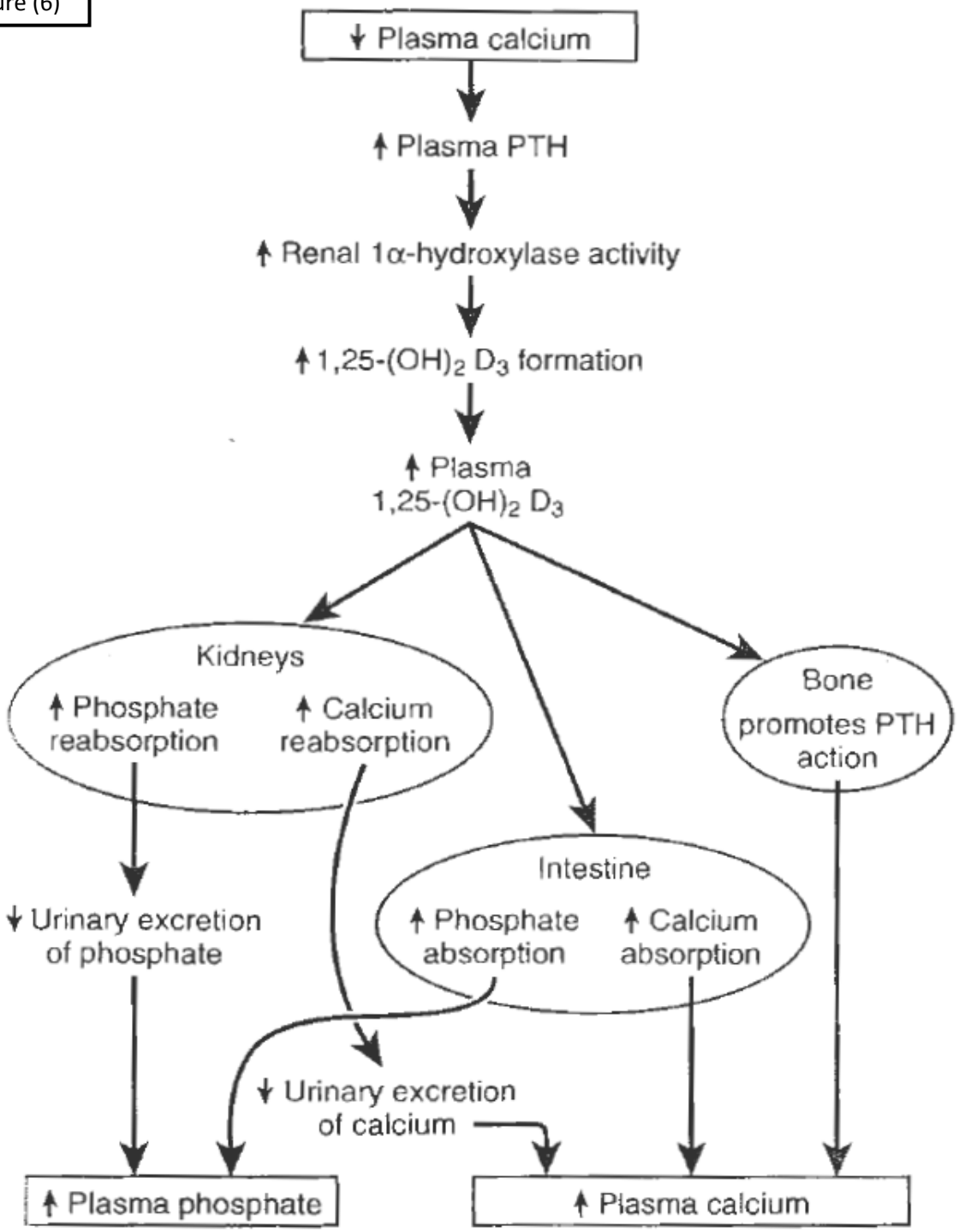


FIGURE 36.9 Effects of 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] on calcium and phosphate metabolism.

