Vitamin D, Rickets and Osteoporosis

Endocrine Block

Objectives

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

- Understand the functions, metabolism, regulation and deficiency of vitamin D
- Discuss the role of vitamin D in calcium homeostasis
- Identify the types and causes of rickets
- Correlate vitamin D and calcium deficiency in osteoporosis
- 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 lower animals and plants
- D3, D2 are also available as supplement

Vitamin D distribution

- Dietary sources:
  - Ergocalciferol (vitamin D2) found in plants
  - Cholecalciferol (vitamin D3) found in animal tissue

- Endogenous vitamin precursor:
  - 7-Dehydrocholesterol is converted to vitamin D3 in the dermis and epidermis exposed to UV in sunlight

Vitamin D metabolism

In skin:

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

In liver:

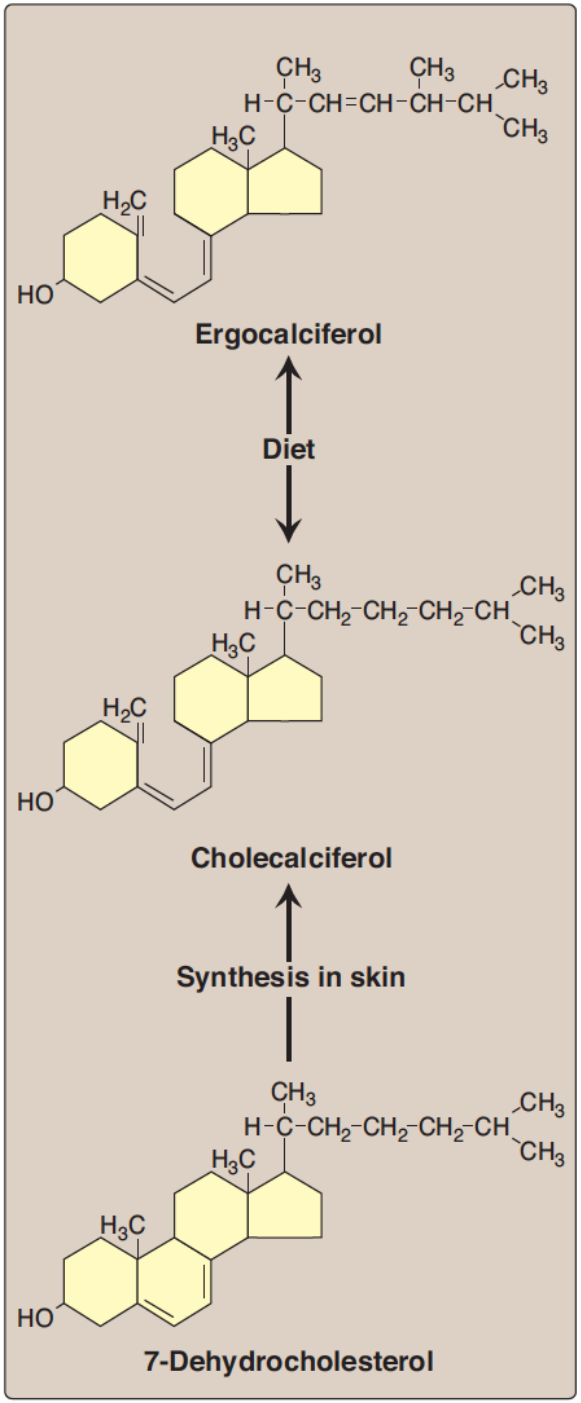
- Cholecalciferol is converted to 25-hydroxycholecalciferol (calcidiol) by the enzyme 25-hydroxylase

