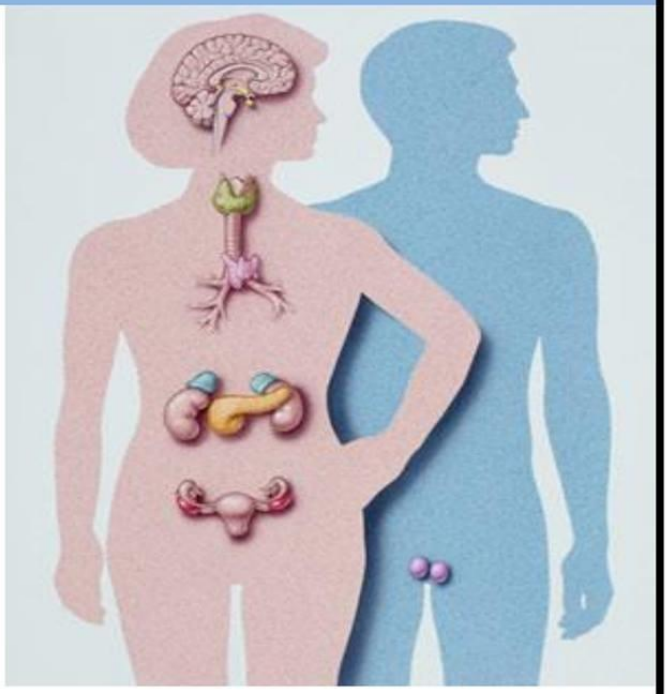
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



- ☐ Anatomy/Embryology/Histology
- ☐ Biochemistry
- ☑ Physiology
- ☐ Pharmacology
- ☐ Pathology
- ☐ PBL

☐ Slide ☒ Sheet ☐ Handout ☐ Other

Lecture #: 6

Date:

Dr's Name: Dr. Salim Khresha

Price:

Written by: Adnan Najada

Designed by: Zakaria W. Shkoukani

PARATHYROID GLANDS (CONTINUED..)

Calcium Regulation

Starting off with some physiological functions of calcium:

- Required for the maintenance of normal sodium permeability in nerves
- Involved in triggering the release of acetylcholine from nerve endings at the neuromuscular junction
- Necessary in excitation-contraction coupling in muscle cells
- Serves as an intracellular signal for some hormones(2^{nd} Msn)
- Required by some enzymes for normal activity
- Required for blood clotting to occur normally
- Required for protein secretion
- Constituent of bone

About **99%** of our body's calcium is deposited in the bones and teeth. The remaining 1% is present in body fluids, almost equally divided between **diffusible** and **non-diffusible** calcium. The non-diffusible calcium is bound to blood proteins, chiefly to **albumin**, although a small amount is bound by the **globulins** in the blood.

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

Our focus is on the ionized Ca^{2+} concentration for it is the indicator which PTH secretion depends on, not the protein-bound Ca^{2+} concentration, though in normal conditions both concentrations are almost equal (almost 1mmol/L as seen in table 21-1 in the previous page.).
When aren't they "almost" equal?

- When there are disturbances in plasma protein levels. (e.g. hypoalbuminemia)
- When there are disturbances in blood pH. (e.g. **alkalemia** [alkalosis] causes **hypocalcaemia**, and **acidemia** [acidosis] causes **hypercalcaemia**)