III. Regulation of 1, 25 $(OH)_2$-D

Figure (7)

- As we said before, 25(OH)-D is processed in the liver and then transferred to the kidney where 1,25$(OH)_2$-D can be produced.
- 1, 25 $(OH)_2$-D works mainly on the intestine (notice the thick arrow) as well as the kidneys and bones.
- 1, 25 $(OH)_2$-D also gets transferred to: mammary glands, placenta, skin, and Avian shell glands.

- The glands that affect the production of 1,25$(OH)_2$-D (through affecting the 1-alpha hydroxylase enzyme in the kidneys) are:
  - **P**ituitary → through Prolactin (PRL) and Growth Hormone (GH)
  - **P**ancreas → through Insulin
  - **P**arathyroids → through PTH

- Notice that low Ca^{+2} and low phosphate also stimulate the production of 1,25 $(OH)_2$-D.
- From the previous underlined factors, two are considered as the major two factors influencing the production of 1,25 $(OH)_2$-D :
  Low phosphate & PTH

Figure (7)

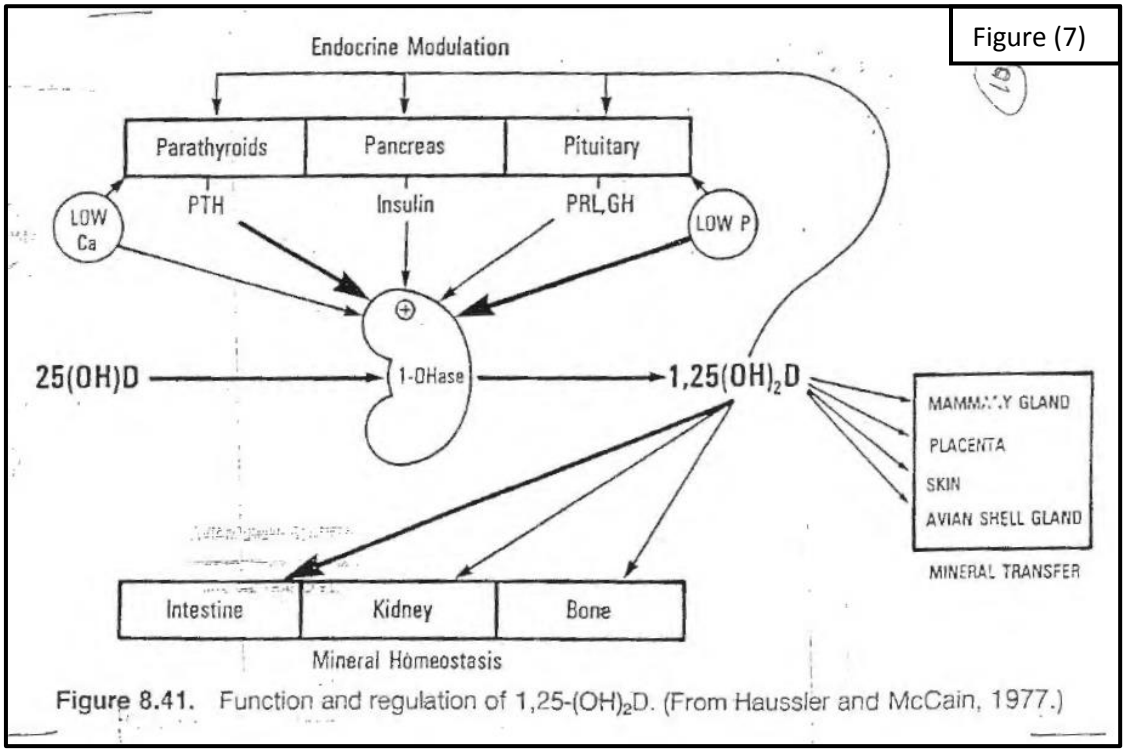


Figure 8.41. Function and regulation of 1,25-$(OH)_2$D. (From Haussler and McCain, 1977.)

