Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

VITAMIN D, RICKETS AND OSTEOPOROSIS

* Please check out this link to know if there are any changes or additions.

Revised by
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Color index: Important | Doctors notes | Further explanation.

OBJECTIVES:

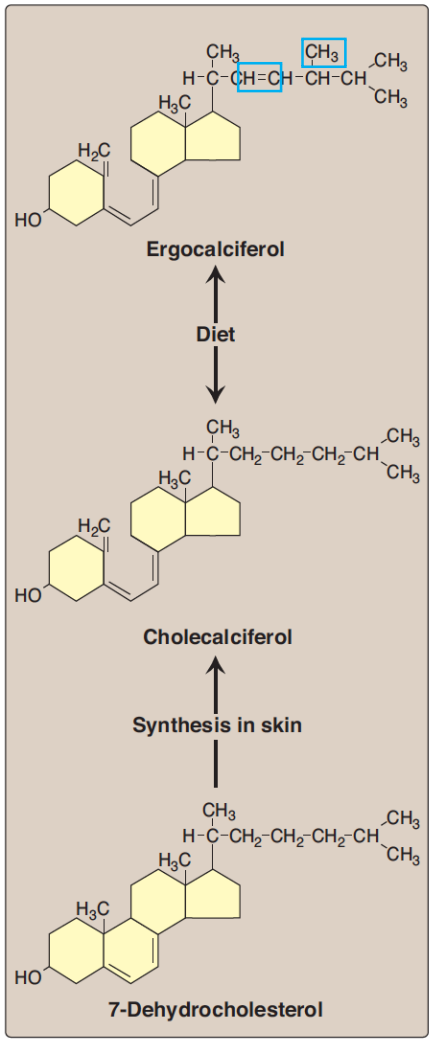
By the end of this lecture, the students should be able to:

- ✓ 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.

Introduction

❖ Vitamin D is considered a **steroid hormone**. The precursor is cholesterol

Dietary sources:		Endogenous vitamin precursor:
Ergocalciferol (vitamin D2)	**Cholecalciferol (vitamin D3)**	**7-Dehydrocholesterol** is converted to vitamin **D3** in the **dermis** and **epidermis** exposed to **UV** in sunlight.
Derived from **ergosterol** in lower animals & **plants**.	Found in **aniMal** tissue. Synthesized in the **skin** by the sunlight (**UV**). fatty fish specifically is a source of vitamin D, but not all kinds of fish.	
D3, D2 are also available as **supplement**.		
The biologically **active** form is **1,25-dihydroxycholecalciferol** (**calcitriol**).		



Daily requirement (IU/day):

-Adults: 600 - Children: 400 - Elderly: 800.

-Upper limit of intake: 4000 (for deficient people).

-high doses (10000 IU for 4-6 weeks or months) can lead to toxicity → hypercalcemia & Ca deposition in arteries and kidneys.

❖ Vitamin D is the only vitamin that is considered as a hormone. (WHY? because it affects gene expression). While other vitamins are considered as co-enzymes.

❖ Vitamin D toxicity is **easy** because its fat soluble.

❖ The only difference is that d2 has a double bond and a methyl group as for d3 it does not.

Metabolism and actions of vitamin D

1-In skin:

- **7-dehydrocholesterol** is converted into Cholecalciferol (Vitamin **D3**).
- **By:** the **sunlight**.

2-In liver:

Cholecalciferol is converted to 25-hydroxycholecalciferol (**calcidiol**).

- **By the enzyme**: **25-hydroxylase.**
- **How?** Hydroxylation at the carbon no. 25.

3-In kidneys: Further hydroxylation

- **25-hydroxycholecalciferol is converted** to **1,25-dihydroxycholecalciferol** (**calcitriol**). (**biologically ACTIVE**).
- **By the enzyme**: **1- α -hydroxylase**.
- **How?** By further hydroxylation at the 1 position.

