

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

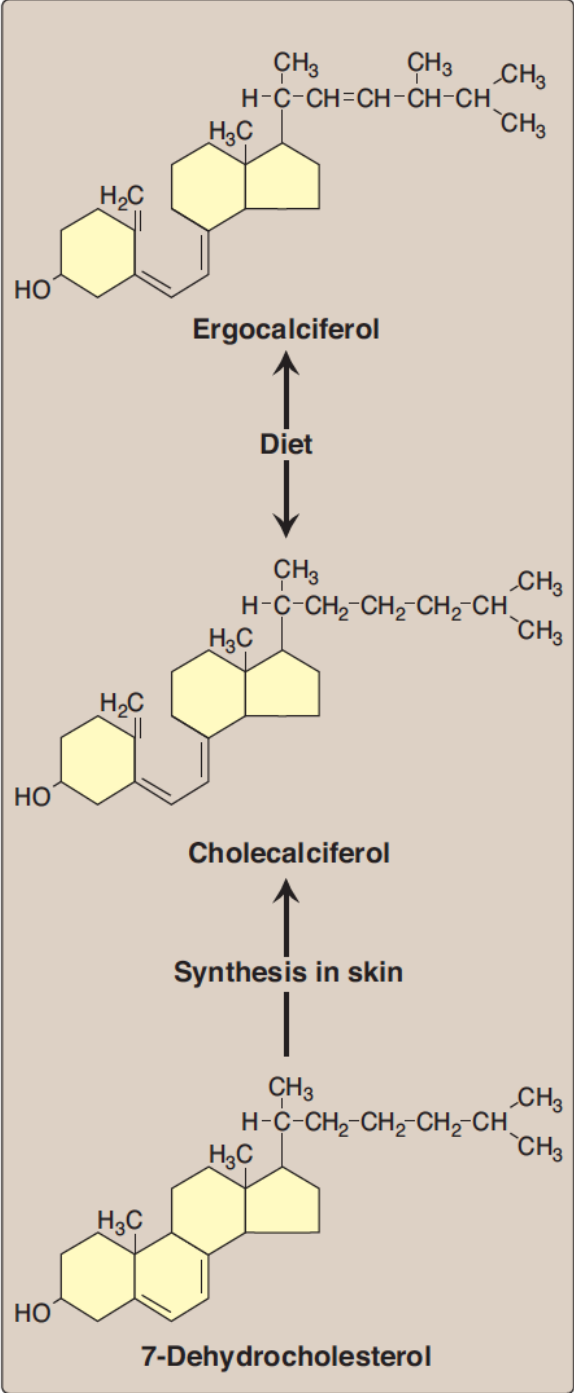
Vitamin D

- 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