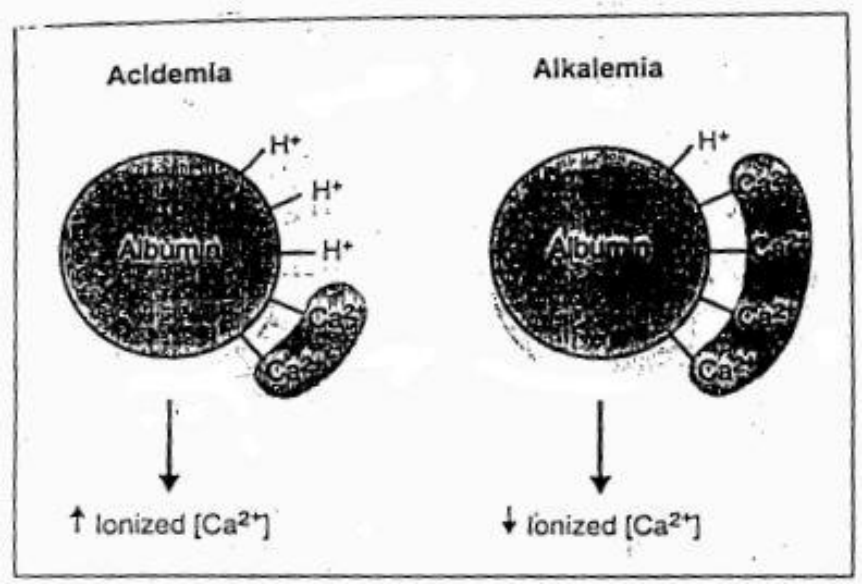


FIGURE 9–32. Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

Many factors are involved in calcium regulation some of which include 3 hormones; ***PTH***, ***Calcitonin*** and ***Vitamin D*** (its primary active form 1,25-$(OH)_2$-D [calcitriol] is considered a calcium-regulating hormone since it is synthesized in the body).

PTH was discussed in the previous lecture so let us discuss the other two.

Vitamin D:

It is the second major regulator of Ca^{2+} and phosphate metabolism. The role of vitamin D is to promote mineralization of new bone, and its actions are coordinated to increase both Ca^{2+} and phosphate concentrations in plasma (by increasing the absorption of Ca and Phosphate from the GI tract mainly, same effect on the Kidney and on the bones it activates the osteoclats to work on them) so that these elements can be deposited in new bone mineral.

Vitamin D can be obtained either from UV light/skin and here it is called ***D_3*** (Cholecalciferol), or from dietary sources and here it is called ***D_2*** (Ergocalciferol). Both of these prohormones are the same with only slight differences in their structure, still they undergo identical processing that converts them into the active form.

D_2 and D_3 get concentrated in the **liver** where they are converted into ***25-(OH)-D*** (vitamin D that is hydroxylated on carbon number 25) and then this molecule is transported to the **kidney** where it is converted to either **24,25-$(OH)_2$-D** by **24-hydroxylase** or **1,25-$(OH)_2$-D** by **1α-hydroxylase**.

How does the kidney know what it should convert 25-(OH)-D into?

If we have Vitamin D deficiency, Ca^{2+} deficiency, phosphate deficiency, or PTH stimulation, then the enzyme 1α-hydroxylase is activated and 1,25-$(OH)_2$-D is formed. Why? Because this molecule can:

- Increase Ca^{2+} and phosphate absorption from the intestines
- Increase their reabsorption from the kidneys and decrease their excretion
- Promote PTH action
- Overall result: increase in blood Ca^{2+} levels

And when we have excess Ca^{2+}, excess phosphate, or excess 1,25-$(OH)_2$-D, the enzyme 24-hydroxylase is activated and 24,25-$(OH)_2$-D is formed. Why? Because this molecule can serve to dispose of excess vitamin D.

