PHYSIOLOGY

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Parathyroid glands

- We have more than one gland, usually 4 small glands that are located behind the thyroid gland. The weight of each one ranges between 20-50g in an adult.
- We have two types of cells in the parathyroid glands:
  1. **Chief cells:** cells that produce the parathyroid hormone (functional hormone).
  2. **Oxyphil cells:** which have no known function up till now, they may play a role in metabolism.
- There are usually 4 glands but sometimes abnormally we have more than 4 glands that are sometimes not present behind the thyroid gland.
- The functional hormone is parathyroid hormone (PTH). There is another element (substance) that is involved which is called parathyroid related protein. Its function is similar to that of PTH.
- The parathyroid glands develop at about 5-14 weeks of gestation (variable development/ wide range).

Parathyroid Hormone (PTH)

- PTH produces two types of second messengers
  1. cAMP
  2. IP3 and DAG

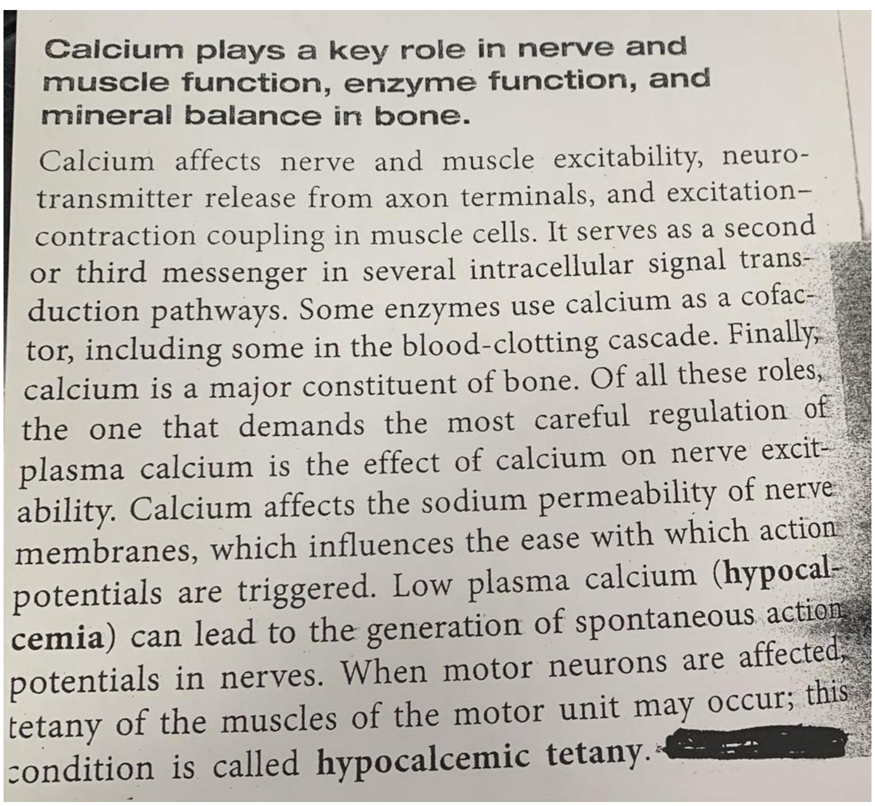
and its function is to increase the concentration of calcium in the blood.

- PTH is a **single chain protein** hormone (its receptors are found on the cell membrane).
- Its biological activity resides in the first 34 amino acids, which means that if we cut the protein in half, the activity resides in the first half.
- PTH is found free in the plasma with a half life of 25 minutes.
- PTH is essential because it regulates calcium levels. (Calcium is essential for life, when calcium falls in the plasma, neuromuscular excitability increases, tetany and death occur).
- The dominant regulator of PTH is calcium level. Calcium also regulates the number and size of the parathyroid cells. Hypomagnesimea

stimulates PTH secretion like calcium but is less potent. It arises in an increase in plasma phosphate concentration indirectly which causes a transient increase in PTH secretion.