Any kidney problems may affect vitamin D levels

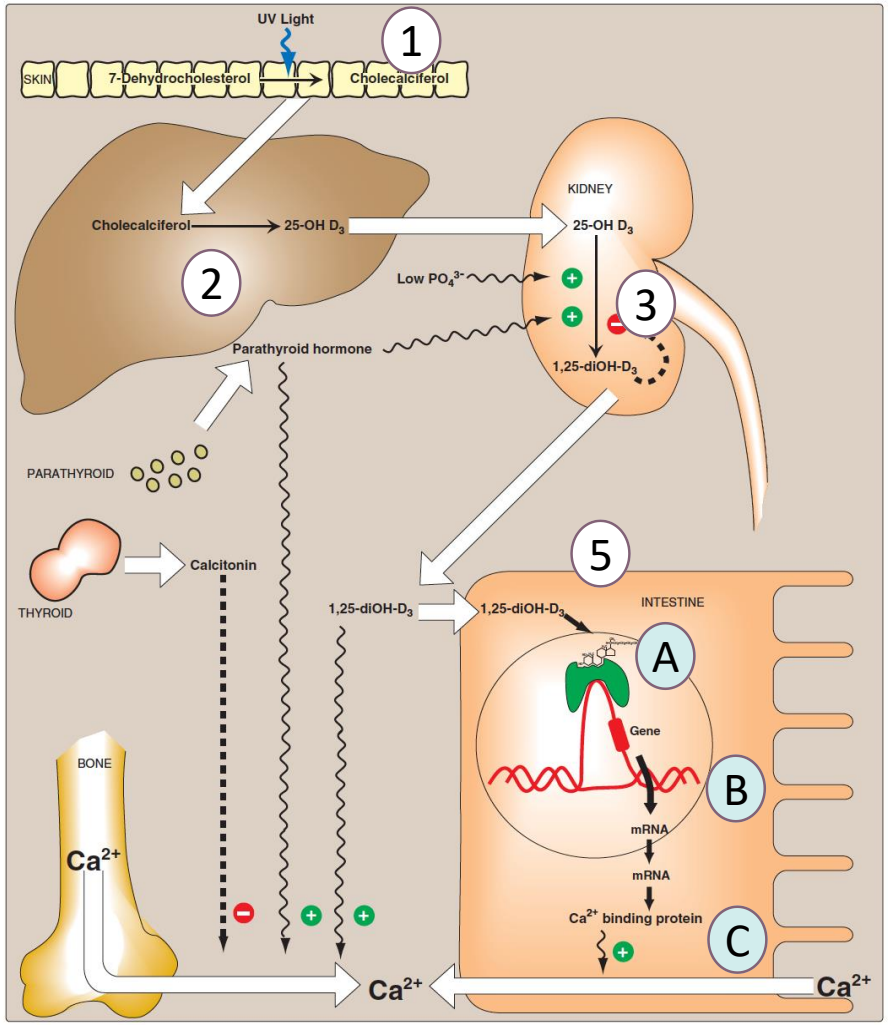
4- Active vitamin D is transported in blood by **gc-globulin** protein.

5- In intestinal cells: Vitamin D action is typical of **steroid hormones**.

A-It **binds** to **intra**cellular receptor proteins.

B-The **receptor complex** interacts with target **DNA** in cell **nucleus**.

C-This stimulates or represses gene expression.



It is very important to know that:

Calcidiol → predominant from of vitamin D in the plasma + form measured in the labs.

