Vitamin D, Ricket's and Osteoporosis

Biochemistry Team

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Red: important notes
Green: team's notes
Gray: not important

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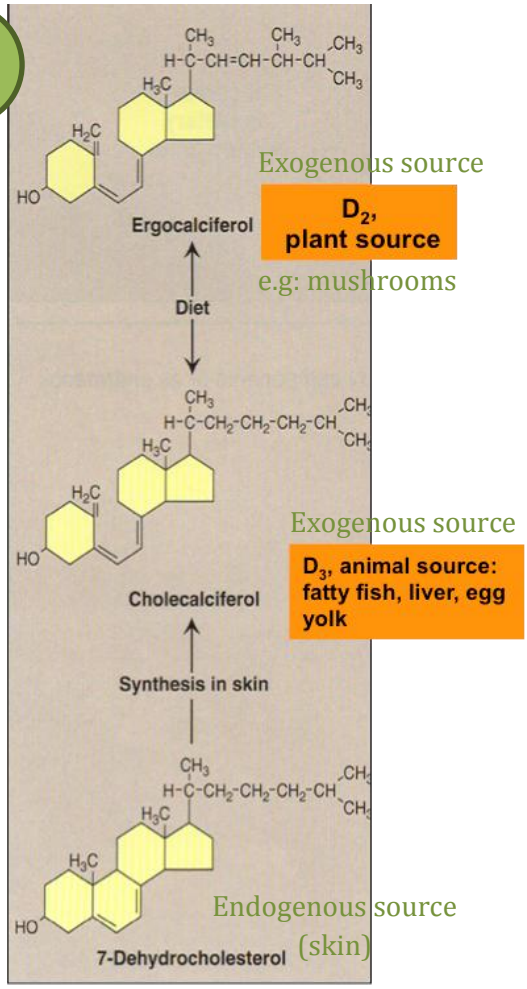
D Vitamins:

- A group of sterols (cholesterol) with a hormone-like function.
- **Calcitriol** (1, 25 diOH cholecalciferol = 1, 25 diOH D_3) is the biologically active molecule.
- ***Vitamins D_2*** *(Ergocalciferol is derived from ergosterol in plants & lower-*life forms***) & D_3*** *(from animals):*
  - Preformed Vitamin D in the diet: they are needed only in exposure to sunlight is limited.(available as supplement)
  - They are available as supplement
  - They are NOT biologically active, **but they have some biological activity.**
  - They are activated in vivo to the biologically active form

Note: D_2 is structurally different from D_3, and has different activating mechanism

- ***Recommended dietary allowance (RDA):***

5 mg cholecalciferol = 200 IU (International Units) of vit D_3 (or more)



Vitamin D Functions:

- Regulates calcium and phosphorus levels in the body (calcium homeostasis)
- Maintains healthy bones and teeth

These functions are through:

- Promoting absorption of calcium and phosphorus from the intestine
- Increasing reabsorption of calcium and phosphorus by renal tubules
- Increasing bone mineralization

Vitamin D Metabolism:

1

2 Cholecalciferol (vit D_3) is derived from 7-dehydrocholesterol in the skin by sunlight

In Liver

3

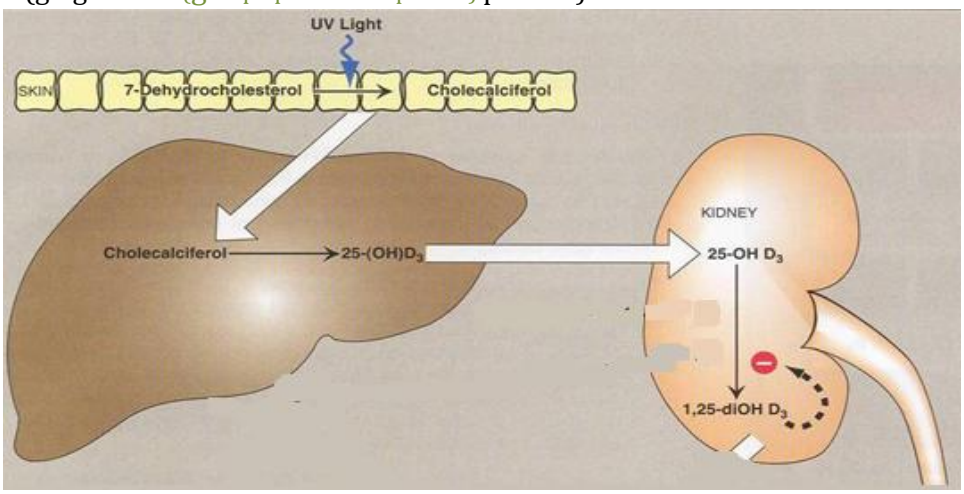
Cholecalciferol is converted to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase

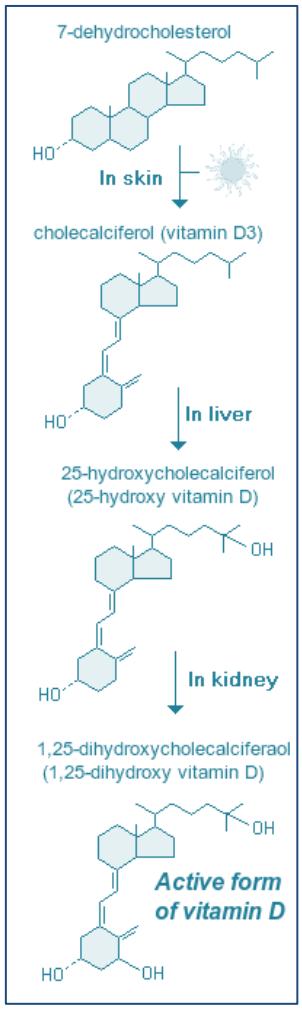
25-hydroxylase will add one hydroxyl group

In Kidneys

4

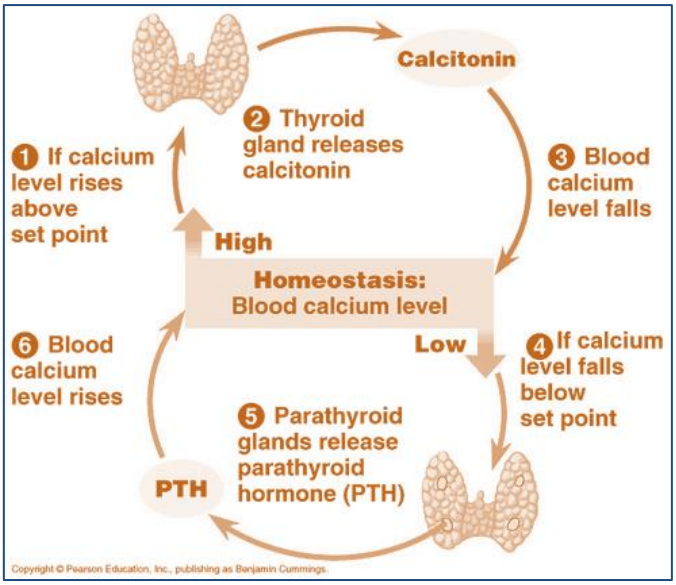
- The 1-α-hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)
- Active vitamin D is transported in blood by vitamin D-binding protein (gc-globulin (Group-specific Component) protein).





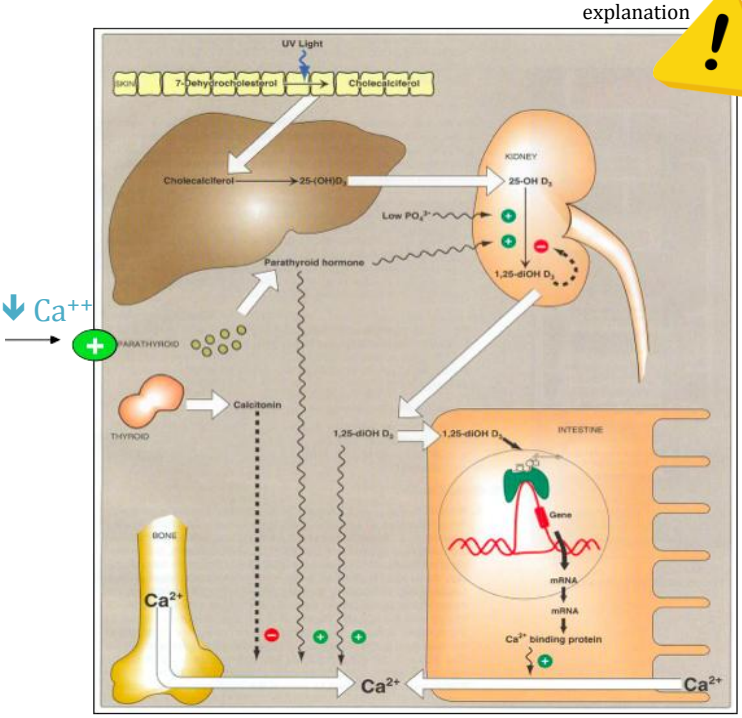
Vitamin D regulation and Calcium homeostasis:

- Vitamin D has essential role in calcium homeostasis
- (Direct) Calcium homeostasis is maintained by parathyroid hormone (**PTH**) and **calcitonin**
- Regulation of active Vitamin D synthesis is strictly controlled in the **kidneys** by **PTH**
- Hydroxylation of 25-hydroxycholecalciferol is PTH-dependent in kidneys
- Calcium absorption in the gut:
  - Indirectly depends on PTH
  - Directly depends on vitamin D



Calcium Homeostasis

Click here for explanation



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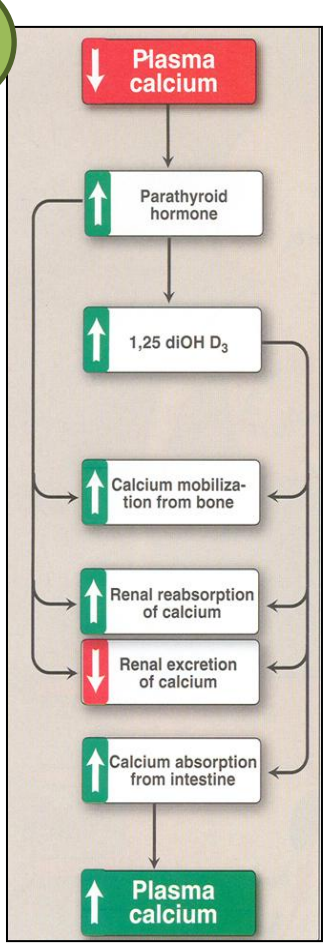
Osteomalacia and Ricket's:

Osteomalacia: Defective bone mineralization in adults
Rickets: Defective bone and cartilage mineralization in children
- Before introduction of vitamin D-supplemented milk, children with insufficient exposure to sunlight developed Vit D deficiency, causing Ricket's disease, due to impaired intestinal absorption of calcium
- Not common these days as foods (milk, oils) are now supplemented with vitamin D



These conditions are due to:
- Vitamin D deficiency
- Impaired vitamin D metabolism
- Calcium deficiency
- Imbalance in calcium homeostasis (calcitonin and PTH imbalance)

Serum levels of **25-hydroxycholecalciferol** is low, if the disease is due to Vitamin D deficiency
- In severe forms:
  - Serum **calcium** falls (hypocalcaemia) ↓
  - **PTH** level increases ↑
  - **Alkaline phosphatase** activity increases ↑

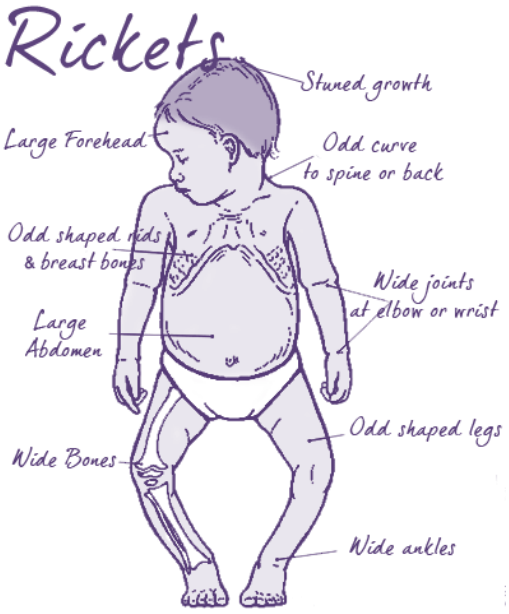
Alkaline phosphatase increases the activity of osteoblasts (bone forming cells)
It is normally high in pregnant women and children

Vitamin-D-dependent rickets types 1 and 2 (genetic disorders)

- Rare bone diseases
- Due to:
  - Defects in vitamin D synthesis: **type 1** (can be overcome by ↑ doses of Vit D)
  - Defects in vitamin D receptor: **type 2** (cannot be overcome by ↑ doses of Vit D, as the hormone is unable to act)

Clinical Features:

Rickets Soft bones	Osteomalacia Soft bones
Bone pain	Bone pain
↑ tendency of bone fractures	Bone fractures
Muscle weakness	Muscle weakness
Skeletal deformity (bowed legs) Dental problems Growth disturbance	Compressed vertebrae



