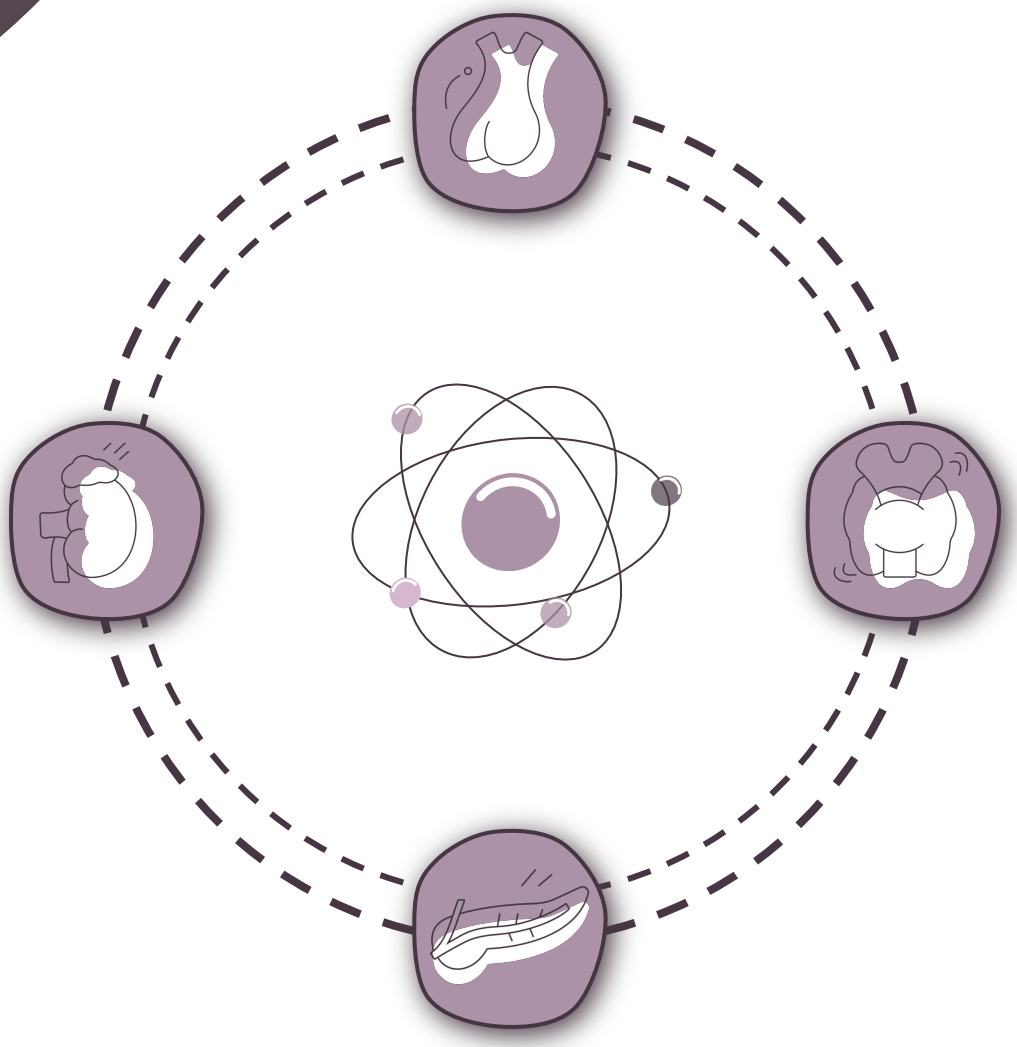
Biochemistry
Team 443



L3: Vitamin D and rickets

Presented by:
Dr. Khalid AlSumaily & Dr. Rana

Color Index:
Main Text
Male's Slides
Female's Slides
Important
Doctor's Notes
Extra Info

Editing File link:

Objectives

1. **Understand the functions, metabolism, regulation and deficiency of vitamin D**
2. **Discuss the role of vitamin D in calcium homeostasis**
3. **Identify the types and causes of rickets**
4. **Correlate vitamin D and calcium deficiency in osteoporosis**
5. **Identify biomarkers used for the diagnosis and follow up of osteoporosis**

To be in touch: click on the icons

Biochemistry 443 team channel:

Academic Announcement channel:

Editing File link:

1

Vitamin D

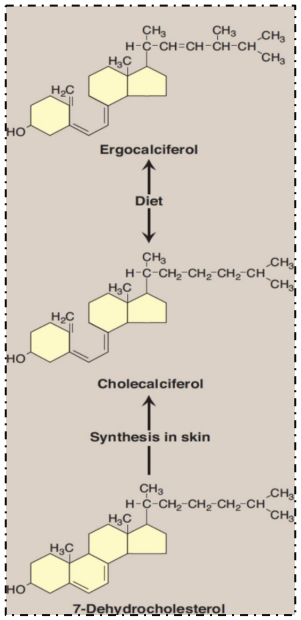
1. Vitamin D is considered a steroid hormone
2. Cholecalciferol (vitamin D3) is synthesized in the skin by sunlight (UV).
3. The biologically active form of cholecalciferol is 1,25-dihydroxycholecalciferol (calcitriol)
4. Ergocalciferol (vitamin D2) is derived from ergosterol in lower animal and plants
5. D3, D2 are also available as supplements

Vitamin D Distribution

Daily requirement (IU/day):
- Adults:600
- Children:400
- Elderly:800

Endogenous vitamin precursor

7-Dehydrocholesterol is converted to vitamin D3 in the dermis and epidermis exposed to uv in sunlight.



Dietary sources

Ergocalciferol(vitamin D2) found in plants

Cholecalciferol (vitamin D3) found in animal tissue

Metabolism

In skin

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

Transporter

Active vitamin D is transported in blood by gc-globulin protein (vit D binding protein Because it is hydrophobic)

In liver

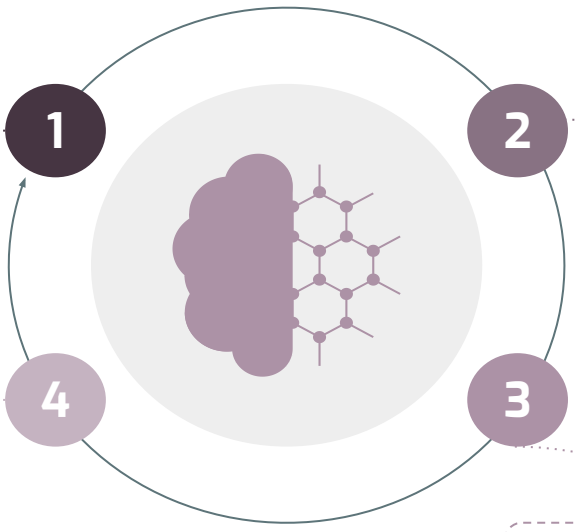
Cholecalciferol is converted to 25-hydroxycholecalcif erol (calcidiol) by the enzyme 25-hydroxylase.

In kidneys

The 1- α-hydroxylase enzume converts 25-hydroxycholecalciferol to 1,25- dihydroxycholecalciferol (due to 20H) (biologically active)

2

Vitamin D Regulation and calcium homeostasis



Vitamin D synthesis is tightly regulated by plasma levels of phosphate and calcium