Vitamin D metabolism

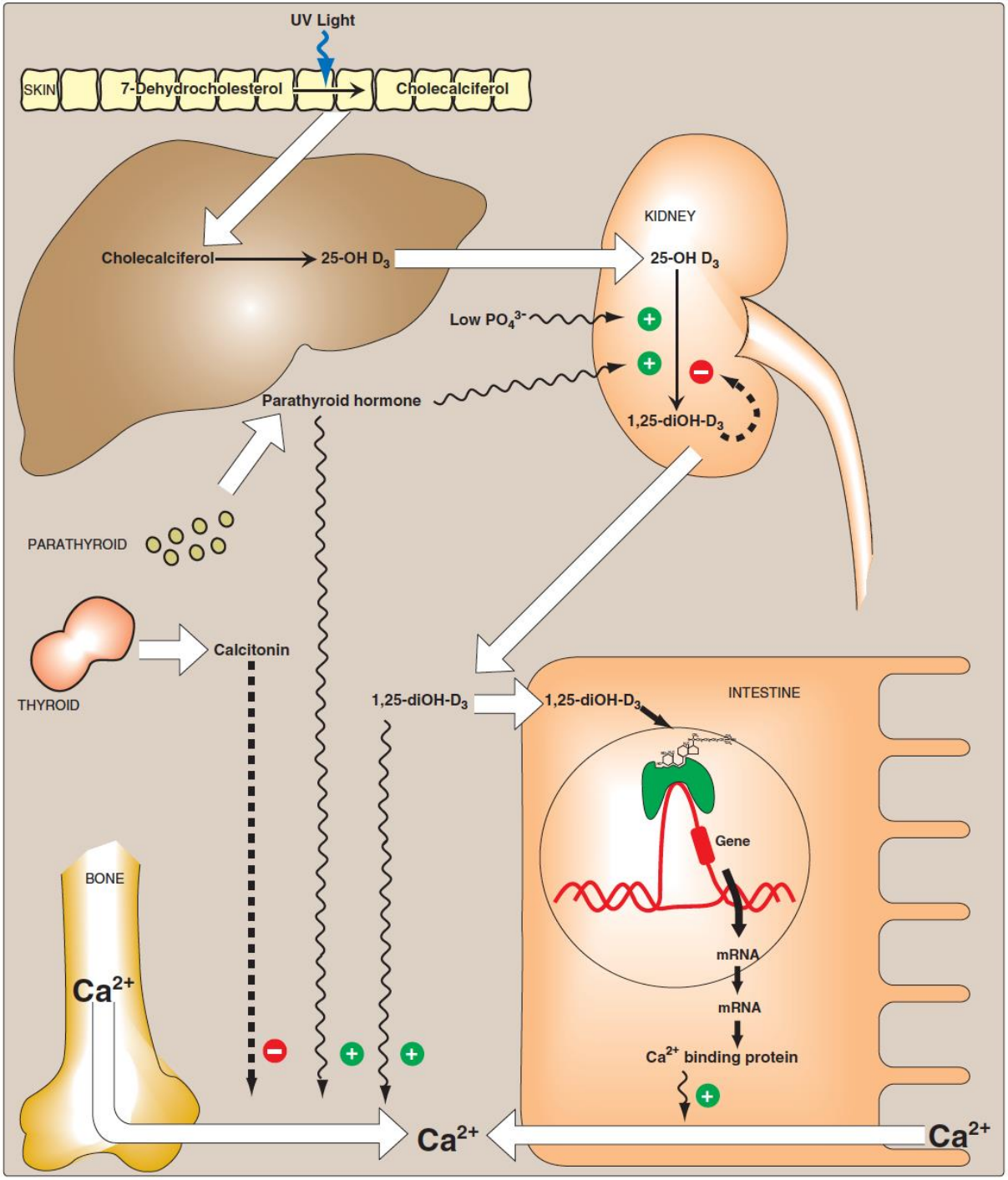
In kidneys:

- 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

Sources of Vitamin D

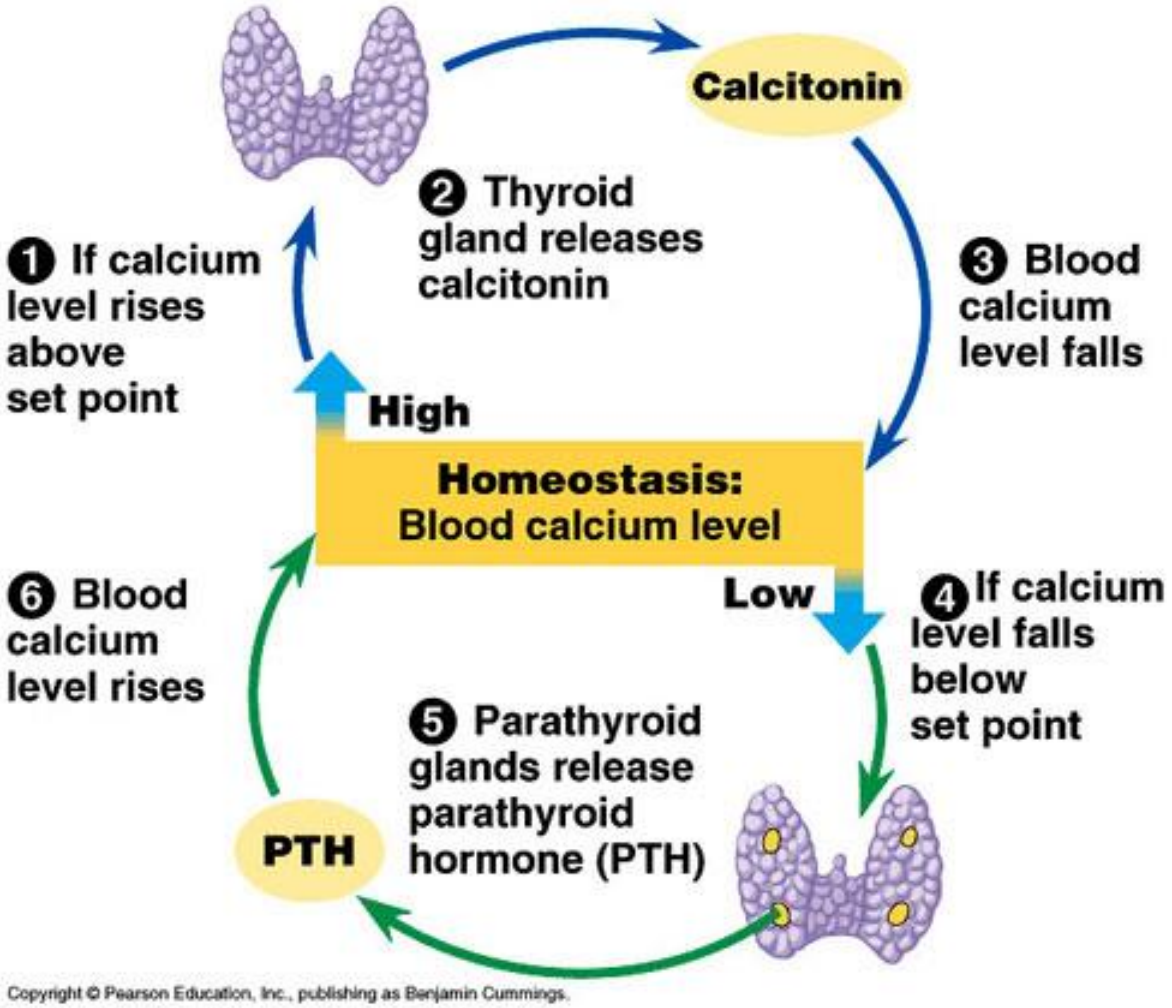


Metabolism and actions of vitamin D



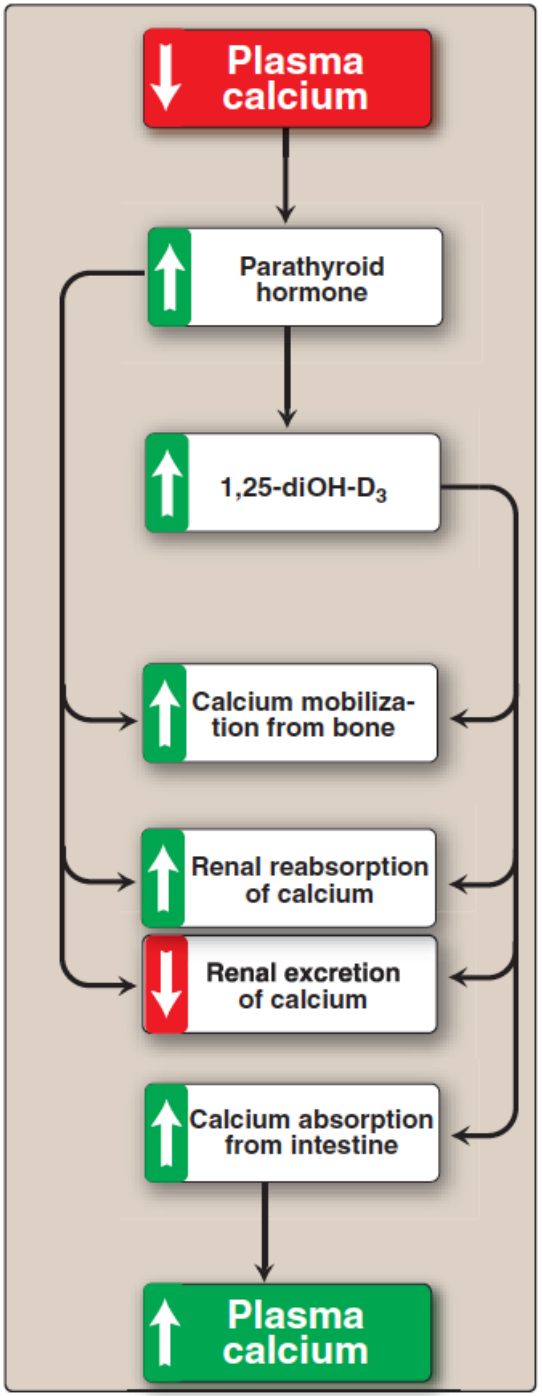
Vitamin D regulation and calcium homeostasis

- 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 via parathyroid hormone (PTH) due to low plasma calcium
  - PTH increases vitamin D synthesis in kidneys
- Vitamin D has essential role in calcium homeostasis
- Calcium homeostasis is maintained by parathyroid hormone (PTH) and calcitonin



Calcium homeostasis

Vitamin D response to low plasma calcium



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 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