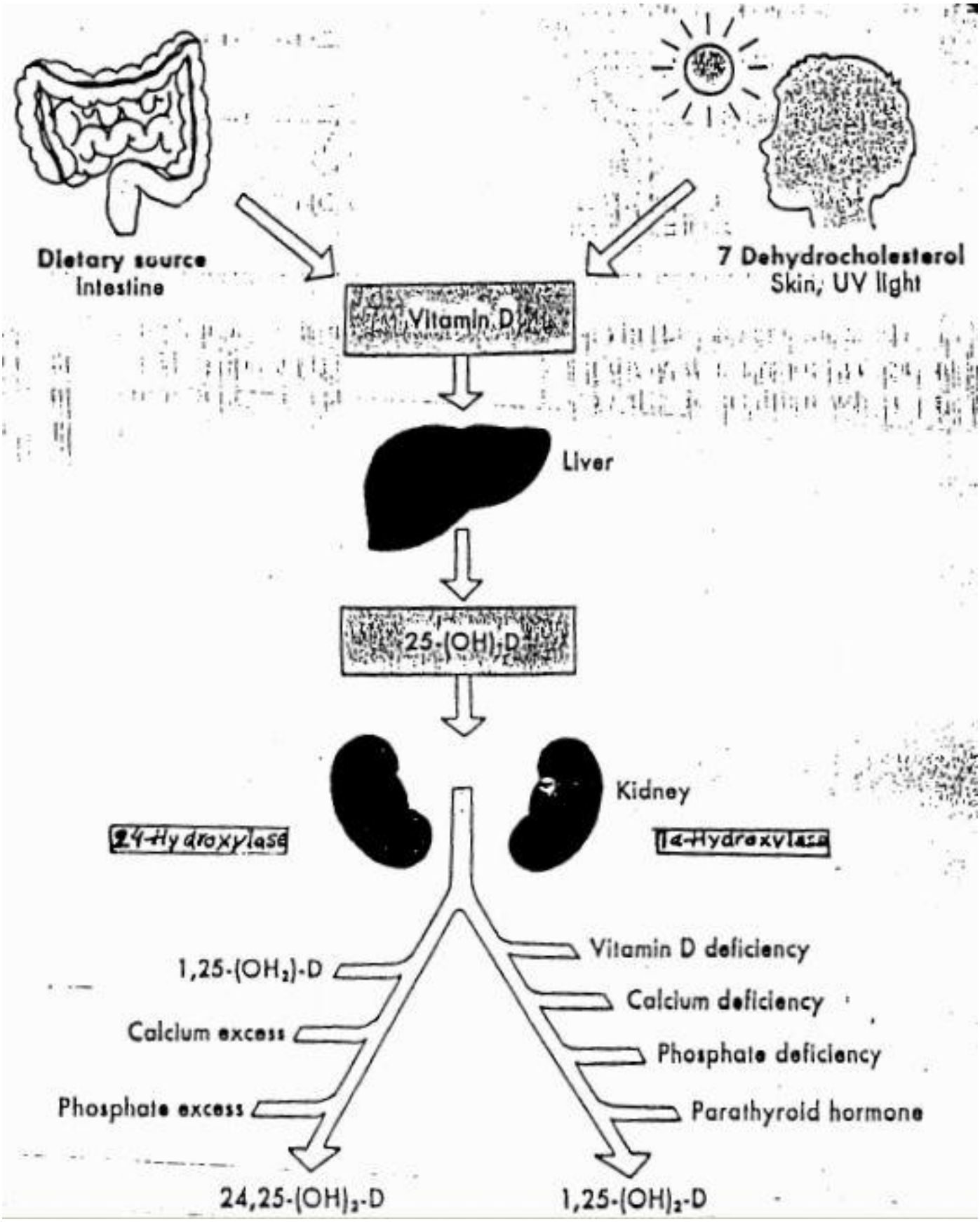
Notes (from the slides):