- ❖ The most potent of vitamin D derivatives is 1,25 and it directly reduces PTH secretion.
- ❖ PTH functions on the bone, the kidney, and the intestines:
  - ✓ **Bone:** increases the resorption of bone and therefore releases calcium in the plasma.
  - ✓ **Kidney:** produces vitamin D 1,25 which increases calcium reabsorption and decreases phosphate reabsorption from the kidney tubules. As a result, it normalizes plasma phosphate and increases plasma calcium.
  - ✓ **Intestine:** increases calcium absorption.
  - ❖ Deficiency of PTH:

    Reduces plasma calcium levels (normal level of calcium is 10-11 mg/ 100 mL of plasma), where sometimes it can reach 5-6 mg/ 100 mL of plasma. When the concentration of calcium is this low, it causes **muscle tetany** which causes death. Why???



Calcium plays a key role in nerve and muscle function, enzyme function, and mineral balance in bone.

Calcium affects nerve and muscle excitability, neurotransmitter release from axon terminals, and excitation–contraction coupling in muscle cells. It serves as a second or third messenger in several intracellular signal transduction pathways. Some enzymes use calcium as a cofactor, including some in the blood-clotting cascade. Finally, calcium is a major constituent of bone. Of all these roles, the one that demands the most careful regulation of plasma calcium is the effect of calcium on nerve excitability. Calcium affects the sodium permeability of nerve membranes, which influences the ease with which action potentials are triggered. Low plasma calcium (**hypocalcemia**) can lead to the generation of spontaneous action potentials in nerves. When motor neurons are affected, tetany of the muscles of the motor unit may occur; this condition is called **hypocalcemic tetany**. [redacted]

When the concentration of calcium decreases, the sodium channels will not close properly so sodium will keep entering the cell which causes continuous tetanus.

- Overactivity increases the concentration of PTH, which therefore causes an increase in plasma calcium levels through absorption by the intestine, reabsorption by kidney, and increase in bone resorption (concentration sometimes reaches 16 mg/ mL of plasma).
- An increase in bone resorption causes a disease called **osteitis fibrosa cystica**, where there is release of calcium from the texture or structure of the bone. Usually, bone is released from around the structure of the bone (from the synovial fluid), but in this case the release of calcium is from within the structure of the bone and this causes softening of the bones which is called osteitis fibrosa cystica. This is not osteoporosis, the cause is different.

Vitamin D

- There is another regulator of calcium: **vitamin D**
  - Vitamin D is considered a vitamin and a hormone. It is concentrated in the liver, stored in adipose tissue, and released into the blood.
  - Deficiency causes failure of bone remineralization.
  - There are two types of vitamin D (**D_2, D_3**):
    1. Produced in the body
    2. Obtained from food
  - They are almost identical in function and structure. Vitamins D_2 and D_3 are essentially prohormones that undergo identical processing that converts them into molecules with identical qualitative and quantitative actions.
  - None of them is sufficient alone in a human being, **both are needed.**
  - Vitamin D enters the circulation from the skin or the intestines and is concentrated in the liver.
  - Vitamin D metabolism
    (shown in the picture next page)

poliomyelitis: شلل

rickets: كساح

Rickets is caused of vitamin D deficiency therefore calcium.

