Biochemistry Bandits 434

VITAMIN D, RICKETS AND OSTEOPOROSIS

OBJECTIVES:

- Understand the functions, metabolism and regulation of vitamin D
- Discuss the role of vitamin D in calcium homeostasis
- Identify the types and causes of rickets
- Identify biomarkers used for the diagnosis and follow up of osteoporosis

❖ Important ❖ Extra ❖ Biochemistry Edit

ENDOCRINE BLOCK

INTRODUCTION:

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

VITAMIN D & ITS DISTRIBUTION:

- Vitamin D is considered a steroid hormone.
- Dietary sources:
  - **Ergocalciferol (vitamin D2)** found in plants
  - **Cholecalciferol (vitamin D3)** found in animal tissue
- Endogenous vitamin precursor:
  - **7-Dehydrocholesterol** (provitamin that's derived from cholesterol and found in the skin) is converted to vitamin D3 by being exposed to UV in sunlight[1]
- D3, D2 are also available as supplement only for individuals with limited exposure to light
- The biologically active form is **1,25-dihydroxycholecalciferol (calcitriol)**
- Daily requirement (IU/day): Adults: 600 Children: 400 Elderly: 800

1: The application of sunscreen lotions or presence of dark skin color decreases this synthesize

VITAMIN D METABOLISM

IN SKIN

- **Cholecalciferol** (Vitamin D3) is derived from **7-dehydrocholesterol** by sunlight.

IN LIVER

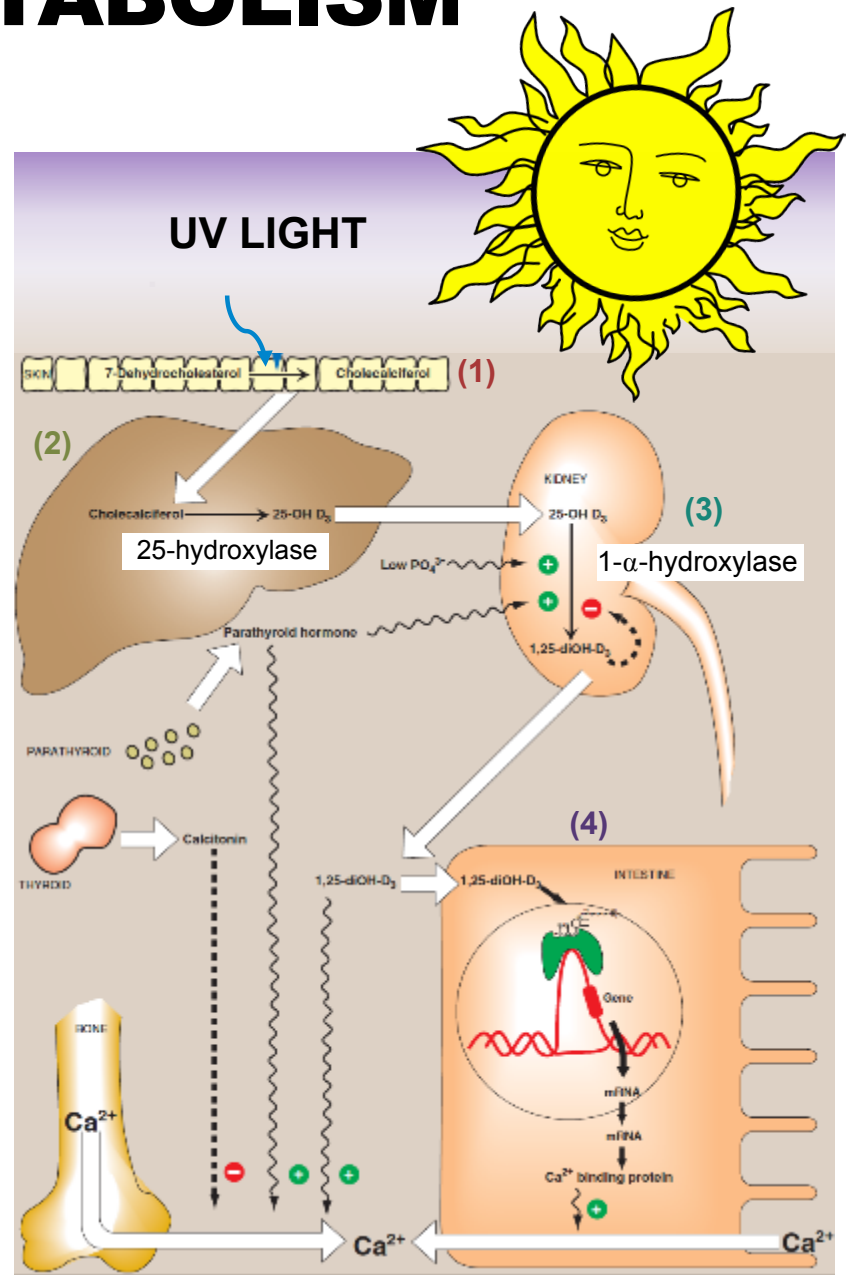
- **Cholecalciferol** is converted to **25-hydroxycholecalciferol** (calcidiol) by the enzyme **25-hydroxylase**