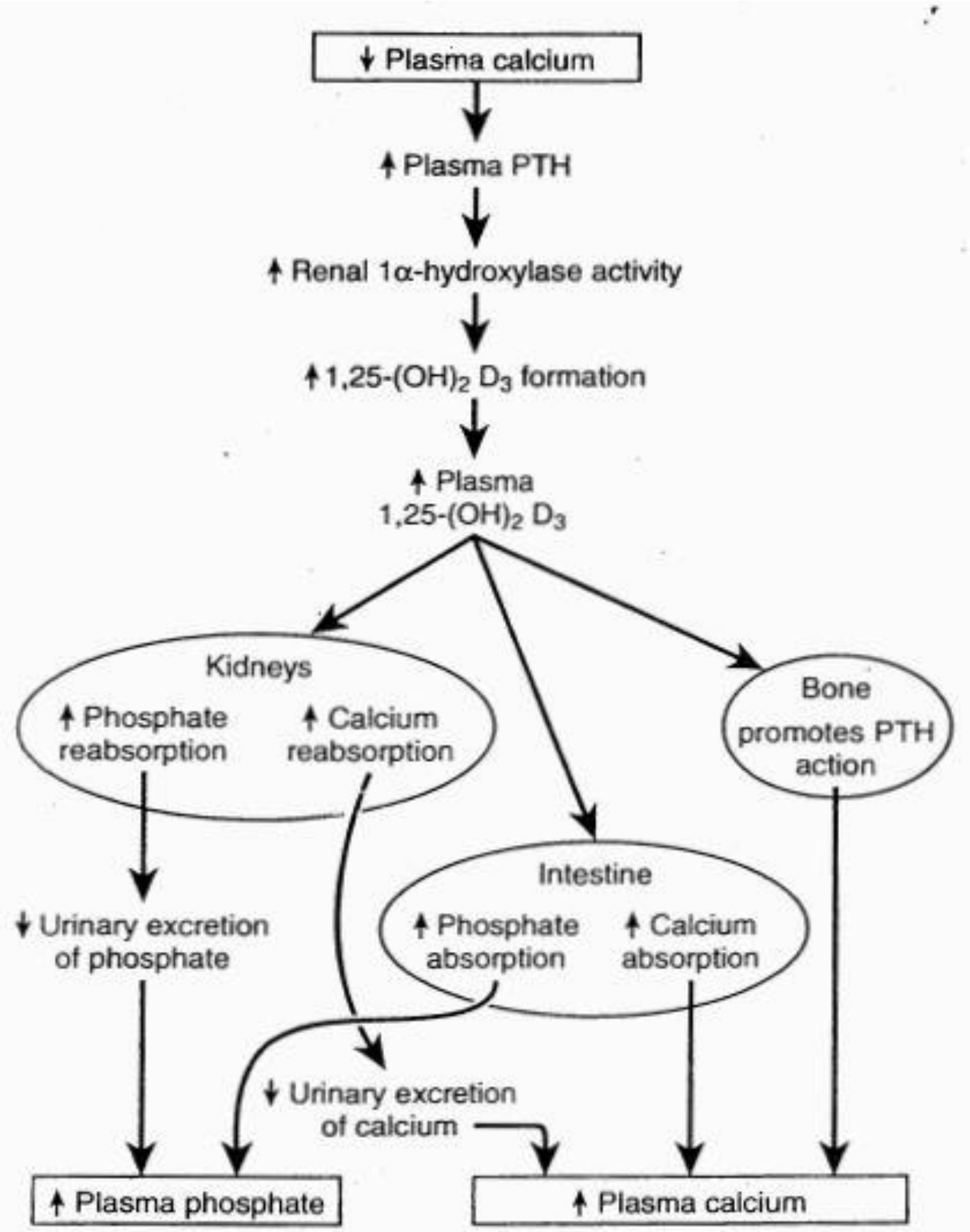
- 24,25-$(OH)_2$-D is $1/20^{th}$ as potent as 1,25-$(OH)_2$-D
- 1,25-$(OH)_2$-D has the lowest plasma concentration and the shortest half life. (out of the 3 molecules)
- 25-(OH)-D has the highest plasma concentration. (out of the 3 molecules)

TABLE 51-2. Vitamin D metabolism in humans

	Plasma concentration (μg/L)	*Plasma half-life (days)*	*Estimated production rate (μg/day)*
1.25-$(OH)_2$-D_3	0.03	1 to 3	1
24,25-$(OH)_2$-D_3	2	15 to 40	1
25-OH-D_3	20	5 to 20	10

The next three pages show figures from the slides to help make things clearer.