Sources of Vitamin D



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

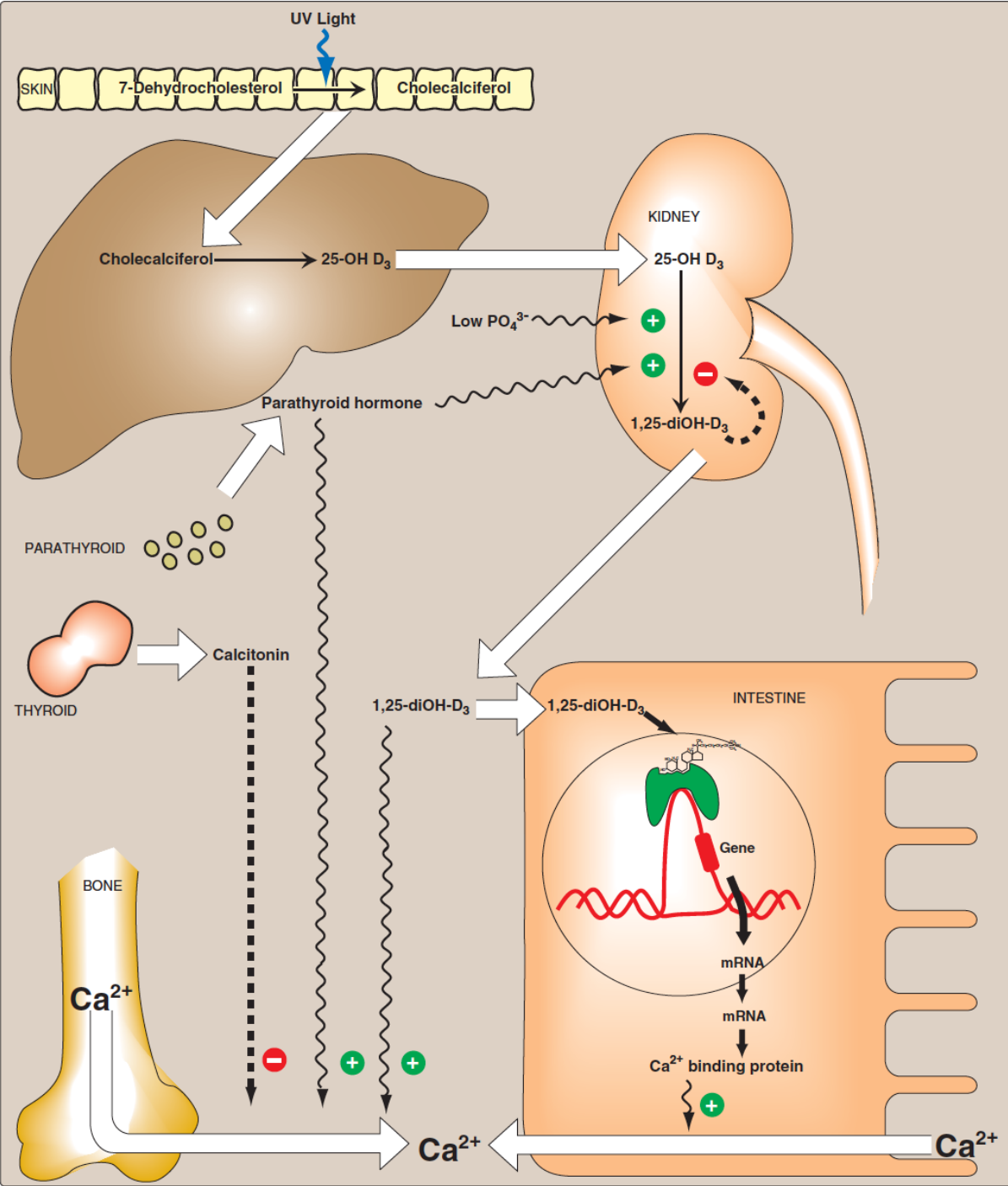
In kidneys:

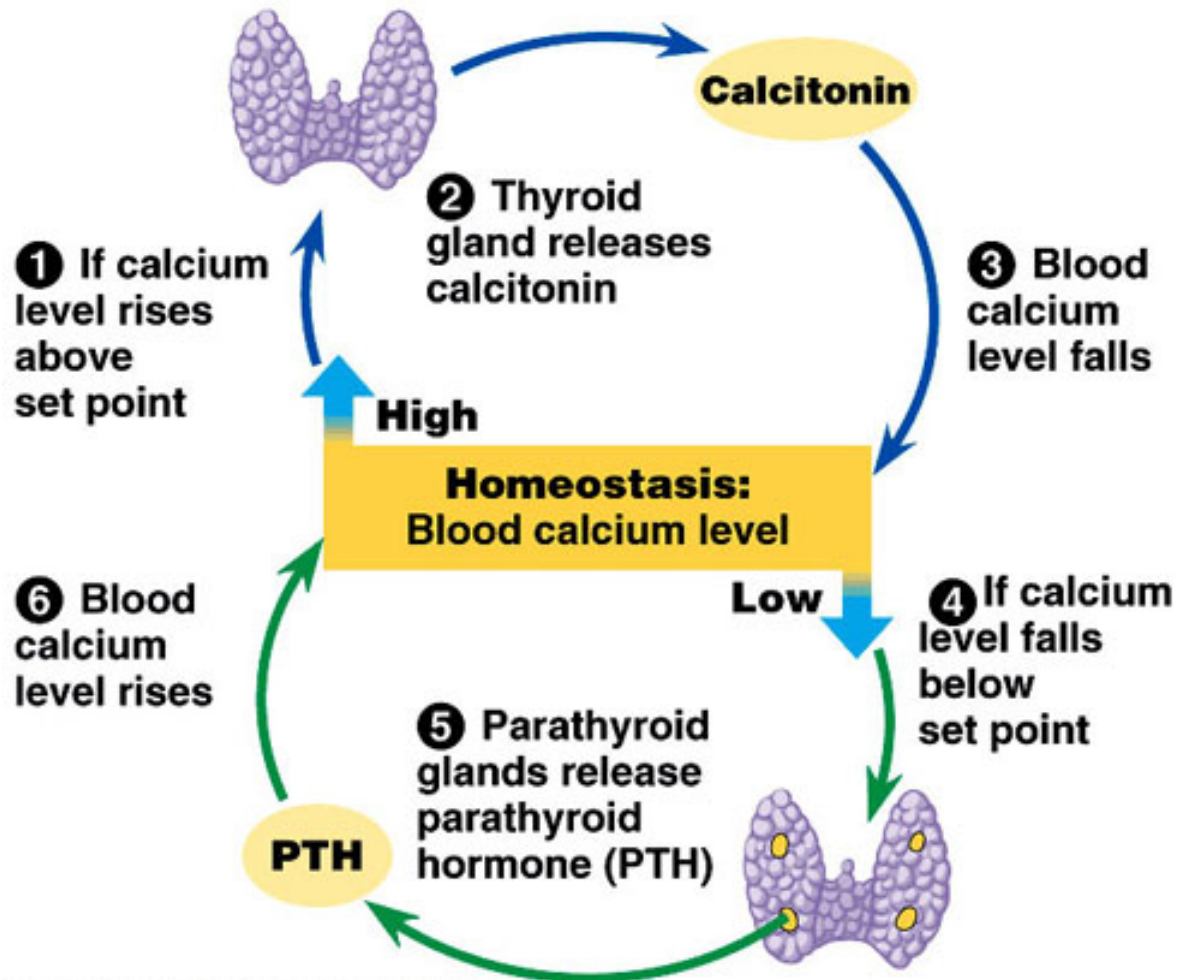
- The 1- α -hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)
- Active vitamin D is transported in blood by gc-globulin protein