❖ Calcitonin

I. About Calcitonin:

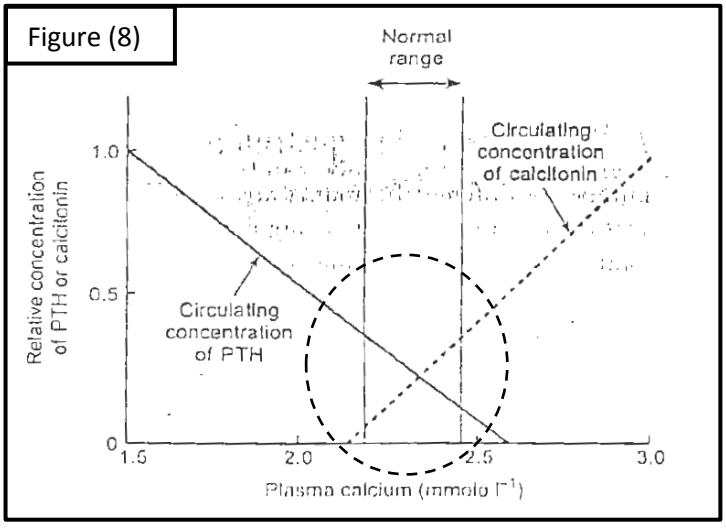
- Calcitonin is a straight-chain peptide of 32 amino acids. It has a molecular weight of 3400.
- The biologically active core of the molecule probably resides in its central region (in the middle).
- It is secreted by the **thyroid parafollicular cells** known as "C" cells.

II. Functions:

- Calcitonin (CT) decreases plasma calcium levels by antagonizing the actions of PTH on bone.
- Calcitonin is also present in nervous tissue, where it may function as neuromodulator (neurotransmitter).
- The major stimulus to CT secretion is a rise in plasma calcium concentration (opposite to the major stimulus to PTH secretion which is a fall in plasma calcium concentration).
- The hypocalcemic action of CT is caused by inhibition of both, osteocytic osteolysis & osteoclastic bone resorption particularly when these are stimulated by PTH. In other words, CT inhibits the release of Ca^{+2} from bones to plasma.

- PTH and Calcitonin are considered as an example on antagonism.
  - *Figure (8)*
  - PTH increases plasma Calcium while calcitonin decreases it.
  - When Ca^{+2} level increases (look at the X axis in the figure), PTH level decreases while calcitonin level rises, and vice versa.

Figure (8)



- The importance of CT in humans is controversial. CT deficiency does not lead to hypercalcemia, and CT hypersecretion does not produce hypocalcemia. It may be that abnormal CT secretion is easily compensated for by adjustment in PTH and vitamin D levels.

- Calcitonin is degraded within the liver and kidney (like other hormones), after half-life of 30-60 minutes.

III. The actions of calcitonin on calcium and phosphate metabolism

Figure (9)

On the bone: CT inhibits bone resorption (via inhibition of osteoclast activity), and accordingly, calcium release from the bone is decreased. (Opposite to the effect of PTH)
On the kidneys: CT decreases calcium and phosphate reabsorption, resulting in an increase in the urinary excretion of both, Ca^{+2} and phosphate.

Final effects:

- **Decrease in plasma Ca^{+2}** concentration (opposite to PTH)
- **Decrease in plasma phosphate** concentration (similar to PTH)

Figure (9)