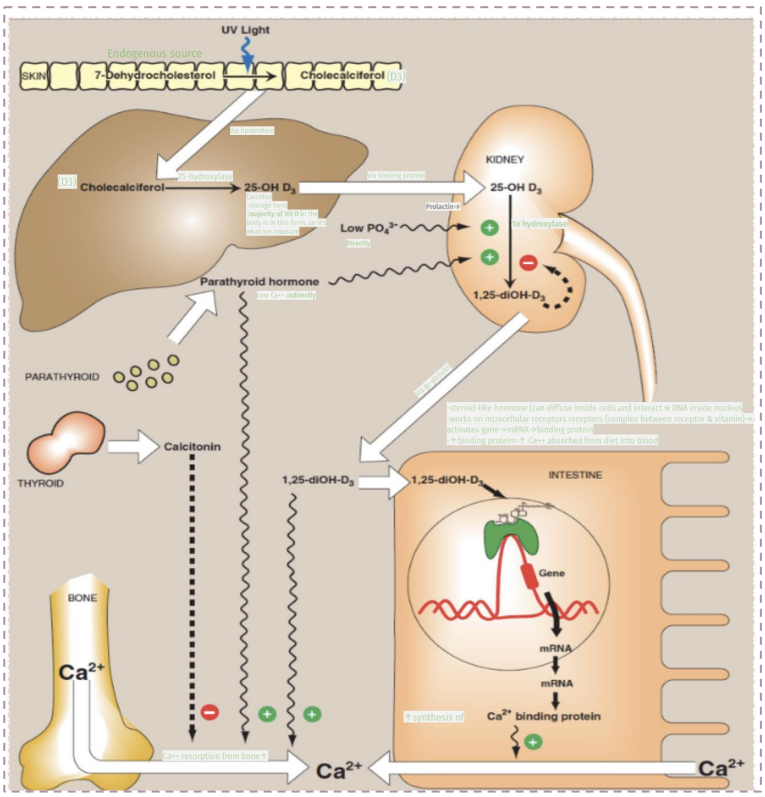
Calcium homeostasis is maintained by parathyroid hormone (PTH) and calcitonin

Vitamin D has essential role in calcium homeostasis

Activity of 1- a-hydroxylase in kidneys is:

- Directly ↑ increased due to low plasma phosphate
- Indirectly ↑ increased via parathyroid hormone (PTH) due to low plasma calcium
- PTH ↑ increases vitamin D synthesis in kidneys

Metabolism and actions of vitamin D



- In the skin, after 7-dehydrocholesterol is converted to cholecalciferol, all cholecalciferol will transported by binding proteins (because it is hydrophobic) to the liver.

-In the liver, carbon number 25 on cholecalciferol is hydroxylated(by 25-hydroxylase), converting cholecalciferol to 25-hydroxycholecalciferol . 25-hydroxycholecalciferol will be transported by a binding proteins to the kidney.

-In the kidney, anther hydroxylation will happen(at carbon number 1) by 1-α-hydroxylase enzyme, converting 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.

-We call these two reactions 2 sequential hydroxylations. The 2nd hydroxylation is very important because it forms the most active form(1,25-dihydroxycholecalciferol), so it is tightly regulated:
A) Negative feedback to stop/slow down this reaction
B) Positively regulated by:
1. Directly will be stimulated by Low PDF
2. Indirectly by low Ca^{++} which lead to stimulation of PTH⇒stimulation of 1-a-hydroxylase enzyme.

1,25-dihydroxycholecalciferol is considered a steroid hormone. Because it has steroid-like activity, it can diffuse inside the intestinal cell. Then, the Vitamin D and receptor complex interacts with DNA inside the nucleus and stimulates the synthesis of Ca^{++}-like Protein. Ca^{++} like Protein is like a car (taxi) and will transport the Ca^{++} from intestine (Milk or food) to inside the body.

- 25-hydroxycholecalciferol: (عادة يتم تخزينه بالجسم وهو اللي يتم قياسه)

- 1,25-dihydroxycholecalciferol: the most powerful , and consider as steroid hormone because it has steroid like activity, it can diffuse inside the intestinal cell.

