"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Vitamin D, Ricketts

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Revised By
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Endocrine block

Objectives:

By the end of this lecture, the students should be able to:

- 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.

Overview:

- Vitamin D distribution, metabolism, regulation and functions
- Vitamin D in calcium homeostasis
- Vitamin D deficiency “most people are deficient in vit D1”
- Nutritional and inherited rickets : Types, diagnosis and treatment
- Osteoporosis: Diagnosis, biomarkers, treatment and prevention

Vitamin D

- Vitamin D is considered a steroid hormone.
- **Cholecalciferol** (vitamin D3) is synthesized in the skin by the sunlight (UV).
- The biologically active form is **1,25-dihydroxycholecalciferol** (calcitriol).
- Ergocalciferol (vitamin D2) is derived from ergosterol in plants.
- D3, D2 are also available as supplement.

- Cholesterol is a precursor of most steroid hormones.
- Vit D are of two types endogenous and exogenous.
- Vit D is **fat soluble**, can be stored in the liver and cause **toxicity** so it is very important to take it in a controlled way.

Vitamin D Distribution

- **Dietary sources:**
  1) Ergocalciferol (vitamin D2) found in **plants**
  2) Cholecalciferol (vitamin D3) found in **animal tissue** "the endogenous form as well and the form measured in labs"

- **Endogenous vitamin precursor:**

  –7-Dehydrocholesterol is converted to vitamin **D3** in the dermis and epidermis exposed to UV in sunlight

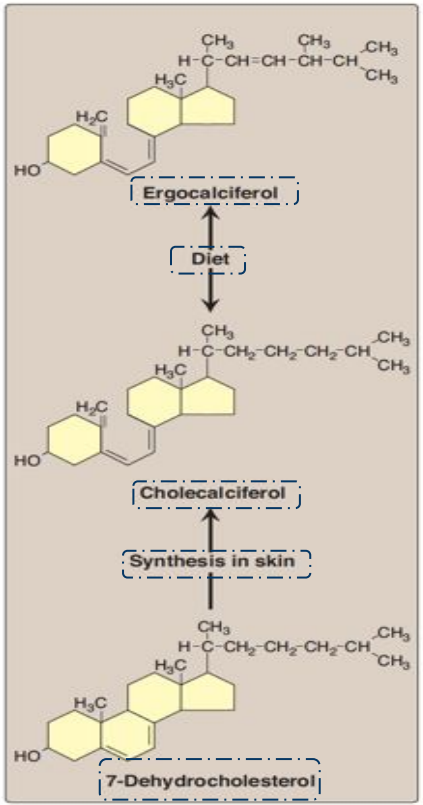
- **Daily requirement** (IU/day):
  - **Adults:** 600
  - **Children:** 400
  - **Elderly:** 800

tip

Dr. Rana said that we should memorize the numbers of the daily requirement.
IMPORTANT

- **Major dietary sources of vit D are:**
  1. Fatty fish 2.Egg yolk 3. Liver
- Some foods don't have vit D in them naturally like milk for example, but it is added to it to prevent deficiencies.
- Both VitD2 and VitD3 can be converted to the active form(1,25dihydroxycholecalcifrol)

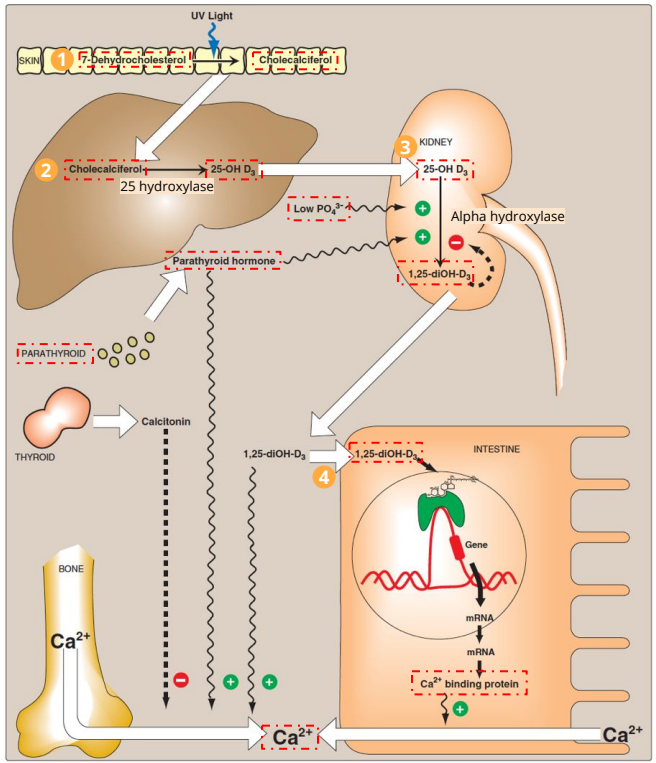
Sources of Vitamin D



IMPORTANT!