Calcitrol → Most active form

Vitamin D regulation and calcium homeostasis

❖ Regulation of 1-α-hydroxylase activity in kidneys :

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

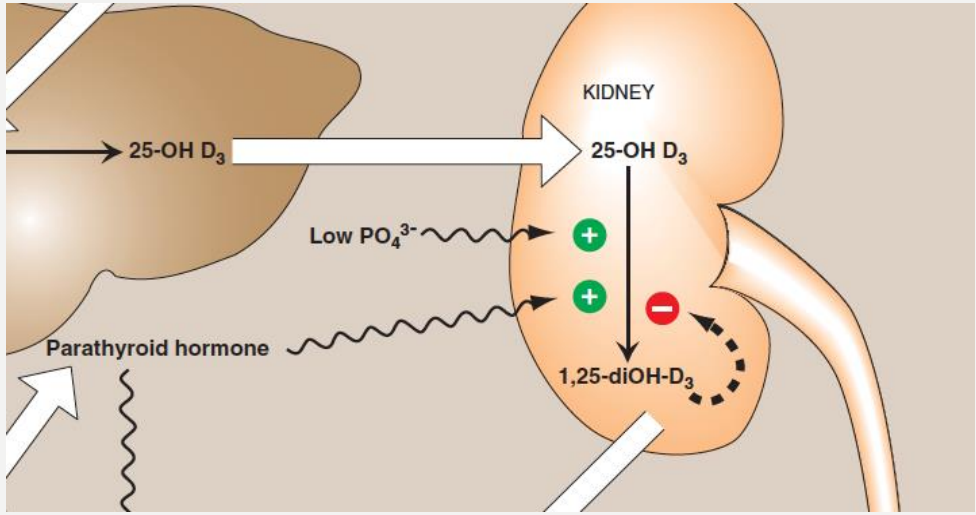
By plasma phosphate	By plasma calcium
Direct effect	**In**direct effect
↓ plasma phosphate → ↑ 1-α-hydroxylase activity.	**↓ plasma calcium → ↑ parathyroid hormone → ↑ 1-α-hydroxylase activity.**
➢ **Directly** increased due to **low** plasma **phosphate.**	➢ **Indirectly** increased via parathyroid hormone (**PTH**) due to **low** plasma **calcium**. ➢ SO **PTH increases** vitamin D synthesis in kidneys. It's the most potent stimulus

❖ Vitamin **D** has essential role in **calcium homeostasis**.