Vitamin D deficiency

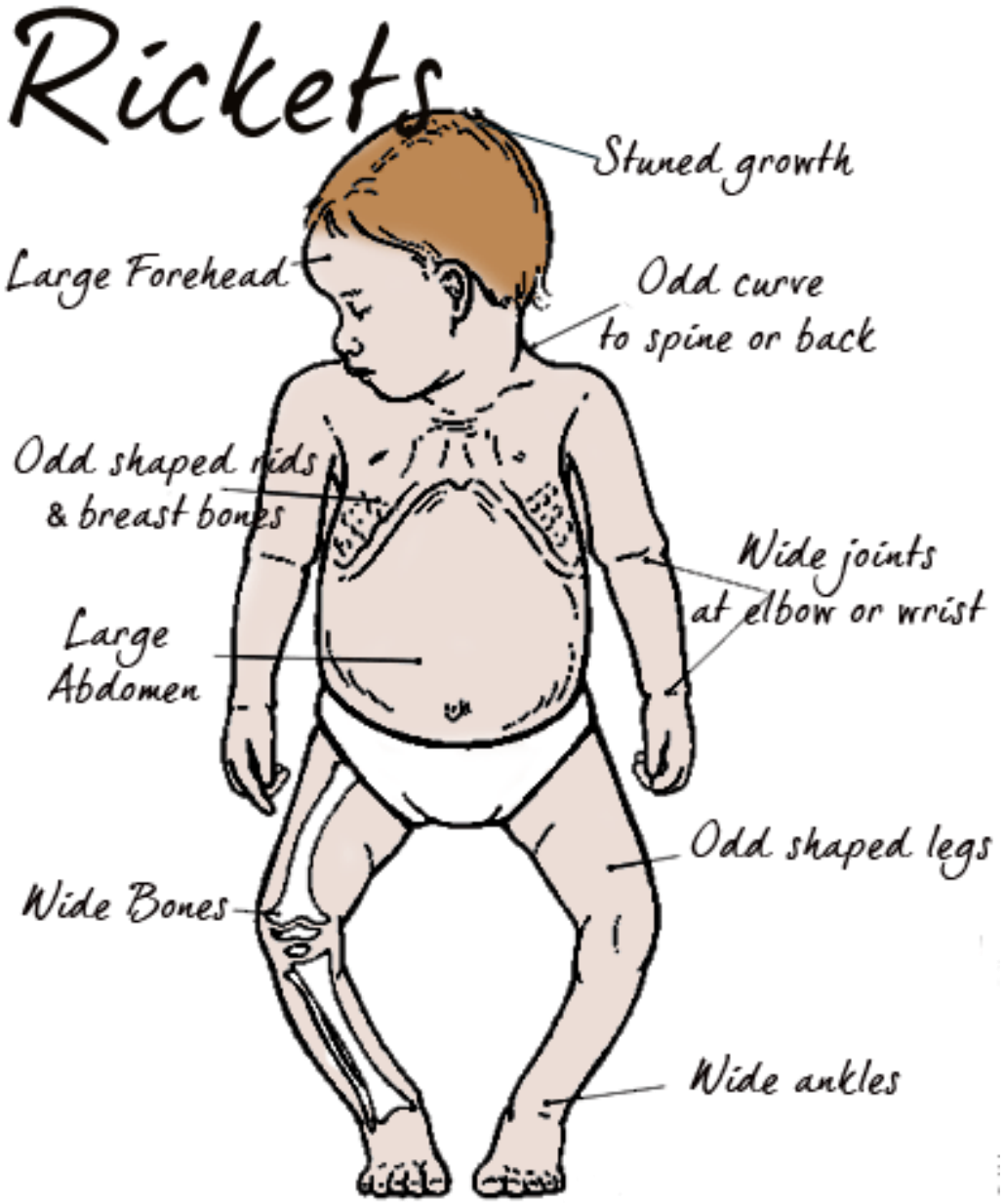
- Deficiency most common worldwide
- High prevalence in Saudi Arabia due to:
  - Low dietary intake
  - Insufficient exposure to sun
  - Lifestyle (eg. clothing esp in women)
- Circulating level of >75 nmol/L is required for beneficial health effects

Vitamin D intake and toxicity

- Daily requirement (IU/day):
  - Adults: 600
  - Children: 400
  - Elderly: 800
  - Upper limit of intake: 4000
- High doses (10,000 IU for weeks or months) can lead to toxicity
- Hypercalcemia and deposition of calcium in arteries and kidneys

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


Rickets
Stuned growth
Large Forehead
Odd curve
to spine or back
Odd shaped rids
& breast bones
Wide joints
at elbow or wrist
Large
Abdomen
Odd shaped legs
Wide Bones
Wide ankles

- Osteomalacia is demineralization of bones in adults
- Due to nutritional deficiency of vitamin D