Dietary source
Intestine
7 Dehydrocholesterol
Skin, UV light
Vitamin D
Liver
25-(OH)-D
Kidney
24-Hydroxylase
1α-Hydroxylase
1,25-(OH2)-D
Calcium excess
Phosphate excess
Vitamin D deficiency
Calcium deficiency
Phosphate deficiency
Parathyroid hormone
24,25-(OH)2-D
1,25-(OH)2-D


↓ Plasma calcium
↑ Plasma PTH
↑ Renal 1α-hydroxylase activity
↑ 1,25-(OH)2 D3 formation
↑ Plasma 1,25-(OH)2 D3
Kidneys
↑ Phosphate reabsorption
↑ Calcium reabsorption
Bone
promotes PTH action
Intestine
↑ Phosphate absorption
↑ Calcium absorption
↓ Urinary excretion of phosphate
↓ Urinary excretion of calcium
↑ Plasma phosphate
↑ Plasma calcium

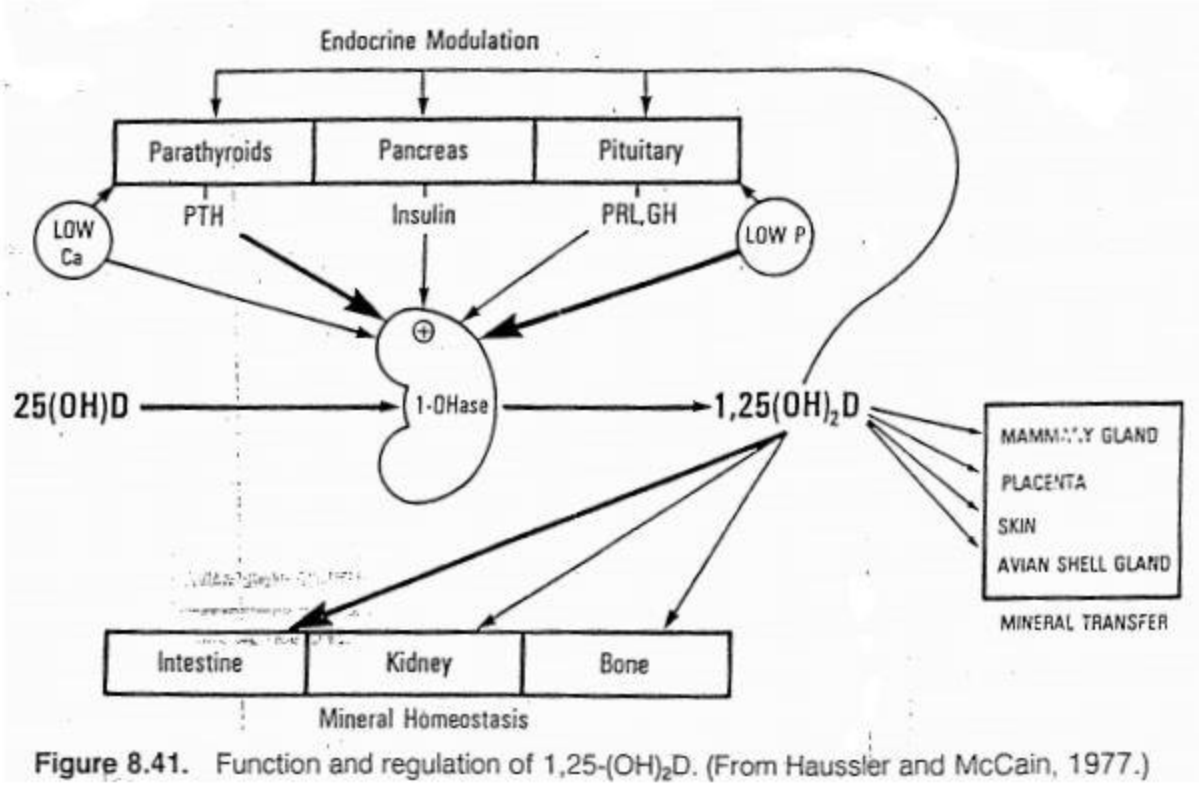


Figure 8.41. Function and regulation of 1,25-$(OH)_2$D. (From Haussler and McCain, 1977.)