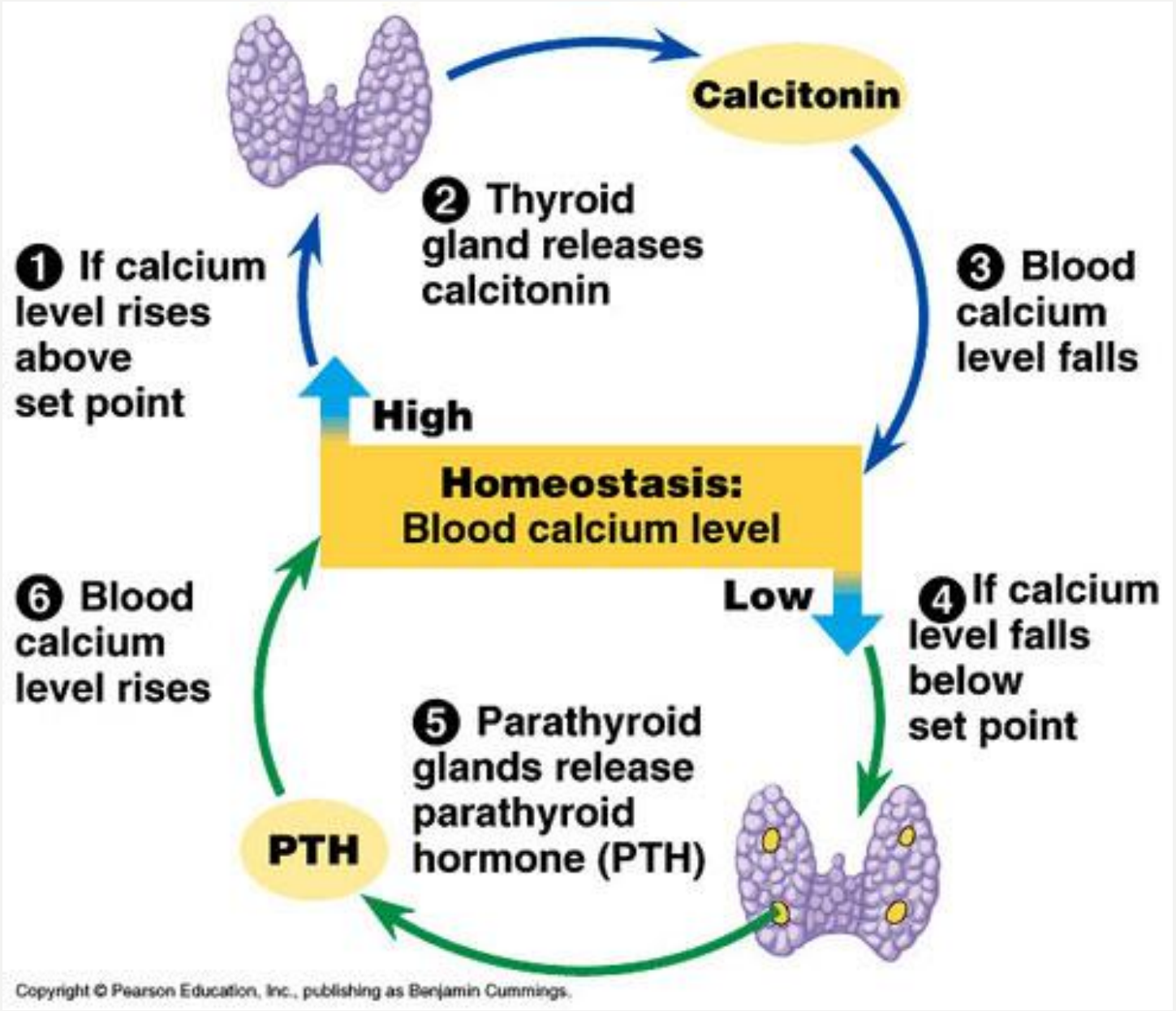
❖ **Calcium homeostasis is maintained by:**

- ✓ Parathyroid hormone (PTH).
- ✓ Calcitonin.

➢ **if I asked you what activates VitD?**
Low phosphate low calcium and high PTH.

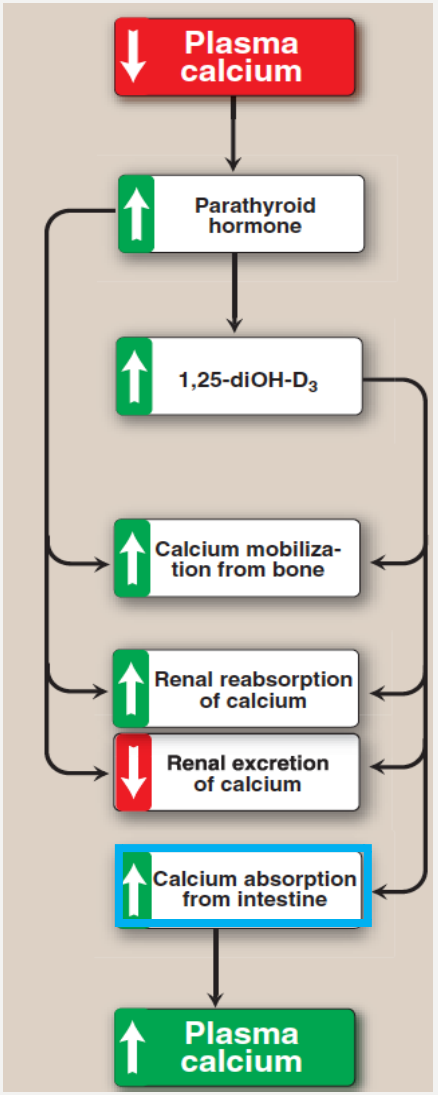


- PTH has the upper hand in regulating calcium levels.
- calcitonin has an inhibitory action



Vitamin D functions

1. **Regulates** plasma levels of calcium and phosphate
2. **Promotes intestinal absorption** of calcium and phosphate.
3. **Stimulates synthesis** of calcium-binding protein for intestinal calcium uptake.
4. **Minimizes loss** (excretion) of calcium by the **kidneys**
5. **Mobilizes** calcium and phosphate from **bone** to maintain plasma levels.



