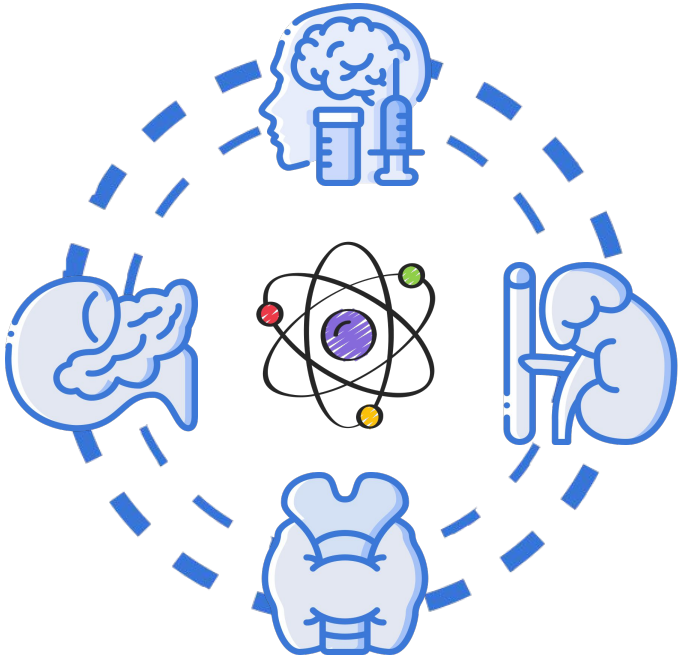
Vitamin D , Rickets & osteoporosis



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- Main Topic
- Main content
- Important
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- Extra info

Editing File

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

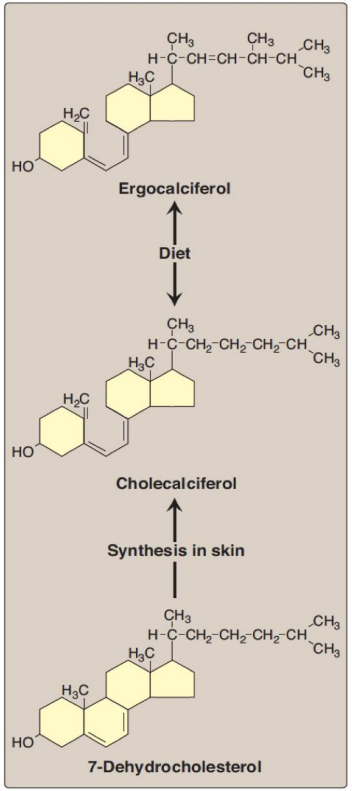
Overview:

- Vitamin D distribution, metabolism, regulation and functions
- Vitamin D in calcium homeostasis
- Vitamin D deficiency
- 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

Vitamin D Sources & Distribution



Vitamin D distribution

- **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

Daily requirement (IU/day)

- Children 400
- Adults 600
- Elderly 800

Vitamin D Metabolism

Vitamin D Metabolism

1 in skin	Cholecalciferol (Vitamin D3) is derived from 7-dehydrocholesterol by the sunlight
2 in liver	Cholecalciferol is converted to 25-hydroxycholecalciferol (calcidiol) (the storage form which is measured in the plasma) by the enzyme 25-hydroxylase
3 in kidney	The 1-a-hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)
4	Active vitamin D is transported in blood by gc-globulin protein

Vitamin D Action

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

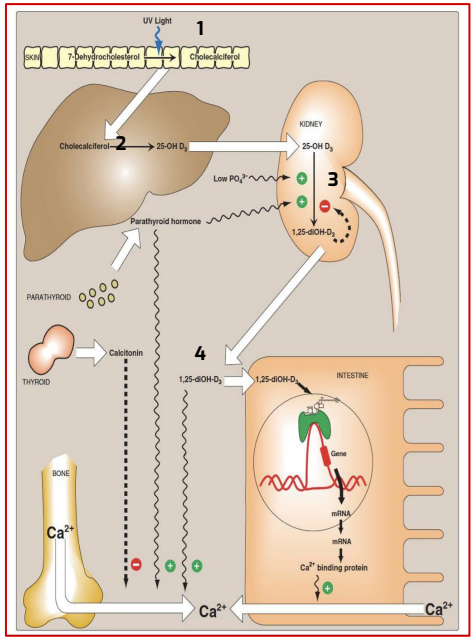
Vitamin D Regulation & Calcium Homeostasis

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

Activity of 1-a-hydroxylase in kidneys

Directly Increased	Indirectly Increased
Due to low plasma phosphate	Via increased parathyroid hormone (PTH) due to low plasma calcium