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

Metabolism and actions of vitamin D

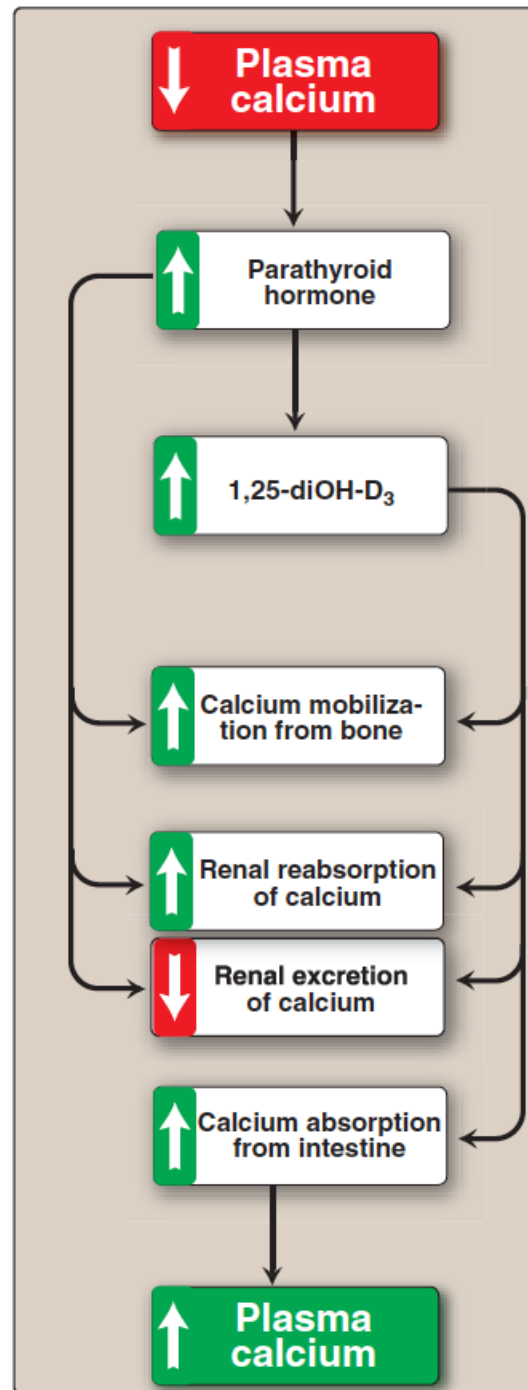




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Calcium homeostasis

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

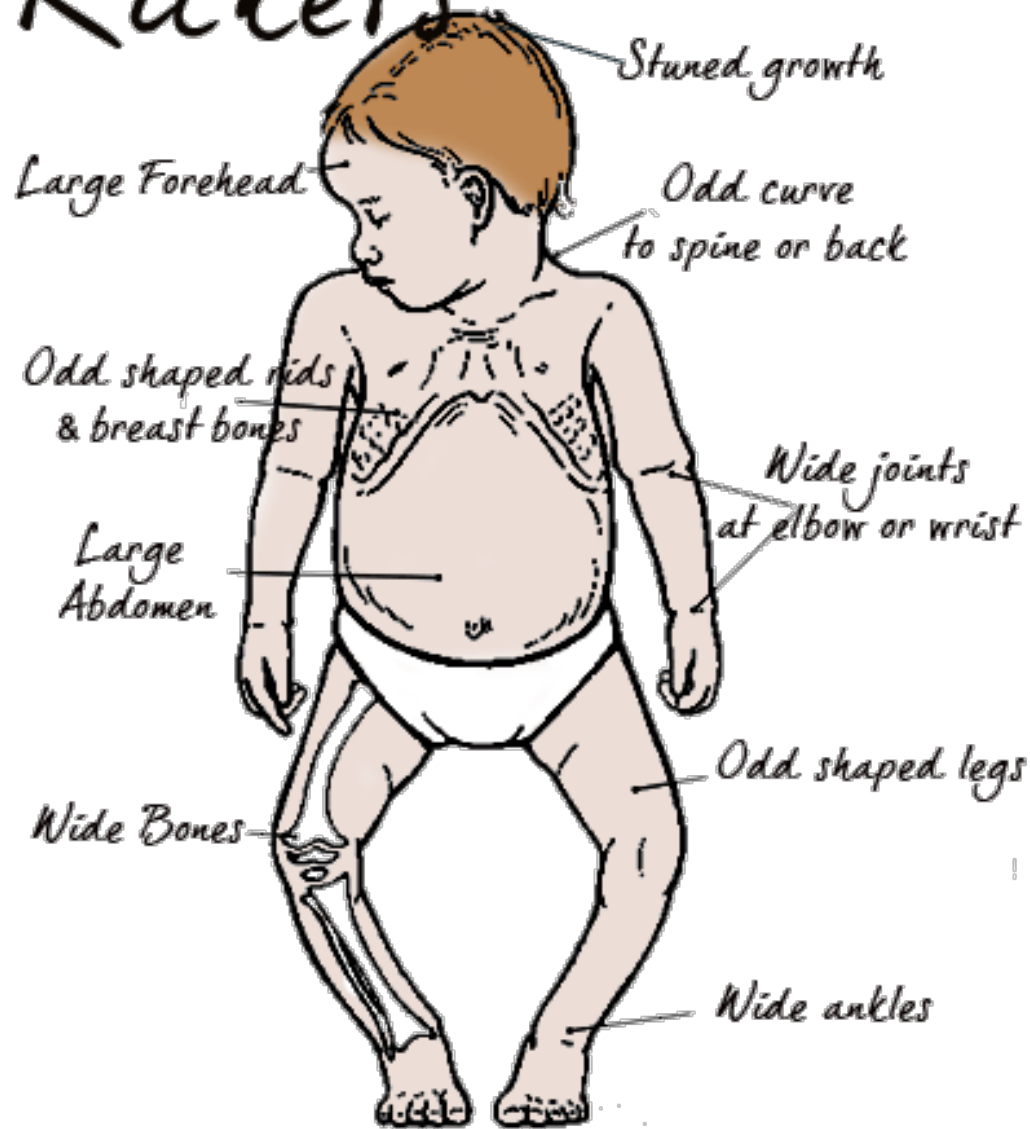
Vitamin D intake and toxicity

- 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



- 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

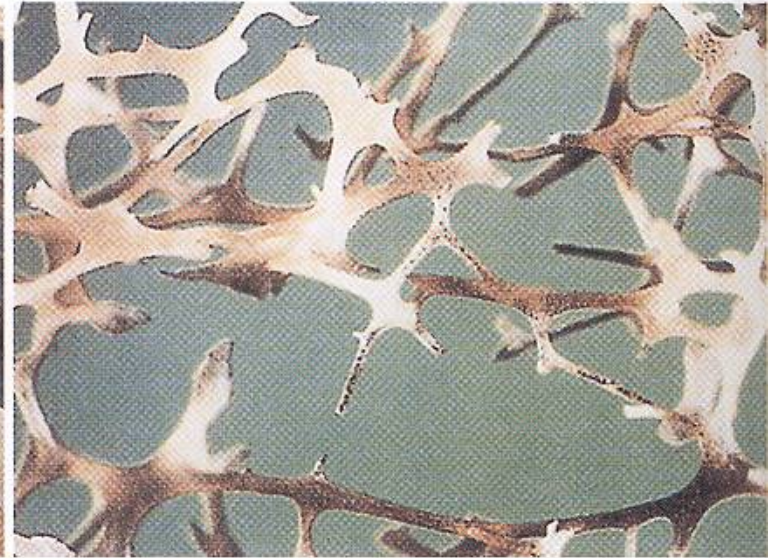
- **Measuring serum levels of:**