IN KIDNEY

- The **1-a-hydroxylase** enzyme converts **25-hydroxycholecalciferol** to **1,25-dihydroxycholecalciferol** (active form)
- Active vitamin D is transported in blood by **gc-globulin protein**[1]

IN THE INTESTINE

- Vitamin D binds to intracellular receptor proteins
- The receptor complex interacts with target DNA in cell nucleus
- It stimulates synthesis of **calcium-binding protein** for intestinal calcium uptake



1. group-specific component (vitamin D binding protein).

Activity of 1-a-hydroxylase in kidneys will:

❑ Directly increase due to low plasma phosphate

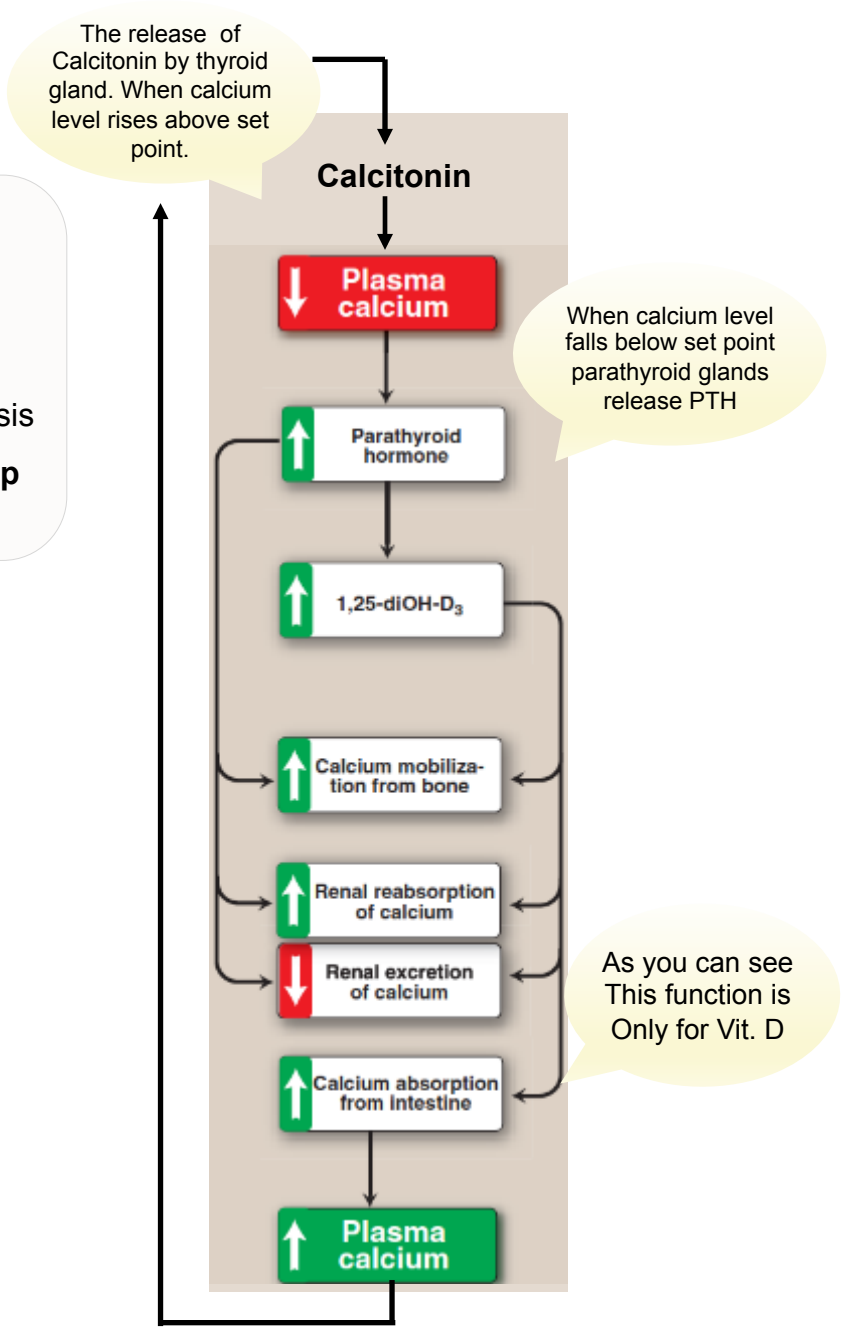
❑ Indirectly increase via PTH due to low plasma calcium:

↓ Ca^{++}→ ↑ PTH → ↑1-a-hydroxylase activity → ↑ vit D synthesis

calcium homeostasis is maintained by Vitamin D with the help PTH and calcitonin

VITAMIN D FUNCTIONS

- Regulates plasma levels of calcium and phosphate
- Promotes intestinal absorption of phosphate and calcium by Stimulating the synthesis of calcium-binding protein for intestinal calcium uptake.
- Minimizes loss of calcium by the kidneys
- Mobilizes calcium and phosphate from bone to maintain plasma levels
- Circulating level of >75 nmol/L is required for beneficial health effects



RICKETS It's a disease in children causing net demineralization of bone

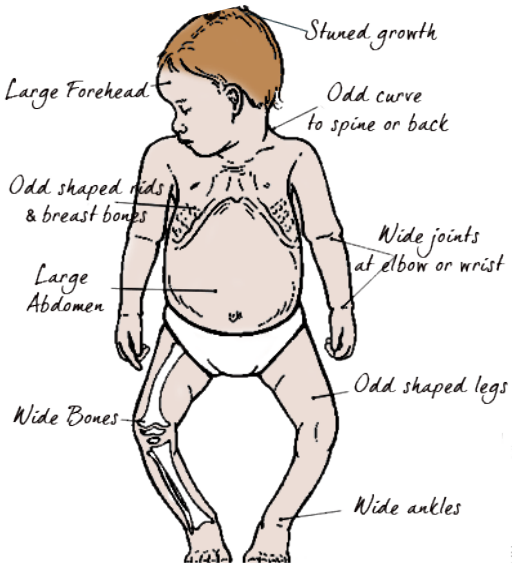
Nutritional Rickets

- continued formation of collagen matrix of bone
- Incomplete bone mineralization
- **Patients have low serum levels of vitamin D because:**

1. Poor nutrition
2. Insufficient exposure to sun
3. Renal osteodystrophy[1]
4. hypoparathyroidism (hypocalcemia)

Inherited Rickets

- Vitamin D-dependent rickets (types 1 and 2)[2]
- Rare
- **Deficiency is mainly because of genetic defects in:**
  - Vitamin D synthesis
  - Vitamin D receptor -no hormone action-



Features: bowed legs, soft and pliable[3] bone, bone pain, Increase tendency of fractures, dental problems, muscles wasting, growth disturbance.