Diagnosis:

Measuring serum levels of: (first line markers)

- 25-hydroxycholecalciferol
- PTH
- Calcium & Phosphate
- Alkaline phosphatase activity

Osteoporosis:

3

- Reduction in bone mass per unit volume
- Bone matrix composition is normal but it is reduced
- Post-menopausal women lose more bone mass than men (primary osteoporosis) (More common in females than males)
- The cause is unknown

Prevention

- Prevention from childhood is important
- Good diet and exercise prevent osteoporosis later
- Hormone replacement therapy in menopause prevents osteoporosis

If your bone mass at the age of 16 is at the highest level you will have less chance of getting Osteoporosis

Treatment

In confirmed cases of osteoporosis, treatment options are unsatisfactory

- Oral calcium, estrogens, fluoride therapy may be beneficial

Biochemical diagnosis is by excluding, if: vitamin D, PTH, Calcium and Alkaline phosphatase are normal, then we suspect osteoporosis.

Secondary osteoporosis may be caused by:

- Drugs
- Immobilization
- Smoking
- Alcohol
- Cushing's Syndrome
- Gonadal failure
- Hyperthyroidism
- GI disease

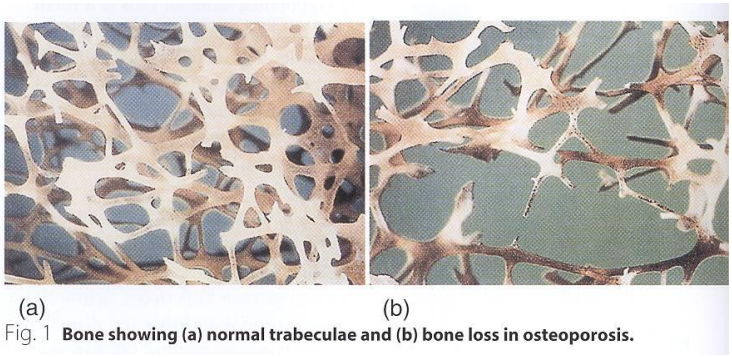
Diagnosis:

Biochemistry diagnosis is unremarkable in Osteoporosis

- Serial measurement of bone density (best way to diagnose osteoporosis)
- No specific biochemical tests to diagnose or monitor primary osteoporosis
- Secondary osteoporosis (due to other causes) can be diagnosed by biochemical tests
- The test results overlap in healthy subjects and patients with osteoporosis

Common biochemical tests:

- Urinary Hydroxyproline (bone resorption)
- Alkaline phosphatase (bone formation)
- Osteocalcin (bone formation)



(a) (b)

Fig. 1 **Bone showing (a) normal trabeculae and (b) bone loss in osteoporosis.**

Fig. 2 **Crush fractures of vertebral bodies in a patient with osteoporosis.**

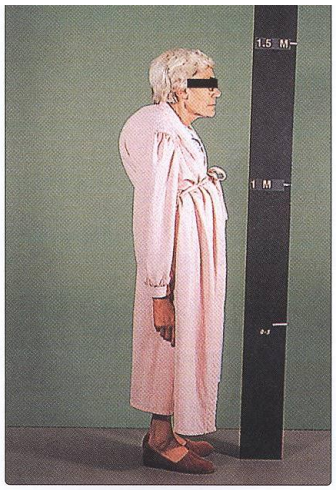


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

**Points:
- There are two types of Ricket's: nutritional defects and rare genetic defects (types 1 &2)
- Osteoporosis has normal composition of bone, while osteomalacia has an abnormal composition of bone (demineralization of existing bone)

Questions:

1. Calcium homeostasis is maintained by?

A. Vitamin D and Vitamin C
B. Cholesterol and Calcium
C. Vitamin D and PTH
D. PTH and Calcitonin

2. The precursor of bile salts, sex hormones and vitamin D is

A. Diosgenin
B. Campesterol
C. Cholesterol
D. Ergosterol

3. The most potent Vitamin D metabolite is

A. 25-Hydroxycholecalciferol
B. 1,25-Dihydroxycholecalciferol
C. 24, 25-Dihydroxycholecalciferol
D. 7-Dehydrocholesterol

4. 25-Hydroxylation of vitamin D occurs in

A. Skin
B. Liver
C. Kidneys
D. Intestinal mucosa

Answers:
1:D – 2:C – 3:B – 4:B

Wishing you best!