Vitamin D Deficiency

- Deficiency **most common** worldwide.
- **High** prevalence in Saudi Arabia due to:
  - **Low** dietary intake.
  - **In**sufficient exposure to Sun.
  - Lifestyle (e.g. clothing especially in women).
- Circulating level of >75 nmol/L is required for beneficial health effects.

PTH and vit D have the **same** effect on bone and kidney.

1-increase the absorption of calcium. 2-Decrease the excretion 3- Increase the mobilization.

BUT **PTH** DOES NOT WORK ON INTESTINES.ONLY VITAMIN D WORKs ON INTESTINE!!!

Nutritional rickets

<table>
<tr><td>Definition:</td><td colspan="4">➢ A disease in children causing net demineralization of bone with continued formation of collagen matrix of bone.
➢ Incomplete bone mineralization.</td></tr>
<tr><td>Clinical features:</td><td colspan="4">• Bones become soft and pliable (can be bent).
• Causes skeletal deformities including bowed legs (cuz the bones can’t bear the body weight, so they bend).
• Patients have low serum levels of vitamin D.</td></tr>
<tr><td rowspan="2">Causes:</td><td colspan="4">Vitamin D deficiency because of:</td></tr>
<tr><td>Poor nutrition</td><td>Insufficient exposure to sunlight</td><td>Renal osteodystrophy
(causes decreased synthesis of active vitamin D in kidneys)</td><td>Hypoparathyroidism
(hypocalcemia)</td></tr>
<tr><td>Diagnosis:</td><td colspan="4">Measuring serum levels of:
➢ 25-hydroxycholecalciferol !!!!لاحظوا اننا مانقيس الاكتف فورم
- Why we measure it instead of calcitriol? 1-Premodminant. 2- Storage form.
- In elderly, hypertensive patients, and uncontrolled DM → they all may have renal problems leading to normal synthesis of 25-hydroxyvitD3 and decreased 1,25-dihydroxyvitD3! → 1,25-diOHvitD3 is measured instead of 25-hydroxyVitD3
➢ PTH. PTH is more potent than Calcitonin, because calcitonin has a transient effect. Its not measured in labs except as a biomarker for carcinoma of thyroid.
➢ Calcium
➢ Phosphate
➢ Alkaline phosphatase</td></tr>
<tr><td>Treatment:</td><td colspan="4">Vitamin D and calcium supplementation</td></tr>
</table>