Metabolism and Actions of Vitamin D

1) On the skin we have cholesterol (7 dehydrocholesterol) ; when the UV light hits the skin it is transformed into cholecalciferol “D3”
2) It is hydrophobic so it binds to a certain protein to be transported to the liver, in the liver it is hydroxylated (adding of OH) to become 25-OH D3) by the enzyme 25 hydroxylase, this form is less active and can be **stored(so it's the storage form)** in the liver.
3) By another type of binding protein it is transported to the kidney where it is **tightly regulated:** 25-OH D3 is converted by the enzyme alpha 1 hydroxylase into 1,25-diOH D3 “the active form”. it is stimulated directly by low phosphate or indirectly by the low calcium, which stimulates the release of the parathyroid hormone which in turn stimulates the enzyme. It is inhibited by negative feedback of 1,25-diOH D3.
4) The 1,25-diOH D3 enters the intestinal cell, where it acts on the nucleus , in the nucleus it is binds to a receptor leading to the transcription of mRNA and translation to form more or less calcium binding protein depending on the body’s need. This leads to **more absorption of calcium**



Note: in labs we usually test for **25 OH D3, but in renal failure we check for the 1,25 diOH D3**

Vitamin D Metabolism

- **In skin:**

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

- **In liver:**

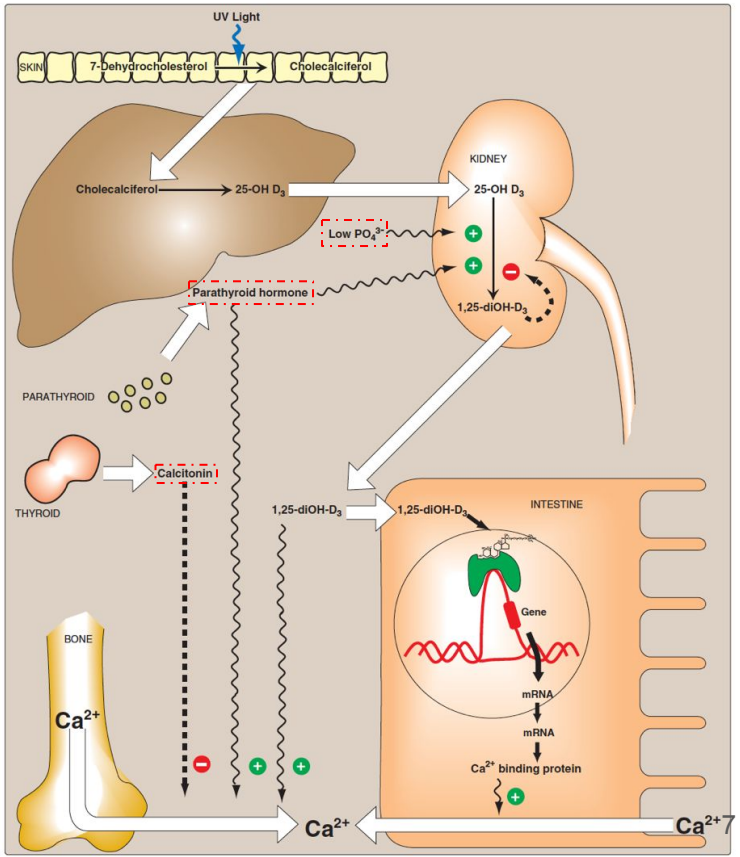
  Cholecalciferol is converted to 25-hydroxycholecalciferol (calcidiol) by the enzyme 25-hydroxylase

- **In kidneys:**
  - The 1-α-hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)
  - Active vitamin D is transported in blood by gc-globulin protein **(VitD binding protein).**

Vitamin D regulation and calcium homeostasis

IMPORTANT!