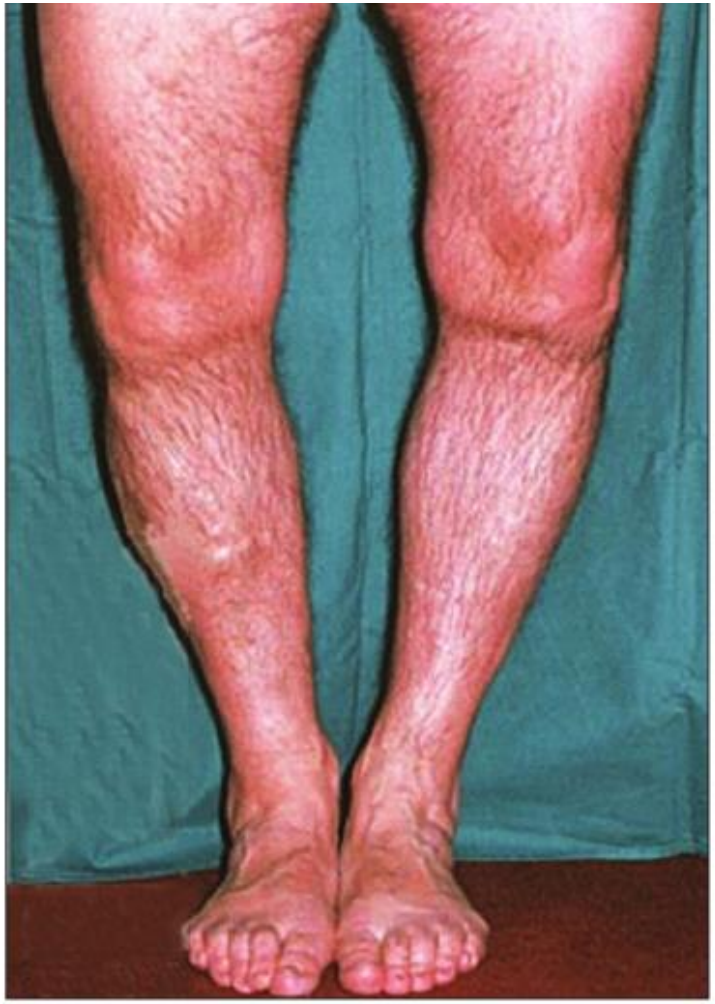


Figure 28.25
Bowed legs of middle-aged man with osteomalacia, a nutritional vitamin D deficiency that results in demineralization of the skeleton.

Nutritional 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)

Inherited rickets

Vitamin D-dependent rickets (types 1 and 2)

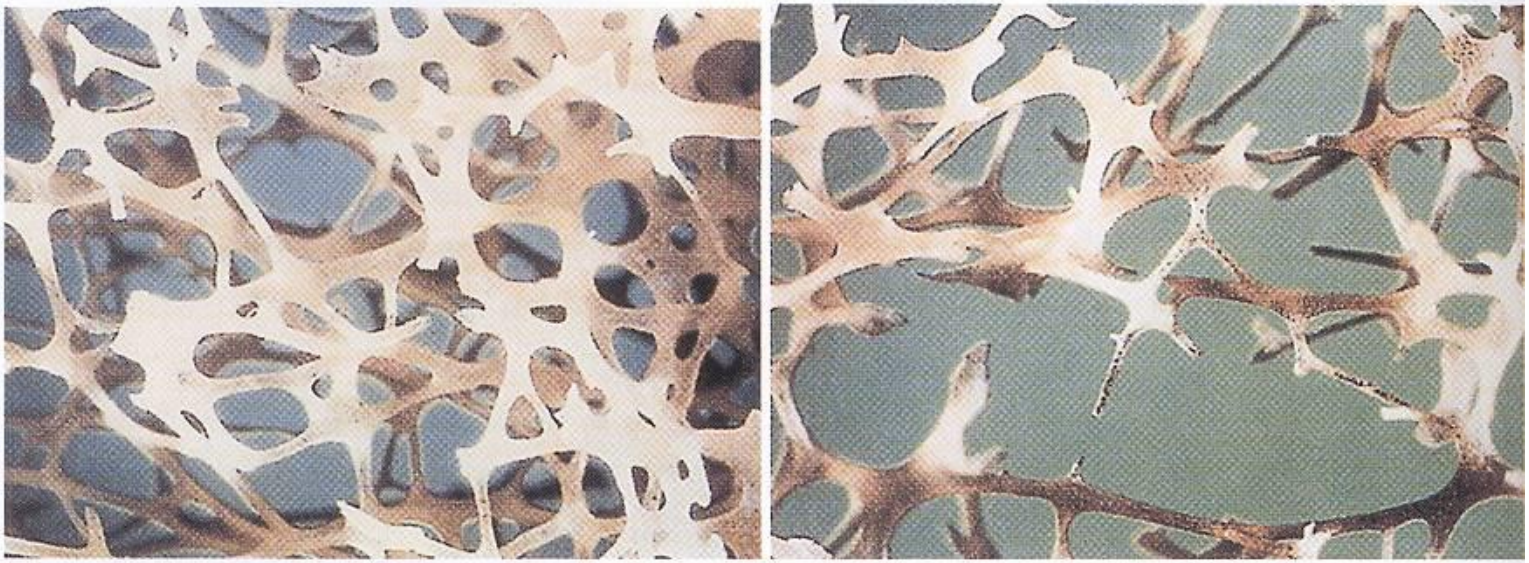
- Rare types of rickets due to genetic disorders
- Causing vitamin D deficiency mainly because of genetic defects in:
  - Vitamin D synthesis
  - Vitamin D receptor (no hormone action)