Diagnosis: **Measuring serum levels of:**

•25-hydroxycholecalciferol[4]↓ •Alkaline phosphatase↑ •PTH↑ •Calcium↓ •Phosphate↓

Treatment: **Vitamin D and calcium supplementation**

1: causes decreased synthesis of active vitamin D in kidneys 3: flexible
2: VDDR I deficiency of the renal 25-hydroxyvitamin D (25(OH)D)-1 alpha-hydroxylase, VDDR II consists of intracellular vitamin D receptor defects
4. the level of 25(OH)D is the best indicator of vitamin D status and stores; it's the main circulating form of vitamin D + has a longer half life.
In contrast, 1,25(OH)2D has a much shorter half life + circulates in much lower concentrations than 25(OH)D

OSTEOPOROSIS

- **Osteoporosis: It's Reduction in bone mass per unit volume, <u>Bone matrix composition is normal but it is reduced</u>.**

VS

↑ fragility[1] of bones ↑ susceptibility to fractures

- **Osteomalacia: demineralization of bones in <u>adults</u>**

❖ Primary osteoporosis causes:

Post-menopausal (women lose more bone mass than men)

❖ Secondary osteoporosis causes:

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

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

❖ How to Diagnosis?

- WHO standard: Serial measurement of bone mineral density
- <u>Secondary</u> osteoporosis can be diagnosed <u>by biochemical</u> <u>tests</u> (calcium, phosphate, vitamin D)
- Biochemical tests alone cannot diagnose or monitor primary osteoporosis. Because the results overlap in healthy subjects and patients with osteoporosis

❖ Treatment

- Treatment options are unsatisfactory in confirmed cases of osteoporosis.
- Oral calcium, estrogens, fluoride therapy
- Bisphosphonates inhibit bone resorption that slows down bone loss

❖ Prevention

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

1: easily broken

BIOMARKERS OF OSTEOPOROSIS

Biochemical monitoring of bone metabolism; measurement of enzymes and proteins released during bone formation and of degradation products produced during bone resorption. Help to monitor responses to therapy.

Bone Formation Markers Produced by osteoblasts	**Osteocalcin**	• Involved in bone remodeling process • Released during bone formation and resorption (bone turnover) • Short half-life of few minutes -which makes it hard to detect- • Blood levels are influenced by vitamin K status and renal function
	alkaline phosphatase Bone-specific	• Its isoenzymes are widely distributed in other tissues • Present in osteoblast plasma membranes • Helps in bone formation • A Non-specific marker
	P1NP[1]	• Involved in the process of type 1 collagen formation • It's used for follow-up, Blood levels indicate: ➢ If **High** = progression and responsiveness to treatment. ➢ If **Low** = the patient isn't responsive to treatment
Bone Resorption Markers	**CTX-1[2]**	• A component of type-1 collagen • It's released during bone resorption • It's used for follow-up • Decreased level in serum and urine provides evidence of compliance and drug efficacy.

1: (Procollagen type-1 amino-terminal propeptide): Procollagen type 1 contains N- and C-terminal extensions>>these extensions are removed by specific proteases during conversion of procollagen to collagen>> The extensions are the C- and N-terminal propeptides of procollagen type 1 (P1CP and P1NP) BUT Measurement of P1NP appears to be a more sensitive marker of bone formation rate than P1CP.

2: (Carboxy-terminal cross-linked telopeptides of type 1 collagen): collagen peptides containing cross-links. a component of type-1 collagen and are released upon the degradation of mature collagens.