Inherited rickets

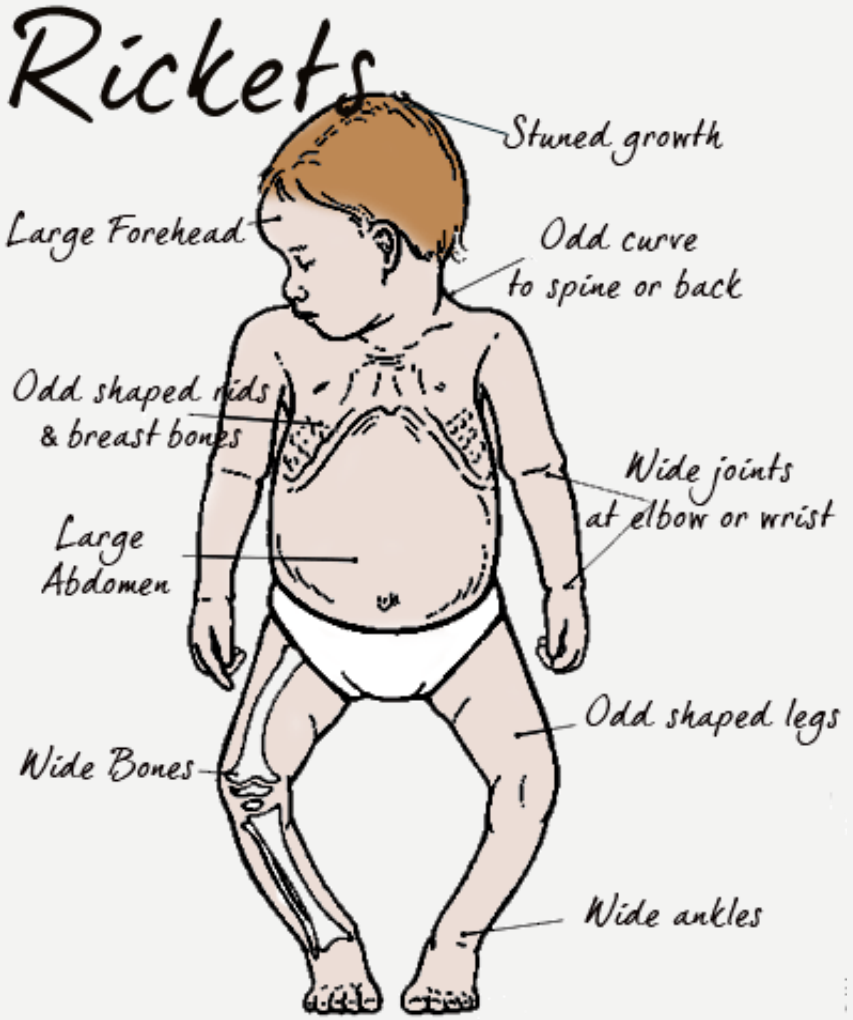
- Vitamin D-dependent rickets (types **1** and **2**).
- **Rare** types of rickets due to genetic disorders causing vitamin D **deficiency**.

Mainly because of genetic defects in:

- Vitamin D synthesis
- Vitamin D receptor (no hormone action).

يا انه مشكلة بالتصنيع.. يصنع بكميات قليلة.
أو انه موجود لكن المشكلة بالرسبتور "ماتقدر ترتبط فيه ← ما تقدر تأثر على الدي ان أي".

- It's the most severe form, where the vitamin can't bind to the receptor or it binds normally but takes a long time to do its action (very slow activity).



Osteomalacia:

- Demineralization of bones in **adults** (due to nutrititional deficiency of vit D).

- Rickets in children = osteomalacia in adults.
- Renal osteodystrophy is seen in adults more causing them to have osteomalacia, they will have:

High: PTH – **Low:** Ca, 1,25-diOH – **Normal:** 25-OH

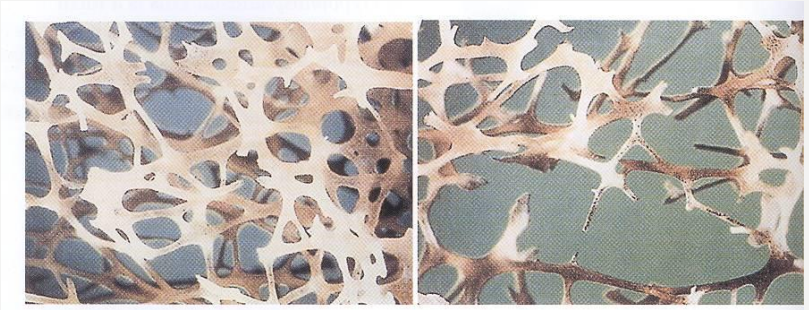
Osteoporosis:

- **Reduction** in bone mass per unit volume.
- Bone matrix composition is **normal** but it is **reduced**.
- **Increases** fragility of bones.
- **Increases** susceptibility to fractures.