 - 25-hydroxycholecalciferol
 - PTH
 - Calcium
 - Phosphate
 - Alkaline phosphatase
- **Treatment:**
 - Vitamin D and calcium supplementation

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.**

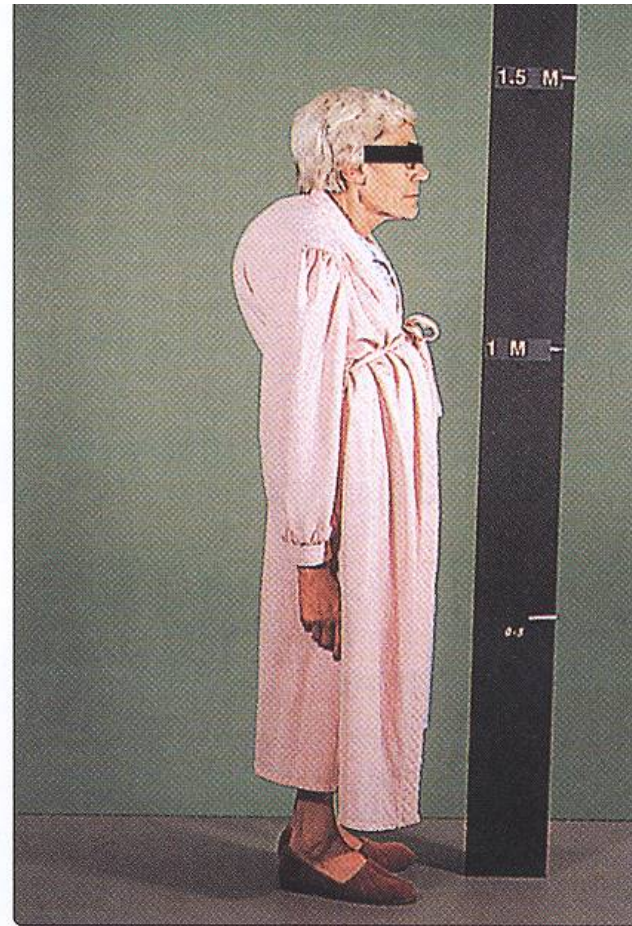


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

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

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

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

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.