MCQS

1. **The regulation of Vitamin D synthesis is tightly regulated by which of the following?**

A. Urine levels of calcium
B. Plasma levels of phosphate
C. Plasma levels of calcium binding protein
D. Plasma levels of fibrinogen

2. **The precursor of vitamin D is:**

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

3. **Calcium homeostasis is maintained by:**

A. Vitamin D and Vitamin C .
B. Cholesterol and Calcium.
C. Vitamin D only.
D. PTH by chief cells

4. **25-OH D3 is converted to 1,25-diOH D3 by which of the following enzymes?**

A. carboxylase
B. 25-hydroxylase
C. epoxide reductase
D. 1-a-hydroxylase

5. **How does estrogen affect bone?**

A. balances resorption and formation
B. controls levels of vitamin D and calcium metabolism
C. inhibit resorption
D. inhibit formation

6. **Deficiency in Vitamin D would result in which of the following?**

A. Sore, Spongy gums
B. Cold Intolerance
C. Compressed vertebrae
D. Dysregulated eye movement.

7. **Calcium absorption in the gut depends indirectly on:**

A. Plasma phosphate
B. Folic Acid
C. vitamin D
D. PTH

8. **Which one of the following is a common feature seen in clinics for recognizing rickets?**

A. Loose teeth
B. Dowager's Hump
C. Bowed Legs
D. Discolored sclera

9. **Which of the following is a disadvantage of Osteocalcin?**

A. Used for bone turnover
B. It has a short plasma half-life
C. A Non-specific marker
D. Involved in bone remodeling process

10. **Low serum level of which of the following biomarkers indicates the patient is responding to the treatment?**

A. Osteocalcin
B. P1NP
C. CXT-1
D. Alkaline phosphatase

Answer Key: 1:B 2:C 3:D 4:D 5:A 6:C 7:D 8:C 9:B 10:C

SAQS

1. Mention the functions of vitamin D:

- Regulates calcium and phosphorus levels in the body (calcium homeostasis)
- Promotes absorption of calcium and phosphorus from the intestine
- Increases bone mineralization
- Increases the reabsorption of calcium and phosphorus by renal tubules
- Maintains healthy bones and teeth

2. Describe the mechanism underlying Vitamin D metabolism:

1. 7-dehydrocholesterol from diet is converted to Cholecalciferol by UV light, in the skin
2. Cholecalciferol converted to 25-OH-D_3 by 25-hydroxylase in the liver
3. 25-hydroxylase is converted to 1,25 diOH-D_3 (biologically active) by 1-a-hydroxylase In kidney
4. 1,25 diOH-D_3 is transported in blood by gc-globulin protein

3. Briefly list the differences between Rickets and Osteomalacia:

	Rickets	Osteomalacia
Definition	defective bone and cartilage mineralization in children	defective bone mineralization in adults
Due to	Vitamin D deficiency(includes any defect/deficiency in the enzymes), Impaired vitamin D metabolism, Calcium deficiency, Imbalance in calcium homeostasis	
Clinical features	Soft Bones, Skeletal deformity ex. bowed legs, Bone pain, Increase tendency of bone fractures Dental Problems Muscles weakness Growth disturbance	Soft bones Bone pain Bone fractures Compressed vertebrae Muscle weakness

4. What are the consequences of renal osteodystrophy?

Decrease ability to form 1,25-diOH-D_3, Increase retention of phosphate, Hypocalcemia

5. Mention two tests used to monitor treatment response of osteoporosis:

1. Bone Formation Marker > P1NP
2. Bone Resorption Marker > CTX-1

Biochemistry Bandits 434

اللهم إني استودعك ما قرأت وما حفظت وما تعلمت
فرده عند حاجتي إنك على كل شيء قدير

DONE BY:

Najla Aldraiweesh

Review:

Malak AlKahtani

Mohammad Alotaibi

For questions and comments. contact us Biochemistry434@gmail.com