- Vitamin D has essential role in calcium homeostasis
- Calcium homeostasis is maintained by parathyroid hormone (PTH) and calcitonin



1- in the skin 7- dehydrocholesterol will be converted to cholecalciferol by UV light (active)
2 - first hydroxylation in the liver covert cholecalciferol to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase (inactive) the stored and prominent form and the one measured in the lab.
3- second hydroxylation convert 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol by the enzyme 1-a-hydroxylase (active)

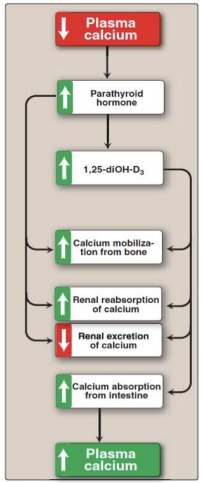
This reaction is tightly regulated by the -level of phosphate (directly) and calcium (indirectly)
-Negative feedback

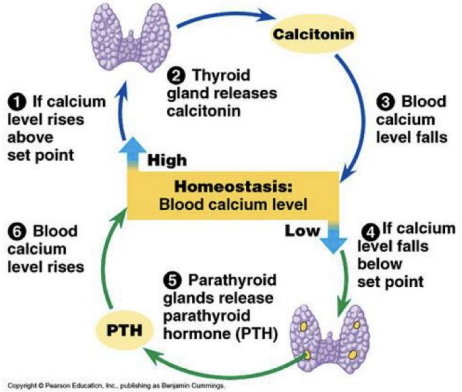
Vitamin D has a steroid like hormone activity, it diffuse through cell membrane and bind to cytosolic receptor this complex then inter into the nucleus to interact with the DNA to increase gene expression of calcium binding protein which will carry calcium from intestinal epithelium to the blood circulation.

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 of calcium by the kidneys
5. Mobilizes calcium and phosphate from bone to maintain plasma levels

Vitamin D Response To Low Plasma Calcium





Calcium homeostasis

Vitamin D Deficiency

- Deficiency most common worldwide

- High prevalence in Saudi Arabia due to:
1- Low dietary intake
2- Insufficient exposure to Sun
3- Lifestyle (e.g. clothing)

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

*
< 25 nmol/L - Vitamin D Deficiency
25-75 nmol/L - Vitamin D Insufficiency

Rickets[1]

Nutritional rickets

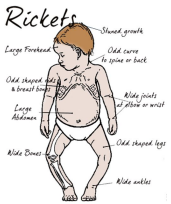
- A disease in children causing net demineralization of bone
- With continued formation of collagen matrix of bone
- Incomplete bone mineralization
- Bones become soft and pliable
- Causes skeletal deformities including bowed legs
- Patients have low serum levels of vitamin D
  (**Osteomalacia**: demineralization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

Rickets	Inherited 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)	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[2] (no hormone action)

Diagnosis

Measuring serum levels of:

- 25-hydroxycholecalciferol (low)
- PTH[3]
- Calcium (low)
- Phosphate (high)
- Alkaline phosphatase (high)



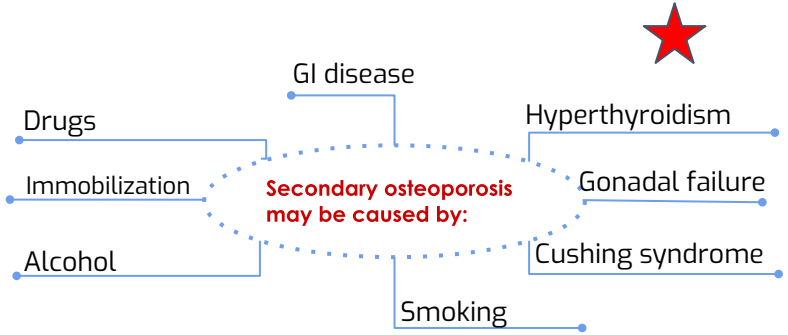
Treatment

–Vitamin D and calcium supplementation

1.Two types of rickets: dietary and inherited
2. Defect in the receptor will cause inability to absorb Ca
3.(if the patient has hypoparathyroidism it will be low,if not it will increase to compensate)

Osteoporosis

- 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
- Increases susceptibility to fractures



Diagnosis of osteoporosis

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

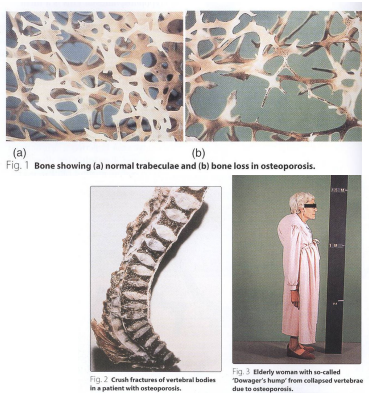

(a) (b)
Fig. 1 Bone showing (a) normal trabeculae and (b) bone loss in osteoporosis.