3

Vitamin D action

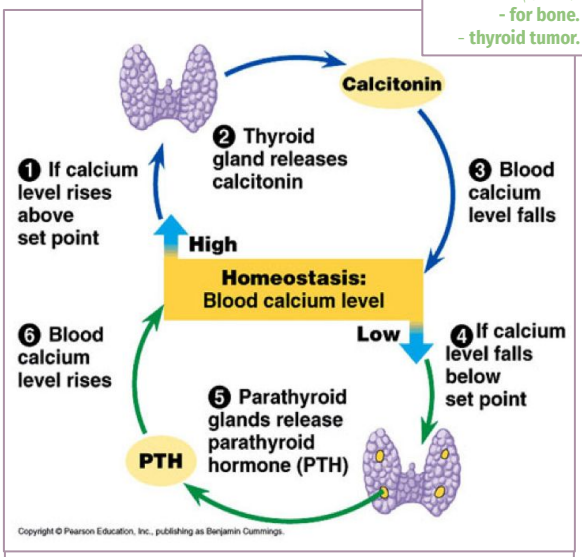
Vitamin D action is typical of steroid hormones

It binds to intracellular (its steroid hormone) receptor proteins

The receptor complex interacts with target DNA in cell nucleus

This stimulates (when we need to have more Ca^{++}) or represses (when we have enough Ca^{++}) gene expression

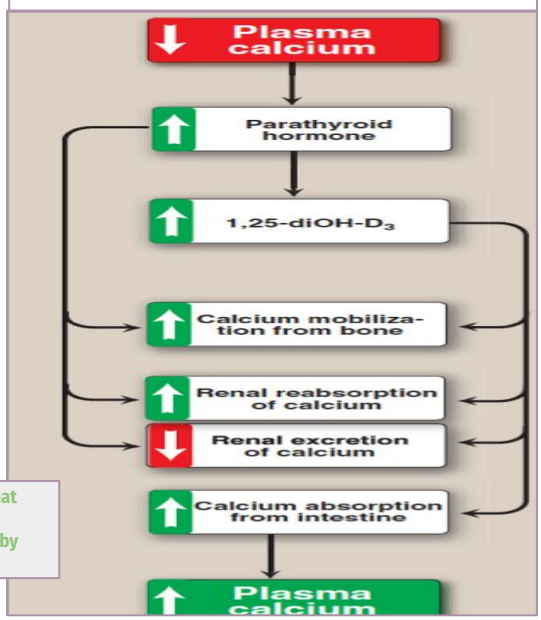
قياسه مهم :
- for bone.
- thyroid tumor.



Calcium homeostasis

Predominant action is for parathyroid

Vitamin D response to low plasma calcium



Male dr: notice that the action on the intestine is done by the vit.d only

Vitamin D functions

- Regulates plasma levels of calcium and phosphate
- Promotes intestinal absorption of calcium and phosphate
- Stimulates synthesis of calcium-binding protein for intestinal calcium uptake
- Minimizes loss of calcium by the kidneys
- Mobilizes calcium and phosphate from bone (biggest reservoir of Ca^{++} in the body) to maintain plasma levels

Daily requirement (IU/day):

Children:	400
Adults:	600
Elderly:	800
Upper limit of intake:	4000

4

Vitamin D intake and toxicity (Male slides only)

01 High doses (10,000 IU for weeks or months) can lead to toxicity

02 Hypercalcemia and deposition of calcium in arteries and kidneys

Vitamin D deficiency

1 Deficiency most common worldwide

2 High prevalence in Saudi Arabia due to:
- Low dietary intake
- Insufficient exposure to sun
- Lifestyle (eg. clothing esp in women) عباية

3 Circulating level of >75 nmol/L is required for beneficial health effects

Rickets

Nutritional rickets:

- A disease in children causing net demineralization of bone (هي اللي تعطي الصلابة للعظام minerals)
- With continued formation of collagen matrix of bone (normal collagen matrix but there is no minerals to make it more strong).
- Incomplete bone mineralization
- Bones become soft and pliable (تتقوس الأقدام لأنها ما تصير قوية، والوزن ينزل على الرجلين).
- Causes skeletal deformities including bowed legs
- Patients have low serum levels of vitamin D