About this last figure:

- Minor factors such as Insulin, prolactin, and GH can also stimulate the enzyme 1α-hydroxylase, in order to form 1,25-$(OH)_2$-D, in addition to the major ones which are low phosphate, low Ca^{2+} , and stimulation by PTH.
- 1,25-$(OH)_2$-D itself can stimulate insulin, prolactin, and GH secretion which in turn stimulates its own synthesis.
- 1,25-$(OH)_2$-D also reaches the following sites: Mammary gland, placenta, skin, and avian shell gland. (mineral transfer)

Clinical application: Rickets disease in children and **Osteomalacia** (adult rickets) in adults (both are the same). Why does it occur? Three main reasons:

- Vitamin D deficiency. Can be due to:
  - ✓ Dietary deficiency
  - ✓ Lack of exposure to sunlight(Relatively unimportant)
  - ✓ Failure to synthesize cholecalciferol (D_3) in the skin (this occurs in dark-skinned people in a temperature climate
  - ✓ Fat-soluble vitamin malabsorption
- Defects in metabolic activation of vitamin D. Can be due to:
  - ✓ 25^{th} carbon hydroxylation failure which occurs in the liver (chronic liver disease; hepatic osteodystrophy)
  - ✓ Rapid metabolism of cholecalciferol and its active metabolites when hepatic enzymes are induced, this is seen in patients taking anticonvulsant (drugs for seizures)
  - ✓ 1^{st} carbon hydroxylation failure which occurs in the kidney (renal failure; renal osteodystrophy)
  - ✓ Hypoparathyroidism (low PTH)
- Impaired action of 1,25-$(OH)_2$-D in target tissues. Can be due to:
  - ✓ Certain anticonvulsants
  - ✓ Receptor defects
  - ✓ Uremia (raised blood Urea levels)

Rickets occur mainly in children who have vitamin D deficiency consequently leading to calcium and phosphate deficiency. Proper exposure to sunlight serves to prevent rickets and that is why this disease tends to occur especially in the **spring** months because vitamin D formed during the preceding summer is stored in the liver and is still available for use during the early winter months.

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 vitamin D and calcium tend to pass into the feces. Under these conditions an adult will have such poor calcium and phosphate absorption that adult rickets (Osteomalacia) can occur, though this almost never proceeds to the stage of tetany but very often is a cause of severe bone disability.

Note: calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

Calcitonin:

It is basically what counteracts PTH. Here is what you need to know:

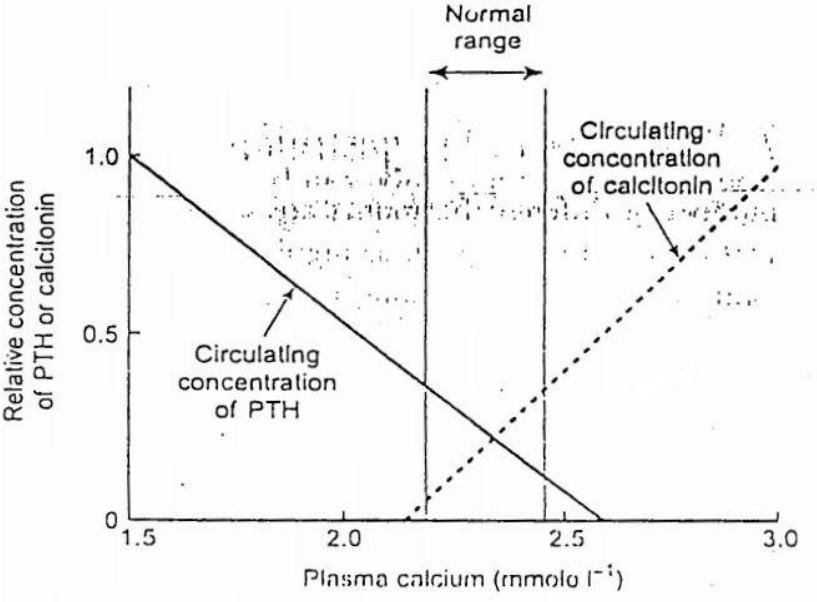
- A straight chain peptide of 32 amino acids, has a molecular weight of 3400
- The biologically active core of the molecule probably resides in its central region
- Calcitonin is secreted by thyroid parafollicular cells known as "C" cells.

- Calcitonin is also present in nervous tissue, where it may function as a neuromodulator.
- The major stimulus to CT secretion is a rise in plasma calcium concentration.