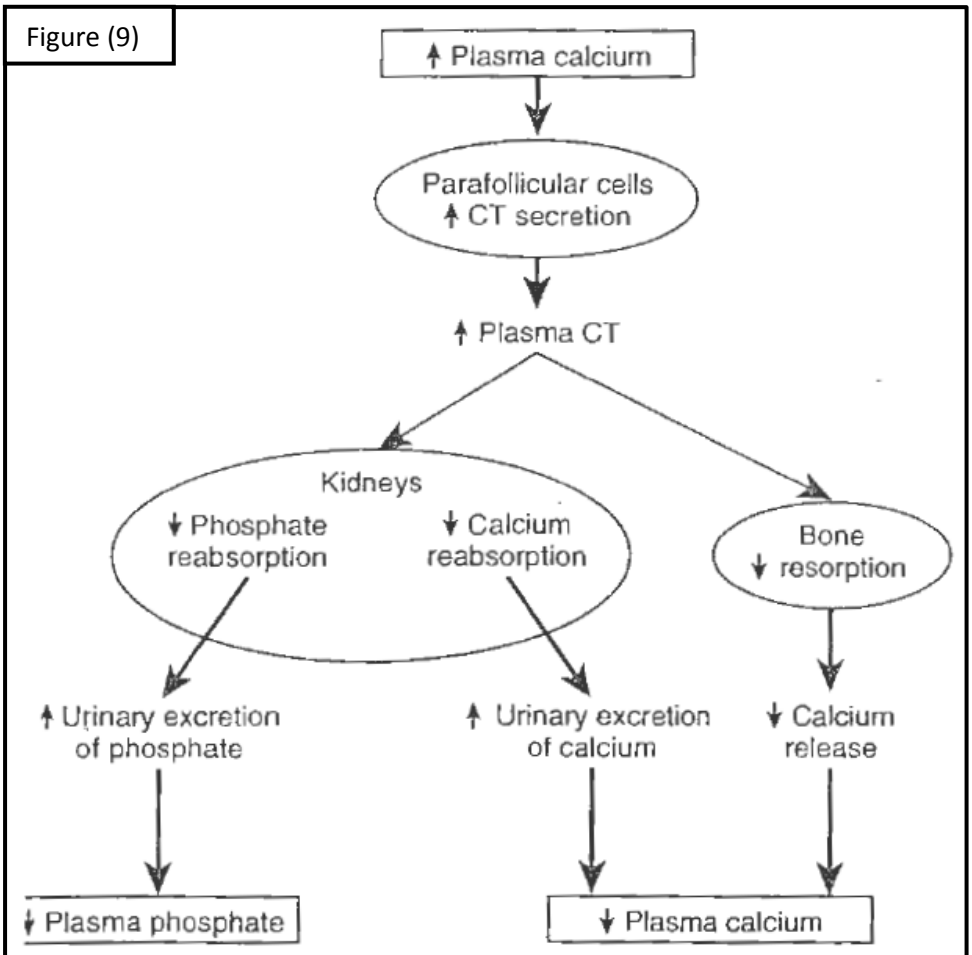


FIGURE 36.8 Effects of calcitonin (CT) on calcium and phosphate metabolism.

❖ Some abnormalities of calcium homeostasis

I. Rickets (الكُساح)

- We said earlier that vitamin D in adults is stored in lipids and it would be sufficient for many months (more than 6 months), but children do not have such store or supplement.

  The following two paragraphs are from Guyton Textbook, page 968. (they were written since what Dr. Saleem mentioned about Rickets was not sufficient, nor clear).

- Rickets occurs mainly in children. It results from calcium or phosphate deficiency in the extracellular fluid, usually caused by **lack of vitamin D**. If the child is adequately exposed to sunlight, the 7- dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier.
- Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementation in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and available for use during the early winter months. In addition, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

Note: poor diet and inadequate skin exposure to sunlight are the two main contributors to the development of rickets in children. Healthy diet and adequate exposure to sunlight are important as two different sources of vitamin D for the human being. (Each one alone is not sufficient).

II. Osteomalacia

- Osteomalacia is rickets in adults, and is frequently called "adult rickets".
- Normal adults rarely have a serious dietary deficiency of vitamin D or calcium, because large quantities of calcium are not needed for bone growth as in children. However, a **serious deficiency of both, vitamin D and calcium**, occasionally occurs as a result of steatorrhea (failure to absorb fat), for vitamin D is fat soluble, and calcium tends to form insoluble soaps with fat; consequently, in steatorrhea both vitamin D and calcium tend to pass into the feces (due to chronic and severe diarrhea usually occuring in these adults).
- Under these conditions, an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, though this almost never proceeds to the stage of tetany- but very often, is a cause of severe bone disability.