Types:				
Primary:	**Secondary:**			
Post-menopausal women lose more bone mass than men .	**Drugs** e.g. Chemotherapy, glucocorticoids	**Immobilization**	**GI disease**	**alcohol**
	Cushing's syndrome	**Gonadal failure** low estrogen > no inhibition to osteoclast > high osteoclast activity	**Hyperthyroidism**	**Smoking**

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.**

osteoporosis is the most common, how do we usually diagnose osteoporosis?
By excluding osteomalacia

Osteoporosis:

Diagnosis:	
WHO standard:	**Biochemical tests:**
Serial measurement of **bone mineral density**. • The test results overlap in healthy subjects and patients with osteoporosis.	➢ **calcium**, **phosphate**, **vitamin D**. ✓ These tests **alone** CANNOT diagnose or monitor primary osteoporosis. ✓ Secondary osteoporosis (due to other causes) can be diagnosed by biochemical tests. نشوف وش السبب ونشتغل على الماركرز الخاصة فيه مثلا لو كان سبب الهشاشة هو نشاط بالغدة الدرقية نقيس التي اس اتش
Treatment:	
Replacement therapy:	**Bisphosphonates**
Oral calcium, **estrogens**, **fluoride therapy** may be beneficial.	Inhibit bone resorption that **slows** down bone loss.
In confirmed cases of osteoporosis → Treatment options are unsatisfactory ☹	

Prevention:		
Prevention from **childhood** is important	**Good diet** and **exercise** prevent osteoporosis later. 😉 الكسل مايفيد	**Hormone replacement** therapy in menopause may prevent osteoporosis**.**

Biomarkers of osteoporosis:

Bone formation markers

Osteocalcin

Osteocalcin

- **Produced by:** **osteoblasts** during bone formation.
- **Involved in:** bone remodeling process.
- **Released during:** bone formation and resorption (bone turnover).
- Short half-life of few minutes.
- Blood levels are influenced by **vitamin K** status and **renal function**.

Bone-specific alkaline phosphatase

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.
- The isoenzymes also interfere with the asaay.

P1NP (Procollagen type-1 amino-terminal propeptide)

P1NP

- **Produced by:** **osteoblasts.**
- **Involved in:** the process of type 1 collagen formation.
- Blood levels are highly responsive to osteoporosis progression and treatment.
- Shows good assay precision.
- Stable at room temperature.

Bone resorption markers

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.

Osteoporosis can be also diagnosed with DEXA.
It is important which is formation and which is reabsorption.

Check your understanding!

Q1: The main dietary source of Vitamin D3 is

A. Plants
B. Animals
C. Synthesis by the skin (UV Exposure)
D. None of the above

Q2: Parathyroid Hormone (PTH) ……. Vitamin D synthesis in the …….

A. Increases, Kidney
B. Increases, Liver
C. Decreases, Kidney
D. Decreases, Liver

Q3: Vitamin D is hydrophilic

A. True
B. False

Q4: In Rickets disease, a deficiency in Vitamin D causes

A. Incomplete bone mineralization
B. Skeletal deformities (e.g. bowed legs)
C. Excessive collagen deposition in the bone
D. A+B

Q5: Primary Osteoporosis refers to the pathological reduction in bone matrix.

A. True
B. False

Q6: One of the biochemical tests used in diagnosis of Secondary Osteoporosis

A. Serum Calcium
B. Serum Phosphate
C. Serum Vitamin D
D. None of the above

Q7: Osteocalcin blood levels are influenced by

A. Vitamin A
B. Vitamin B6
C. Vitamin K
D. Vitamin E

1.B 2.A 3.B 4.D 5.B 6.D 7.C

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"قد تاتيك النعمة لانك تمنيتها لغيرك"

Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition

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