- Calcitonin, (CT), decreases plasma calcium levels by antagonizing the actions of PTH on bone and on the kidney decrease Ca and phosphate reabsorption.
- The hypocalcemic action is caused by inhibition of both osteocytic osteolysis and osteoclastic bone resorption particularly when these are stimulated by PTH.
- **However**, with respect to phosphate, it has the **same** net effect as PTH; that is; CT **decreases** plasma phosphate concentration and increases urinary phosphate excretion slightly.
- CT deficiency **does not** lead to hypercalcaemia & CT hyper secretion **does not** produce hypocalcaemia. It may be that abnormal CT secretion is easily compensated for by adjustment in PTH and vitamin D levels.
- Lastly, it is degraded within the liver and kidney, after half-life of 30-60 minutes.

This graph shows the relationship between plasma Ca^{2+} levels and the secretion of both PTH and CT.

The next page has a figure showing how CT works.



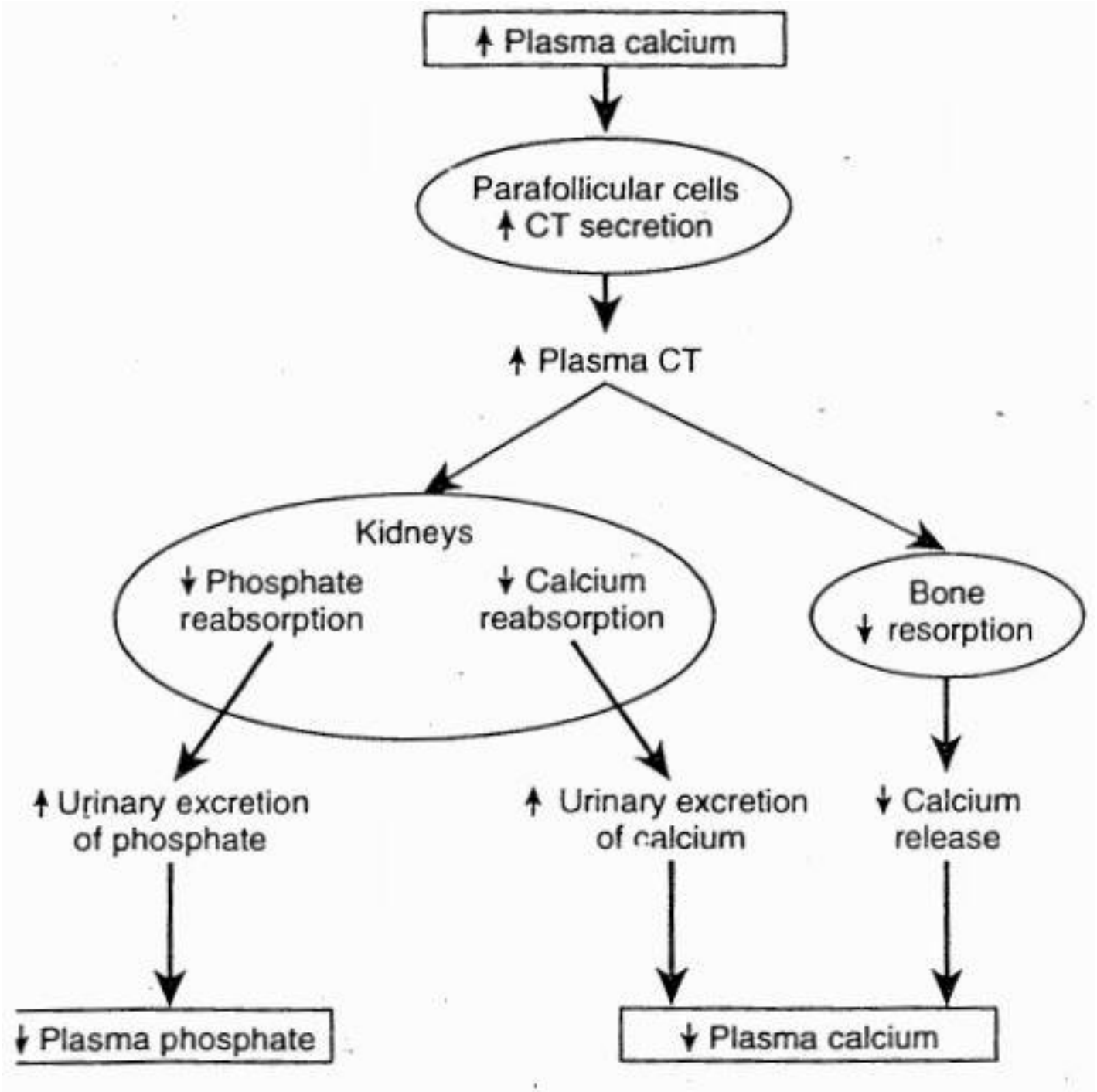


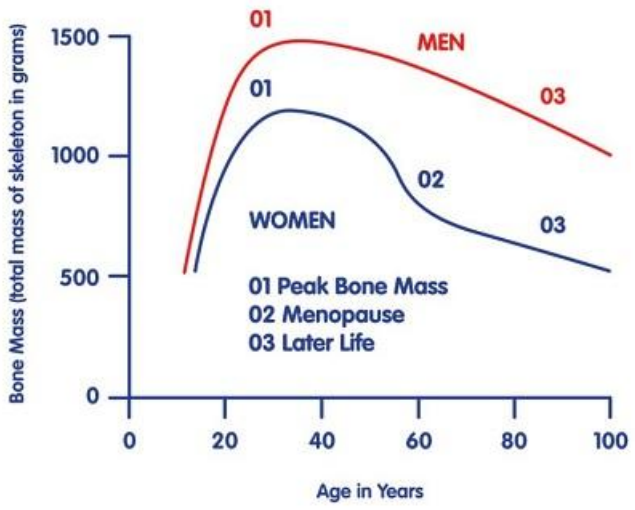
FIGURE 36.8 Effects of calcitonin (CT) on calcium and phosphate metabolism.

A quick summary about Phosphate regulation: its levels are increased by vitamin D and decreased by PTH and CT. Physiological functions include:

- Functions as part of the intracellular buffer system.
- Important constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins.
- Constituent of bone. (about **85%** of our body's phosphate is in the bones)

Note: factors affecting calcium metabolism (other than PTH, CT, and vitamin D) include:

- Glucocorticoids
- Growth hormone and somatomedins
- Thyroid hormones
- Estrogens
- Insulin
- IGF-1
- Epidermal growth factor