Diagnosis and treatment of rickets

- Measuring serum levels of:
  - 25-hydroxycholecalciferol
  - PTH
  - Calcium
  - Phosphate
  - Alkaline phosphatase
- Treatment:
  - Vitamin D and calcium supplementation

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



(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.**

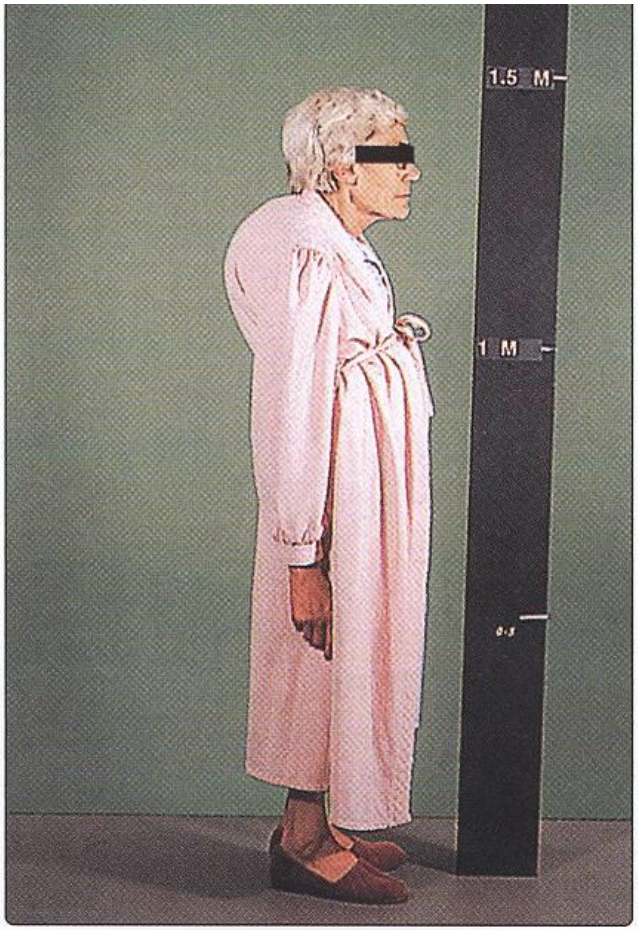


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

Osteoporosis

- Secondary osteoporosis may be caused by:
  - Drugs
  - Immobilization
  - Smoking
  - Alcohol
  - Cushing syndrome
  - Gonadal failure
  - Hyperthyroidism
  - GI disease

Diagnosis of osteoporosis

- WHO standard: Serial measurement of bone mineral density
- Biochemical tests (calcium, phosphate, vitamin D) alone cannot 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

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
  - Blood levels are influenced by vitamin K status and renal function

Biomarkers of osteoporosis

- 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 assay

Biomarkers of osteoporosis

- P1NP (Procollagen type-1 amino-terminal propeptide)
  - 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

Biomarkers of osteoporosis

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 and prevention of osteoporosis

Treatment

- In confirmed cases of osteoporosis
  - Treatment options are unsatisfactory
- Oral calcium, estrogens, fluoride therapy may be beneficial
- Bisphosphonates inhibit bone resorption that slow down bone loss

Treatment and prevention of osteoporosis

Prevention

- Prevention from childhood is important
- Good diet and exercise prevent osteoporosis later
- 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

References

- Lippincott's Biochemistry 6th Edition, pp. 386-389.
- Clinical Biochemistry: An illustrated colour text 5th Edition by Allan Gaw (Churchill Livingstone)
- Wheater, G. et al. The clinical utility of bone marker measurements in osteoporosis. *J. Trans. Med.* 2013, 11: 201-214.