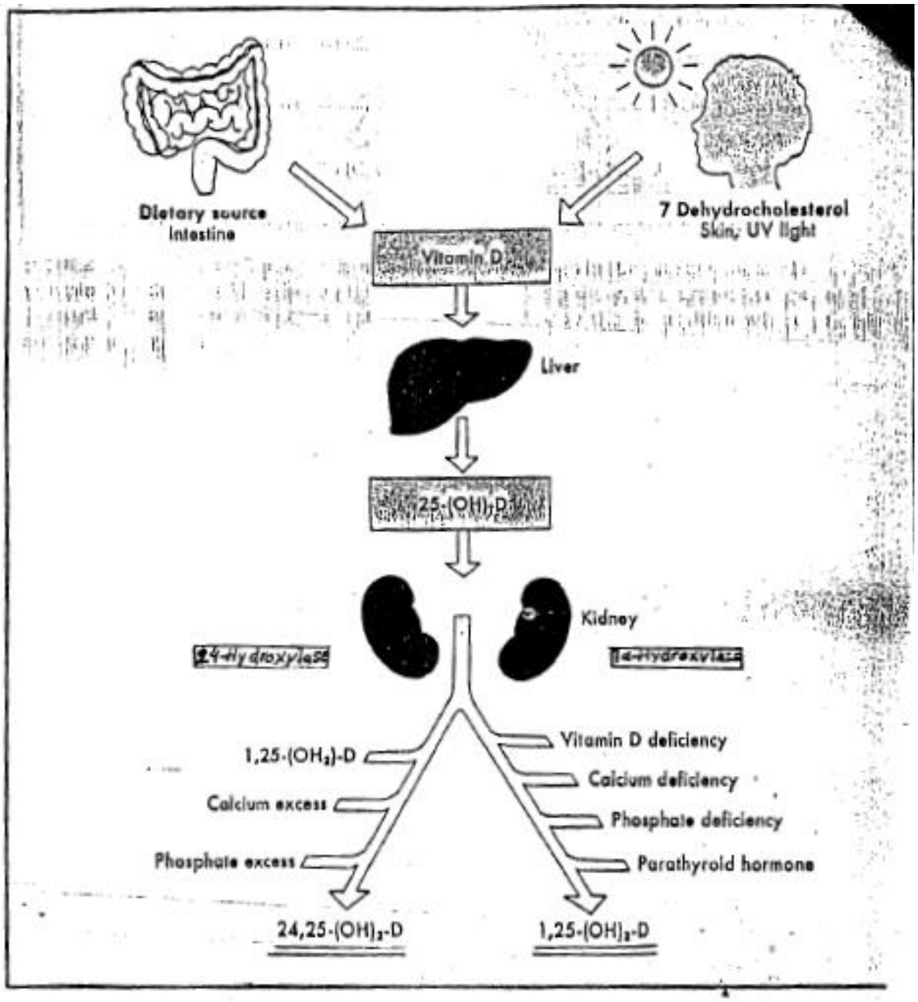


FIGURE 38-5 Vitamin D metabolism. Whether synthesized in the skin or absorbed from the d vitamin D undergoes 25 hydroxylation in the liver. In the kidney, it is further hydroxylated in 1 position when more biological activity is required or in the 24 position when less biol activity is required.

This diagram gives an idea about vitamin D3, major regulator of calcium.

Obtained from the **body under the effect of the sun** and from **food**.

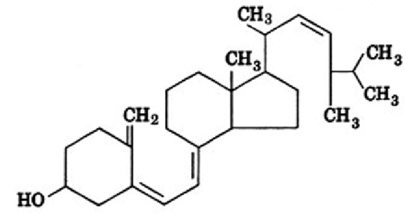
Cholycalciferol D3 and ergocalciferol D2.

D2 and D3 are concentrated in the liver, both produce the 25 derivative of vitamin D, then this 25 is transferred to the kidney. In the kidney when there is need, 1,25 is produced (most potent), when there is less need, 24,25 is produced. Both function in the body.

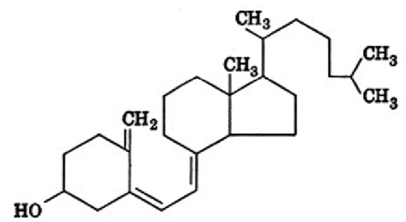
Most potent ⟶ least potent

1,25 > 24,25 > 25

Any one of these can stimulate the production of 1,25 by the action of the enzyme **hydroxylase**.



Vitamin D_2 (ergocalciferol)



Vitamin D_3 (cholecalciferol)

- Vitamin D structure:
  - ✓ Steroid/ lipid bound to protein
  - ✓ Circulates in the plasma
- Vitamin D3 is available from several natural sources including cod liver oil, eggs, and milk. (**The best source of vitamin D is fish**).
- Vitamin D3 is from the body while vitamin D2 is from food.
- Vitamin D2 is obtained from the diet, mostly vegetables.
- Most of the body stores of vitamin D are located in the body fat. The body's pool of vitamin D is large and only 1-2% of the body's vitamin D is turned over each day, therefore several years of low dietary intake is required before the indigenous pool is depleted and vitamin D deficiency occurs.
- In addition to vitamin D2 and D3 and their respective forms (1,25-24,25-25), 15 other metabolites of vitamin D have been identified in the plasma and the specific physiological function of these metabolites, if any, is not yet clear.
- The function of vitamin D
  on the **bone**: similar to the function of PTH
  on the **intestines**: increase in calcium and phosphate absorption
  on the **kidneys**: increase in calcium and phosphate reabsorption
  The result is an increase in plasma calcium level as well as phosphate level. We conclude that vitamin D is **responsible for mineralization of the bone** because mineralization needs both calcium and phosphate.
- What is the relationship between PTH and vitamin D?
  Synergism; both function together, none of them is sufficient alone. Even if vitamin D increases phosphate level.
- Production of the 1,25 form of vitamin D could be modulated by the endocrine system when there is a decrease in calcium and phosphate levels. This form of vitamin D will then act on the bone, intestines, and kidneys as shown in the picture below.