- Fibroblast growth factor
- Platelet-derived growth factor
- Osteoclasts activating factor



Graph shows typical changes in bone mass with age.
Source: National Osteoperosis Society

Note: bone mass in males and females start to differ only after puberty, meaning that in childhood it is the same in both genders.

Note: about 9% of our body's water is in the bones.

Osteoporosis

Most common of all bone diseases especially in the elderly, it is different from rickets and Osteomalacia for it results from diminished organic matrix rather than abnormal bone calcification. Usually the osteoblastic activity in the bone is less than normal, and consequently the rate of deposition is depressed. But occasionally, the cause of the diminished bone is excess osteoclastic activity.

Causes include:

- lack of physical activity
- diabetes mellitus type II
- malnutrition
- lack of vitamin C
- lack of estrogen (postmenopausal women)
- old age
- Diseases like Cushing syndrome and Acromegaly.

How to prevent the development of osteoporosis ?
A) by physical exercise and intake of Ca
B) Medications, they are divided into two categories :
1: Drugs against the reabsorption of bones
2: Drugs that induce bone formation.

Estrogen supplements is the most widely used in fighting osteoporosis, it's most effective when the female patient start taking them from the onset of Menopause.
Now for those how are unable/afraid of taking estrogen
they can take Calcitonin, but they are less effective and Expensive drugs.
Many women nowadays are starting to take Vit(D) combined with calcium from the onset of Menopause.
The Doctor recommends Vit(D) with Estrogen in low doses and under medical supervision.