- Vitamin D synthesis is tightly regulated by plasma levels of Phosphate and Calcium.
- Activity of **1-α-hydroxylase** in kidneys is:
  - Directly increased due to **low plasma Phosphate**.
  - Indirectly increased due to **low plasma Calcium** via Parathyroid Hormone (PTH) .
  - PTH increases vitamin D synthesis in kidneys.
- Vitamin D has essential role in Calcium homeostasis.
  (Discussed more in the next slide)
- Calcium homeostasis is maintained by parathyroid hormone (PTH) and calcitonin.



Vitamin D Actions

Vitamin D action is typical of steroid hormones

It binds to intracellular receptor proteins

The receptor complex interacts with target DNA in cell nucleus

This stimulates or represses gene expression

"Depending on the need"

Vitamin D Functions

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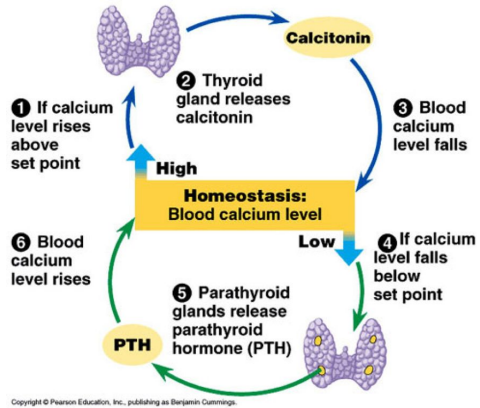
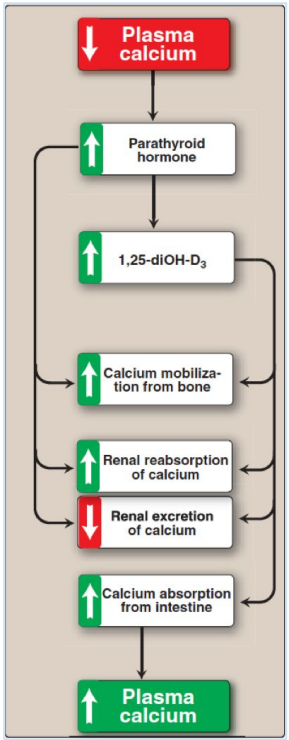
IMPORTANT!

- Regulates plasma levels of calcium and phosphate.
- Promotes intestinal absorption of calcium and phosphate.
- By Stimulating 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.



Calcium Homeostasis

Don't skip the pictures



Vitamin D response to low plasma calcium

Vitamin D deficiency

- Deficiency most common worldwide
- **High prevalence in Saudi Arabia due to:**
  - Low dietary intake
  - Insufficient exposure to Sun
- Circulating level of >75 nmol/L is required for beneficial health effects.

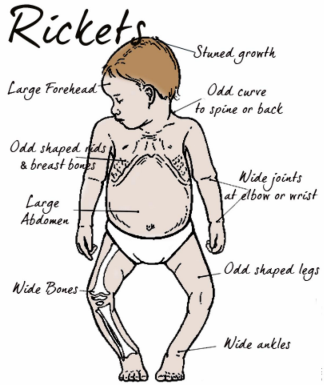
  - < 25 → very deficient
  - 25-75 → insufficient
  - > 250 → toxicity

Nutritional rickets

- **Rickets**: increase in collagen, decrease in bone mineralization leading to disturbed ratio
- **Osteoporosis**: decrease in both collagen and mineralization, so the ratio is normal, but the whole bone mass is decreased

- A **disease in children** causing net demineralization of bone
- With continued formation of collagen matrix of bone
- Incomplete bone mineralization
- Bones become soft and pliable
- Causes skeletal deformities including bowed legs
- Patients have **low serum** levels of vitamin D

(Osteomalacia: demineralization of bones in adults) like rickets but in adults



Rickets	Inherited Rickets
Causes: **Vitamin D deficiency because of:** 1) Poor nutrition 2) Insufficient exposure to sunlight 3) Renal osteodystrophy[1](causes decreased synthesis of active vitamin D in kidneys) 4) Hypoparathyroidism (hypocalcemia) [1]A congenital disease that affects hydroxylation, happens in children and leads to rickets	**Vitamin D-dependent rickets (types 1 and 2)** • Rare types of rickets due to genetic[2] disorders • Causing vitamin D deficiency mainly because of genetic defects in: ○ Vitamin D synthesis ○ Vitamin D receptor (no hormone action) [2]Without an environmental factors or any other disease.