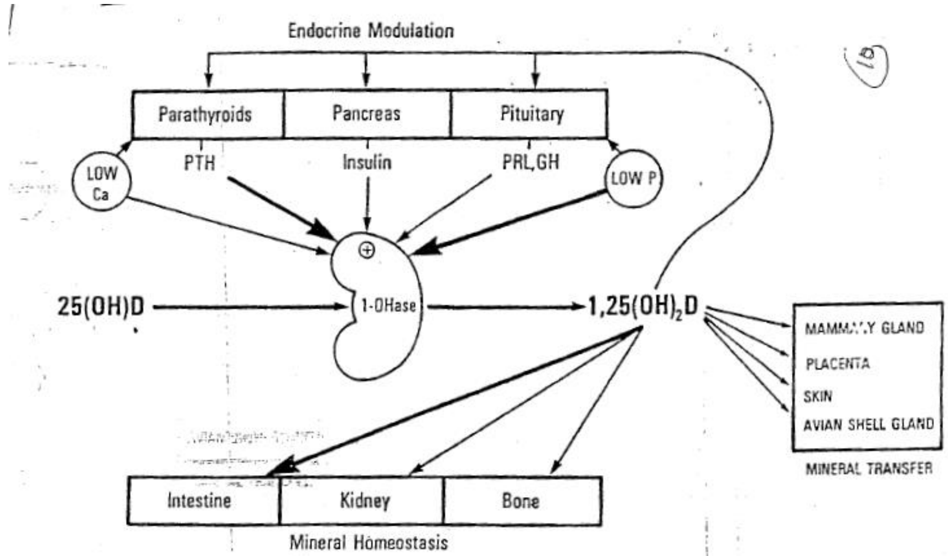


Figure 8.41. Function and regulation of 1,25-$(OH)_2D$. (From Haussler and McCain, 1977.)

Calcium

- Obesity affects plasma calcium level, why??

  In obese individuals, the fat, especially abdominal fat, **traps the calcium** and does not release it. This results in calcium deficiency. They will also have diabetes and heart problems (calcium is needed for the function of the heart; responsible for the action potential of the heart).
- Functions of calcium:
  a) Mineralization of bone
  b) Permeability of sodium in nerves
  c) Blood clotting
  d) Coupling of excitation and contraction
  e) Triggers release of acetylcholine at neuromuscular junction
  f) Serves as a second messenger
  g) Required by some enzymes for normal activity
  h) Constituent of bone (99% of total calcium in the body is found in the bone)

Table 27–4
Major Inorganic Constituents of Bone

Constituent	Total Body Content Present in Bone (%)
Calcium	99
Phosphate	85
Carbonate	80
Magnesium	50
Sodium	35
Water	9

What tissue contains less water than bone?
Adipose tissue; because it contains less water it can act as an insulator.

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

Ionized Ca^{++} concentration, depends on blood pH. Alkalosis increases the protein-bou and decreases the ionized Ca^{++} concentration, whereas acidosis has the opposite eff. ect.

The following table shows the distribution of calcium in the plasma. (We are not required to memorize any numbers).

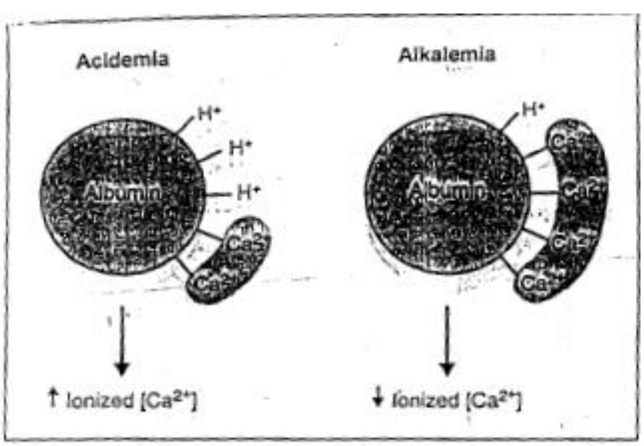


FIGURE 9–32. Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

pH also affects plasma calcium level. 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.** (when I increase calcium binding to the protein, I decrease ionized calcium)

Calcitonin

- Calcitonin is a hormone that **opposes the action of PTH**.
- Calcitonin is produced by **parafollicular cells** in the thyroid gland.
- Whereas PTH causes an increase in plasma calcium levels, calcitonin causes a decrease in plasma calcium levels.
- Calcitonin **decreases bone resorption**, **decreases calcium reabsorption**, and **decreases phosphate reabsorption**.