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.

Biomarkers of osteoporosis

Biomarkers of osteoporosis

Bone formation markers

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

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

P1NP (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

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

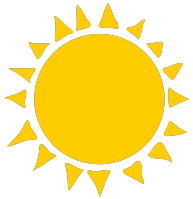
Treatment & Prevention

Treatment	Prevention
In confirmed cases of osteoporosis – Treatment options are unsatisfactory	Prevention from childhood is important
Oral calcium, estrogens, fluoride therapy may be beneficial	Good **diet** and **exercise** prevent osteoporosis later
Bisphosphonates inhibit bone resorption that slows down bone loss	Hormone replacement therapy in menopause may prevent osteoporosis

Take Home Messages

- 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

Summary



Vit 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**
Vitamin D metabolism

In kidneys: The **1-a-hydroxylase** enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)

Vit D regulation

Vitamin D synthesis is tightly regulated by:
1- plasma levels of phosphate(directly) and calcium (indirectly)
- ↓PO_4 → ↑ vitamin D synthesis by kidneys
- ↓Ca2+ → PTH release → ↑ vitamin D synthesis by kidneys
2- ↑Ca2+ →↓ vitamin D synthesis by kidneys (Negative feedback)

Vitamin D action

•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

Vit 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 to maintain plasma levels

Vit D deficiency

• Deficiency most common worldwide
• High prevalence in Saudi Arabia due to:
– Low dietary intake
– Insufficient exposure to Sun

Rickets

-Children, incomplete bone mineralization
-Low serum levels of vit D
Causes:

- nutrition
- exposure to sunlight
- Renal osteodystrophy
- Hypoparathyroidism

Inherited rickets

Genetic defect in: vit D synthesis/receptor

Dx :25-OH D3, PTH,Ca, ALP,PO_4^{3-}

Rx: Vit D & Ca supplements

Osteoporosis

Bone mass per unit volume
2ndry OP causes: drugs,alcohol,smoking,gi,cushing,hyperthyroidism

biomarkers

Bone formation: osteocalcin, bone specific ALP,P1NP

Bone resorption: CTX1

Dx : measure bone mineral density,biochemical tests

Rx : oral Ca,estrogen,fluoride,bisphosphonates

Quiz

MCQs :

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: what is the mechanism of action of vitamin D

a)Ion Channel–Linked Hormone b) G Protein–Linked Hormone
c)Enzyme-Linked Hormone d) Intracellular Hormone Receptors & gene activation

Q3: Chronic renal failure requires oral administration of

a)1-25-dihydroxycalciferol b)25-hydroxycalciferol c)calciferol d)7-dehydrocholesterol

Q4: in diagnosing a patient with rickets, which one of the following will be low:

a)calcium b)alkaline phosphatase c)phosphate d)bone mass

Q5: which one of the following biomarkers involved in bone remodeling process

a)P1NP b)CTX1 c)Alkaline phosphatase d)osteocalcin

Q6: in treating osteoporosis, which one of the following will inhibit bone resorption:

a)fluoride therapy b)bisphosphonate c)oral calcium d)vitamin D

SAQs :

Q1: Explain how vitamin D is regulated.

Q2: enumerate 5 of the causes of secondary osteoporosis.

Q3: enumerate the biomarkers of osteoporosis.

Q4: list the functions of vitamin D.

★ MCQs Answer key:

1) d 2)d 3)a 4)a 5) d 6)b

★ SAQs Answer key:

1) $\downarrow PO_4 \rightarrow \uparrow$ vitamin D synthesis by kidneys (Direct effect)
$\downarrow Ca2+ \rightarrow$ PTH release $\rightarrow \uparrow$ vitamin D synthesis by kidneys (indirect effect)
$\uparrow Ca2+ \rightarrow \downarrow$ vitamin D synthesis by kidneys (Negative feedback)
2) GI disease , smoking , alcohol , drugs , hyperthyroidism .
3) Bone formation: osteocalcin,bone specific alkaline phosphatase,P1NP.
Bone resorption: CTX1
4) Slide 5

Team members

Girls Team:

- Ajeed Al-Rashoud
- **Alwateen Albalawi**
- Amira AlDakhilallah
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- **Sarah Alkhalife**
- Shahd Alsalamah
- Taif Alotaibi

Boys Team:

- Alkassem Binobaid
- Fares Aldokhayel
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ "The way to get started is to quit talking and begin doing"

We hear you