Diagnosis and treatment of rickets

Measuring serum levels of [3]

1) 25-hydroxycholecalciferol **(low)**
2) PTH
3) Calcium **(low)**
4) Phosphate
5) Alkaline phosphatase (ALP)

Treatment:
Vitamin D and calcium supplementation

Additional Information

[3]According to the cause, the levels of these markers will be:

1) Usually low
2) High in renal osteodystrophy, low in hypoparathyroidism
3) Low in kidney failure and hyperparathyroidism
4) Low in kidney failure, high in hypoparathyroidism
5) High, bone trying to compensate, and increases production of bone

New topic! Not part of vit D deficiency!

Osteoporosis

- **Reduction** in bone mass per unit volume [1]
- Bone matrix composition is normal but it is **reduced**
- Post-menopausal women lose more bone mass than men (primary osteoporosis)
- **Increases** fragility of bones
- **Increases** susceptibility to fractures [2]

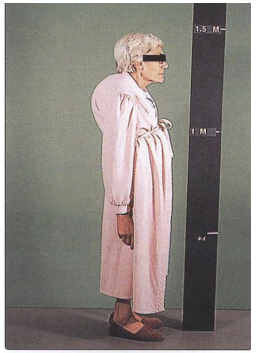
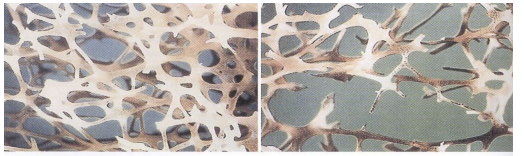


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

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



(a) (b)

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

Secondary osteoporosis may be caused by [3]

Alcohol	Hyperthyroidism
Gonadal failure	Immobilization
Cushing's syndrome	Drugs**(steroid)**
GI disease	Smoking

[3] These are modifiable causes, There are unmodifiable causes such as: gender, Age ethnic and genetics. Diagnosis of the cause is done by elimination

[1] The ratio between collagen and minerals is normal, but there is decrease in the bone mass
[2] Pathological fractures

Diagnosis of Osteoporosis

- WHO standard: **Serial measurement of bone mineral density** [1]
- Biochemical tests (calcium, phosphate, vitamin D) alone **can not**[2] diagnose or monitor primary osteoporosis
- The test results overlap in healthy subjects and patients with osteoporosis
- Secondary osteoporosis (due to other causes) can be diagnosed by **biochemical tests**

[1] DEXA test to assess bone mass.

[2] Usually radiology is better in diagnosing osteoporosis, but the new biochemical markers "next slide" are as good as radiology

- Because the problem is **not** in mineralization of the bone.

Biomarkers of osteoporosis

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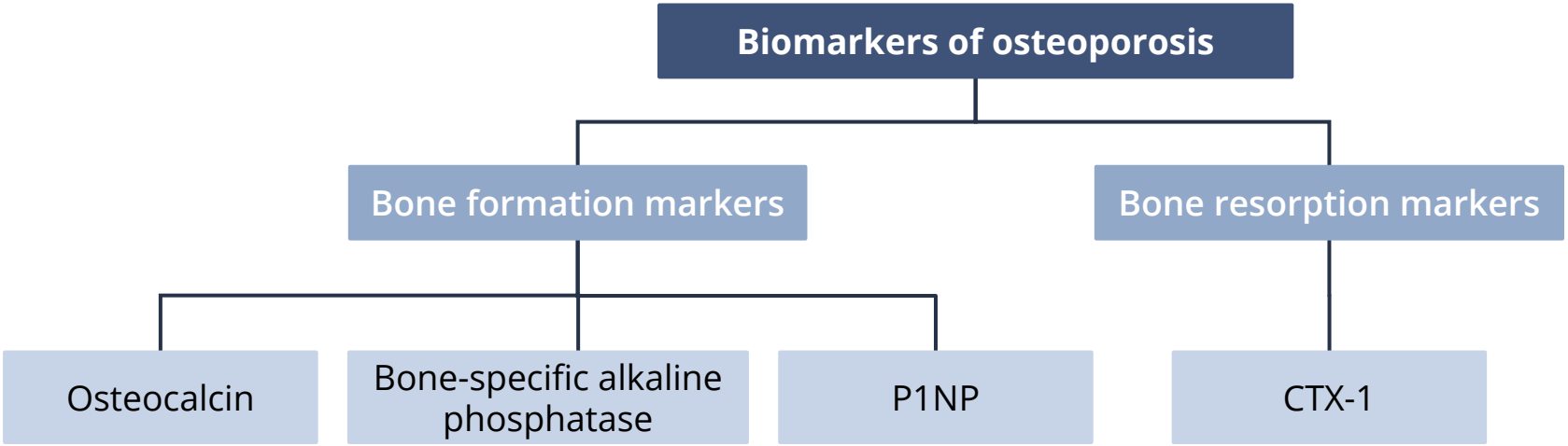
Important to know which one is bone formation and resorption