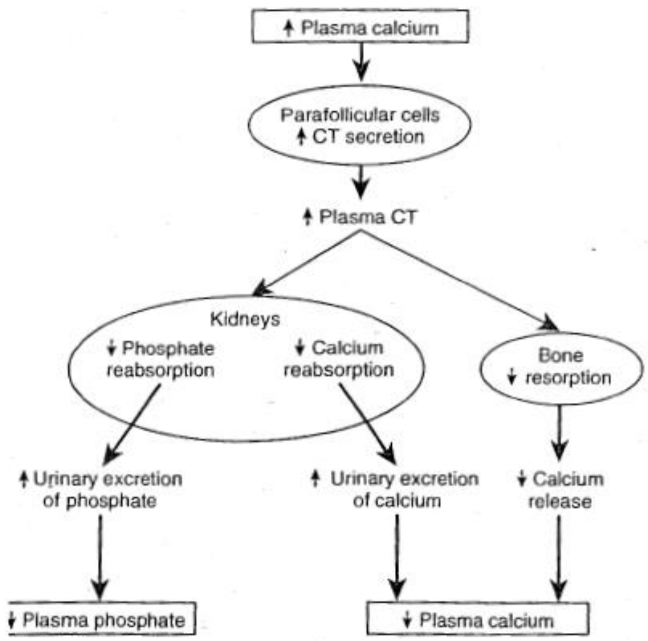


FIGURE 36.8 Effects of calcitonin (CT) on calcium and phosphate metabolism.

- Calcium, magnesium, and phosphate homeostasis is essential for health and life. A complex system acts to maintain normal body contents and ECF levels of these minerals in the face of environmental and internal changes.
- The key elements in this system are:
  1. Vitamin D
  2. PTH
  3. Calcitonin
  4. Other hormones like GH, prolactin, and insulin

- The GIT, kidneys, skeleton, skin, and the liver are all involved in homeostatic regulation.

- Now we will talk about some diseases related to these hormones:

1) Rickets:

The parts that the doctor focused on are highlighted.

RICKETS

Rickets occurs mainly in children as a result of calcium or phosphate deficiency in the extracellular fluid. Yet, ordinarily rickets is due to lack of vitamin D, rather than a dietary lack of calcium or phosphate. If the child is properly exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D_3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter.

Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementary therapy 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 is still available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

2) Osteomalacia:

Osteomalacia is rickets in adults. But here the cause is different. The individuals take vitamin D, calcium, and phosphorus normally but they have diarrhea which releases these minerals along with the stool, therefore there is no time for their absorption, which causes deficiency.

3) Osteoporosis:

OSTEOPOROSIS

Osteoporosis, the most common of all bone diseases in adults and especially in old age, is a different disease from osteomalacia and rickets, for it results from diminished organic matrix rather than abnormal bone calcification. Usually, in osteoporosis the osteoblastic activity in the bone is less than normal, and consequently the rate of bone deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.

Osteoporosis is most common in women and it's called the **silent killer**. It is the most serious of all the previously mentioned diseases.

CAUSES OF OSTEOPOROSIS ARE:

1) Lack of physical stress on the bones because of inactivity.
2) Malnutrition to the extent that sufficient protein matrix cannot be formed.
3) Lack of vitamin C,
4) Postmenopausal lack of estrogen secretion.
5) Old age, in which many of the protein anabolic functions are poor .

The age of menopause is variable in different regions and for different women. Old women, 2-3 years before menopause, are advised to take **vitamin D** and **calcium** and some **estrogen** under the supervision of the physician. (Estrogens also have something to do with beauty). They tried using calcitonin and PTH to activate the bone for osteoporosis but they didn't work.

After menopause the ovaries stop functioning and women will suffer from lack of androgens.

good luck