Inherited rickets:

- Vitamin D-dependent rickets (types 1 and 2)
- Rare types of rickets due to genetic disorders
- Causing vitamin D deficiency mainly because of genetic defects in:
  - ➔ Vitamin D synthesis
  - ➔ Vitamin D receptor (no hormone action)

Osteomalacia(ليونة العظام):

- demineralization of bones in adults due to nutritional deficiency of Vit. D

Cont.. Rickets

causes	**Vitamin D deficiency because of:** • **Poor nutrition** • **Insufficient exposure to sunlight** • **Renal osteodystrophy (causes decreased synthesis of active vitamin D in kidneys)** • **Hypoparathyroidism (hypocalcemia) (due to loss of Ca^{++} Binding Protein, can't Absorb Ca^{++} ⇒ even with Good nutrition).**
Diagnosis	**Measuring serum levels of:** • **25-hydroxycholecalciferol (low)** • **PTH (due to low Ca^{++} > will be high)** • **Calcium (low)** • **Phosphate (low)** • **Alkaline phosphatase (high)**
Treatment	**Vitamin D and calcium supplementation**

Osteoporosis

Osteoporosis: decrease in both collagen and mineralization, so the ratio is normal, but the whole bone mass is decreased

Definition

- **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)**
- **Increases fragility of bones** الضربة البسيطة ممكن تسبب كسور مرضية
- **Increases susceptibility to fractures**

Secondary osteoporosis:

Caused by:

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

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

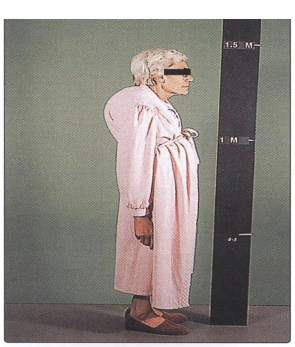
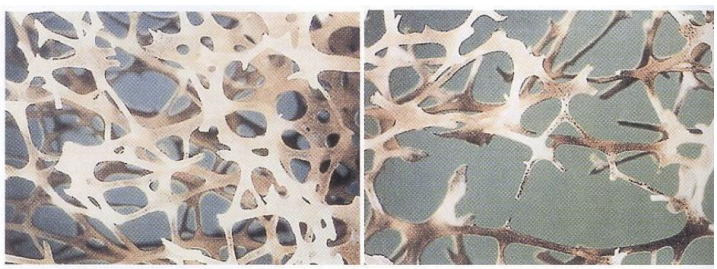


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**



(a) (b)

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

6

Cont..Osteoporosis

Diagnosis

To follow up the treatment of osteoporosis they used to do DEXA every 2 years to measure bone density, but now they can measure these markers every 2-3 months by these markers

- WHO standard: Serial measurement of bone mineral density
- Biochemical tests (calcium, phosphate, vitamin D) alone cannot diagnose or monitor primary osteoporosis. But Rule out Osteomalacia.
- The test results overlap in healthy subjects and patients with osteoporosis
- Secondary osteoporosis (due to other causes) can be diagnosed by biochemical tests

e.g. Cushing syndrome = measure cortisol
Gonadal failure = measure LH + FSH
Hyperthyroidism = measure TSH + T4

Osteoporosis Markers

Bone formation markers

1-Osteocalcin aka Bone Gla Protein #GIT

- Produced by osteoblasts during bone formation
- Involved in bone remodeling process
- Released during bone formation and resorption (bone turnover). The higher the bone turnover, the higher the Osteocalcin
- Short half-life of few minutes so its useful only in research not day-to-day patients in hospital
- Blood levels are influenced by vitamin K status and renal function