***Causes of Osteomalacia and Rickets**

TABLE 36.3 Causes of Osteomalacia and Rickets

Inadequate availability of vitamin D	Dietary deficiency or lack of exposure to sunlight
	Fat-soluble vitamin malabsorption
Defects in metabolic activation of vitamin D	25-Hydroxylation (liver)
	Liver disease
	Certain anticonvulsants, such as phenobarbital
	1-Hydroxylation (kidney)
	Renal failure
	Hypoparathyroidism
Impaired action of 1,25-dihydroxycholecalciferol on target tissues	Certain anticonvulsants
	1,25-Dihydroxycholecalciferol receptor defects
	Uremia

III. Osteoporosis – decreased bone matrix

- Osteoporosis is the most common of all bone diseases in adults, especially in old age.
- It is different from osteomalacia and rickets because it results from **diminished organic bone matrix** *(remember, we said earlier that androgens affect this activity)* rather than from poor bone calcification.
- Usually in osteoporosis, the osteoblastic activity in the bone is usually less than normal, and consequently the rate of bone osteoid deposition is depressed. However, occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.
- Osteoporosis is most common in **old females**, but it can occur in young females because as you know, some females experience very early menopause (at the age of 38 or 40). These females can develop osteoporosis as well as cardiac problems.

Causes of osteoporosis

1. Lack of physical stress on the bones because of inactivity. Why? Because inactivity inhibits the mineralization of bone as well as Ca^{+2} deposition in bones.
2. Malnutrition (poor diet) to the extent that sufficient protein matrix cannot be formed.
3. Lack of vitamin C, which is necessary for the secretion of intercellular substances by all cells, including formation of osteoid by the osteoblasts. *All vitamins are important but vitamin C is the most important one.*

4. Postmenopausal lack of estrogen secretion because estrogens decrease the number and activity of osteoclasts.
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's syndrome, because massive quantities of glucocorticoids secreted in this disease cause decreased deposition of protein.
7. Acromegaly, possibly because of lack of sex hormones, excess of adrenocortical hormones, and often lack of insulin because of the diabetogenic effect of growth hormone.

→ to conclude:

The major risk factor for osteoporosis is the **decline of estrogen level in aging women**. Other endocrine disorders like; hyperthyrodism, hyperparathyroidism, Cushing's disease (hyper cortisol) can also be responsible for the development of osteoporosis.

Prevention and treatment of osteoporosis

- Strategies to prevent the development of osteoporosis begin in the premenopausal years in females.
  High Ca^{+2} intake and consistant program of weight lifting exercises are widely recommended for both, males and females.

- **Pharmacological agents** are now available for preventing or at least retarding the development of osteoporosis or for treating the disease once it has become established.
- These pharmachological agents are classified into two groups:
  - **Anti-resorptive drugs**
  - **Agents that are able to stimulate bone formation**
- Among the former group (anti-resorptive drugs), **estrogen** is by far the most widely used therapy. It is most effective when started at the onset of menopause. (**Note**: it's even better to start it 2-3 years before menopause. In females there are signs for menopause that make women know if menopause will occur soon or not).
- Calcitonin used to be given to women who cannot or unwilling to take estrogen, but it is no longer used because whether calcitonin is effective or not is still controversial. Probably, it is ineffective –according to Dr. Saleem.
- Another class of drugs, **the bisphosphanates**, is becoming popular. These drugs are powerful inhibitors of bone resorption, but some of the first agents of this class have also been found to impair mineralization.

Notes mentioned by Dr. Saleem at the end of the lecture

- The best way for treatment of osteoporosis in females → **Estrogen**.
  The second best way → Vitamin D (with Ca^{+2}).
  (Males cannot use estrogens, and even if they do, the estrogen they take will be converted in the body into testosterone, and the other way around applies in females).
- About cortisol: some athletes use cortisol to increase muscular activity, this is very dangerous because many of them become homosexual (steroids are related to homosexuality).

Final note: In case you did not understand certain points, kindly refer to chapter 79 in Guyton and Hall Textbook for Medical Physiology, more specifically, pages 960-969 in the 12th edition.

I apologize for any mistake I may have made.

Wish you all best of luck **:D**