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

Bone formation markers

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1- Osteocalcin

- Produced by osteoblasts during bone formation
- Involved in bone remodeling process
- Released during bone formation and resorption (bone turnover)[1]
- Short half-life of few minutes[2]

2- Bone-specific alkaline phosphatase

- Present in osteoblast plasma membranes
- Helps osteoblasts in bone formation
- A Non-specific marker
- Its isoenzymes are widely distributed in other tissues[3]

3- P1NP[1] (Procollagen type-1 amino-terminal propeptide)

- Produced by osteoblasts
- Involved in the process of type 1 collagen formation
- Blood levels are highly responsive to osteoporosis progression and treatment

[1] So in case of bone turnover the osteocalcin will be high
[2] That's why It is difficult to measure
[3]Like liver, placenta

[1]We use it for follow up, **no need to know the whole name** just know P1NP
*In polypeptide we have amino-terminal and c-terminal the c terminal is resorption marker and they mainly measure it from the urine more than the blood but the amino-terminal is formation marker

Bone resorption markers

No need to know the whole name just know CTX-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

Mostly from the urine

- Levels vary largely by circadian variation

Treatment and Prevention of Osteoporosis

Treatment:

- In confirmed cases of osteoporosis

  Treatment options are unsatisfactory
- Oral calcium, estrogens[1], fluoride therapy may be beneficial
- Bisphosphonates[2] 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] In postmenopausal we treat them with estrogen
[2] They mostly give it to the elderly given weekly

(اللهم إني أستودعك ما قرأت وما
حفظت وما تعلمت فرده عند حاجتي إليه
إنك على كل شيء قدير)

Summary

	Vit D
Structure	A steroid hormone
Synthesis regulation	strictly controlled by PTH (used for hydroxylation)
Synthesis steps	1) formation of cholecalciferol “Vit D3” subcutaneously by sun 2) liver uses 25-hydroxylase to convert cholecalciferol into 25-hydroxyCholecalciferol 3) kidneys use 1-a-hydroxylase to convert 25-hydroxyCholecalciferol to 1,25-DiHydroxycholecalciferol
More info	cholecalciferol: derived from 7-DeHydroCholesterol (which is derived from cholesterol) -1,25-DiHydroxycholecalciferol: binds to blood Gc-globulin Pr as a transporter
Active form	1,25 DiHydroxyCholecalciferol (aka: calcitriol)
Vit D2	-derived from ergosterol -taken from animals & plants -structure: ergocalciferol -both Vit D2 & 3 are clinically available as supplements
Regulation	-along PTH & calcitonin,they regulate Ca homeostasis -Ca & PO4 (phosphate) absorption in Gi & renal tubules -bone resorption during hypocalcemia -directly: Vit D -indirectly: PTH

MCQs:

1) Which of the following is synthesized in the skin by the sunlight?

A) Vitamin D1
B) Vitamin D2
C) Vitamin D3
D) Vitamin D4

2) Cholecalciferol is converted to calcidiol by

A) 25-hydroxylase
B) 35-hydroxylase
C) 25-hydrolase
D) 35-hydrolase

3) Vitamin D regulates plasma levels of

A) phosphate and chloride
B) phosphate and calcium
C) chloride and calcium
D) chloride and sodium

4) For the diagnosis of rickets you should measure the serum level of:

A) chloride
B) calcium
C) sodium
D) Thyroid hormone

5) The Circulating level of vitamin D which required for beneficial health effects is?

A) more than 65 nmol/L
B) more than 60 nmol/L
C) more than 75 nmol/L
D) more than 70 nmol/L

1- C
2- A
3- B
4- B
5- C

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Girls team

- غادة الحيدري
- لمياء القويز
- مجد البراك
- مشاعل القحطاني
- ليلى الصباغ
- منيرة المسعد
- شهد الجبرين
- اروى الجهني

Boys team

Team leaders

- رهام الحلبي
- معاذ الحمود

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