2-Bone-specific Alkaline Phosphatase

- Present in osteoblast plasma membranes
- Helps osteoblasts in bone formation
- Non-specific marker since its also found in the liver(l#GIT) and placenta
- Its isoenzymes are widely distributed in other tissues
- The isoenzymes also interfere with the assay

3-P1NP (Procollagen type-1 amino-terminal propeptide) Listed under resorption markers in M slides

- Produced by osteoblasts
- Involved in the process of type 1 collagen formation
- Shows good assay precision
- Stable at room temperature
- Blood levels are highly responsive to osteoporosis progression and treatment (best marker) P for: P1NP and Progression
- It's always tasted To follow up on treatment

Bone Resorption markers

1-CTX-1 (Carboxy-terminal cross-linked telopeptides of type 1 collagen)

- A component of type-1 collagen
- Released from type-1 collagen during bone resorption
- Blood and urine levels are highly responsive to post-resorptive treatment
- Levels vary largely by circadian variation(a disadvantage)
- N-terminal telopeptide (NTx) Is also one of the resorption markers.

Cont..Osteoporosis

Treatment	Prevention
In confirmed cases of osteoporosis • Treatment options are unsatisfactory • Oral calcium, estrogens (for menopause lady), fluoride therapy may be beneficial • Bisphosphonates inhibit bone resorption that slow down bone loss أغلب الكبار يعطونهم أسبوعيًا	• Prevention from childhood is important • Good diet and exercise prevent osteoporosis later • Hormone replacement therapy in menopause may prevent osteoporosis

Take home massages

- Overview of vitamin D metabolism and regulation
- Importance of vitamin D functions
- Vitamin D deficiency is common in populations
- Rickets and osteomalacia are due to vitamin D deficiency
- Various biochemical markers clinically important for assessment of osteoporosis

Test Yourself!

MCQs

Answers: 1-D 2-C 3-D 4-D

Q1: which on of the following is the action of 25-hydroxylase enzyme?

A. converts 25-OH D3 to 1,25-diOH-D3
B. converts 7-dehydrocholesterol to cholecalciferol
C. converts 25-OH D3 to cholecalciferol
D- converts cholecalciferol to 25-OH D3

Q2: Cholecalciferol is synthesized by?

A. Liver
B. Kidney
C. skin
D. bones

Q3: Causes of secondary osteoporosis?

A. Drugs
B. Immobilization
C. cushing syndrome
D. all of them

Q4: Which of the following biomarkers involved in bone remodeling process?

A. PINP
B. CTX1
C. Alkaline phosphatase
D. Osteocalcin

SAQs

Q1: Mention 3 functions of Vitamin D?

-Regulate plasma level of calcium and phosphate
-Promotes intestinal absorption of calcium and phosphate
-Minimizes loss of calcium by the kidney

Q2: Enumerate the biomarkers of osteoporosis?

-Osteocalcin ,CTX-1, Bone-specific alkaline phosphatase , P1NP

Meet The Team!

Team Leaders

Abdullah AlDhuwaihy

Yazeed AlSulaim

Jouri Almaymoni

Deena Almahawas

Team Members

- Faisal AlShowier
- Mohammed AlRashed
- Abdulrahman AlOmar
- Mohammed AlEssa
- Mohammed AlSalamah
- Mohammed AlArfaj
- Hamad AlZomaia
- Talal AlGhadir
- Faisal AlZuhairy
- Abdulmalik AlShathri
- Abdulrahman AlOsleb
- Abo Owayed
- Yazan AlAhmari
- Fahad AlMughaiseeb
- Faris AlZahrani
- Khalid AlSobei

- Razan alsoteehi
- Razan Alaskar
- Haya Alzeer
- Dana A Alkheliwi
- Lama Hazzaa
- Afnan Alahmari
- Shaden Alhazzani
- Wasan Alanazi
- Salma Alsaadoun
- Remas Aljeaidi
- Jana Almutlaqah