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

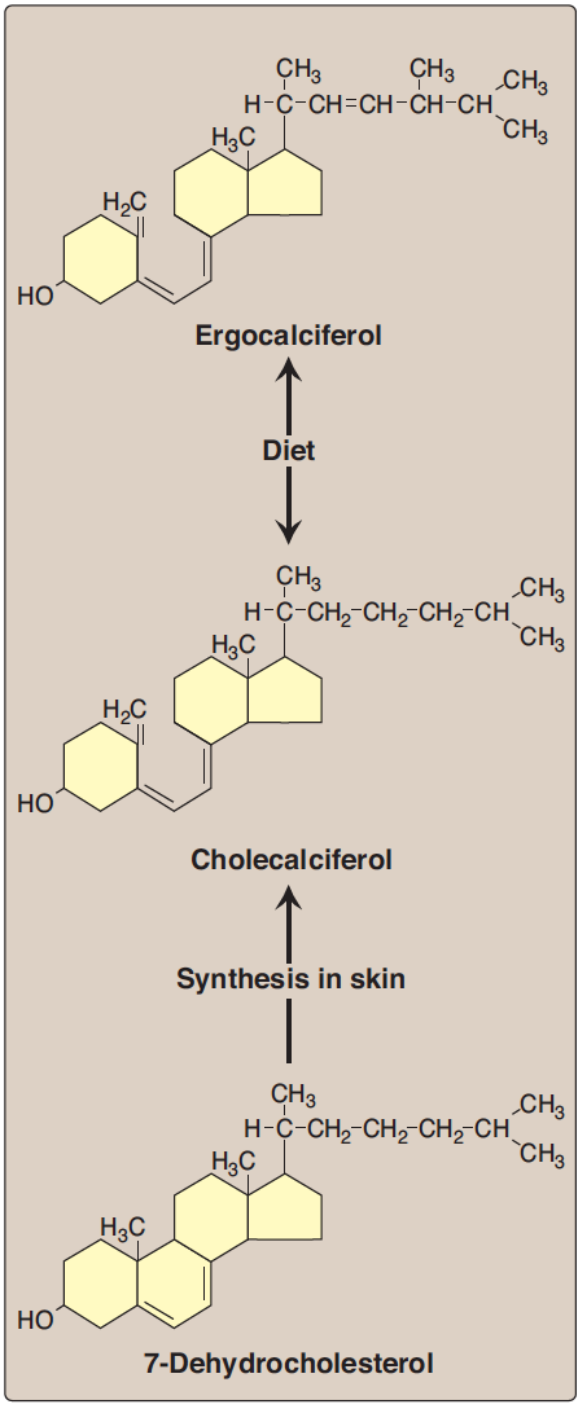
- Vitamin D is considered a steroid hormone
- Cholecalciferol (vitamin D3) is synthesized in the skin by the sunlight (UV)
- The biologically active form is 1,25-dihydroxycholecalciferol (calcitriol)
- Ergocalciferol (vitamin D2) is derived from ergosterol in lower animals and plants
- D3, D2 are also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

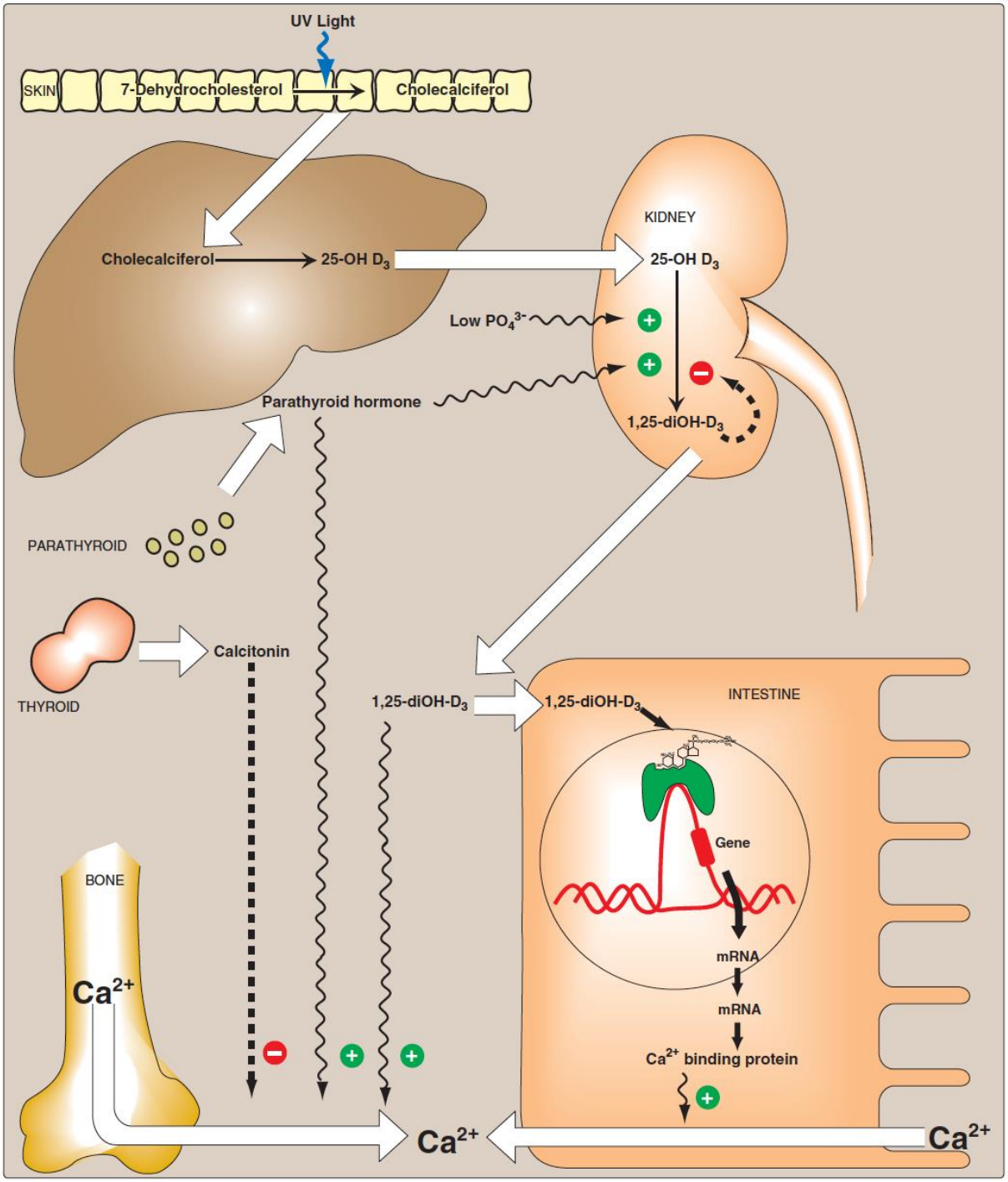
In kidneys:

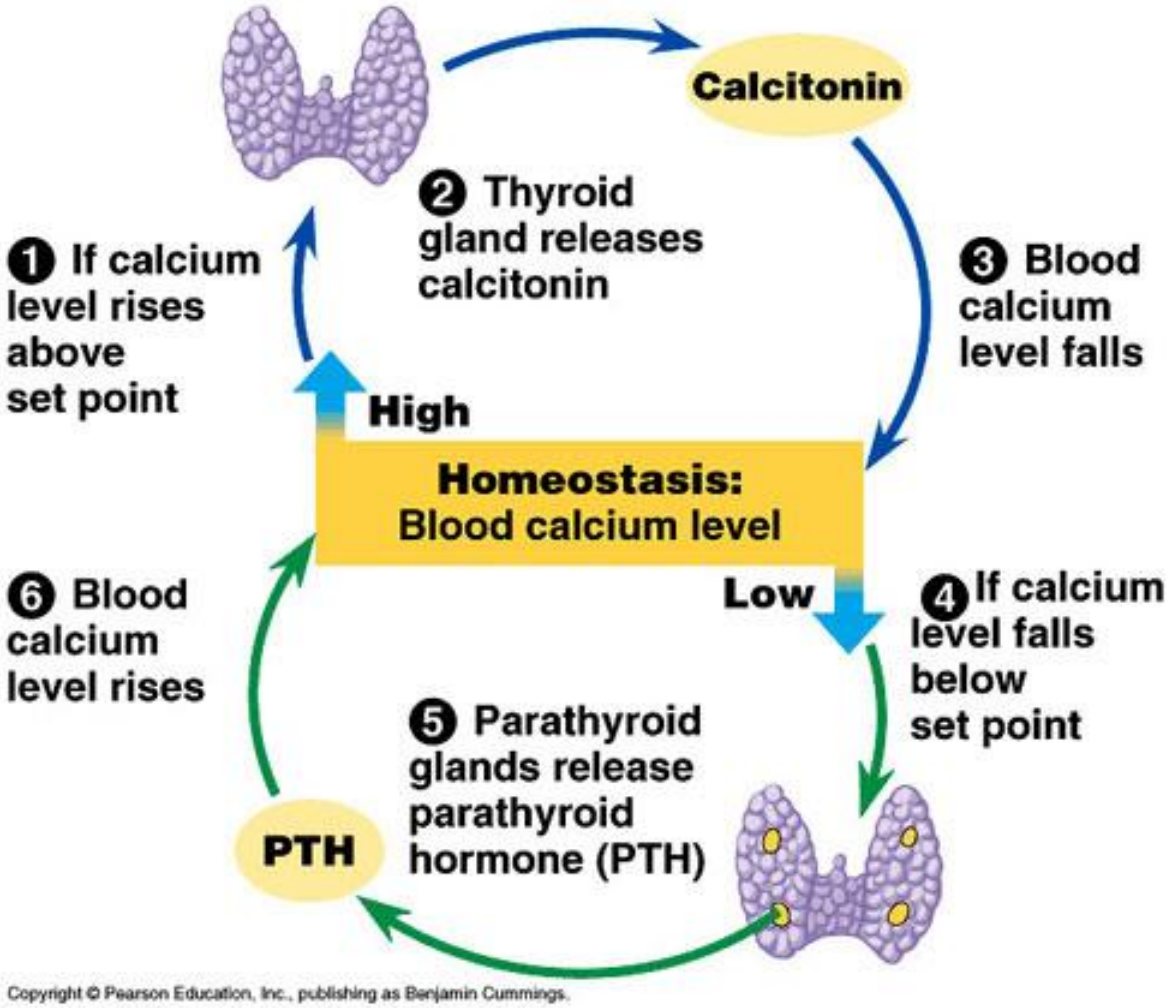
- The 1-α-hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (biologically active)
- Active vitamin D is transported in blood by gc-globulin protein

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

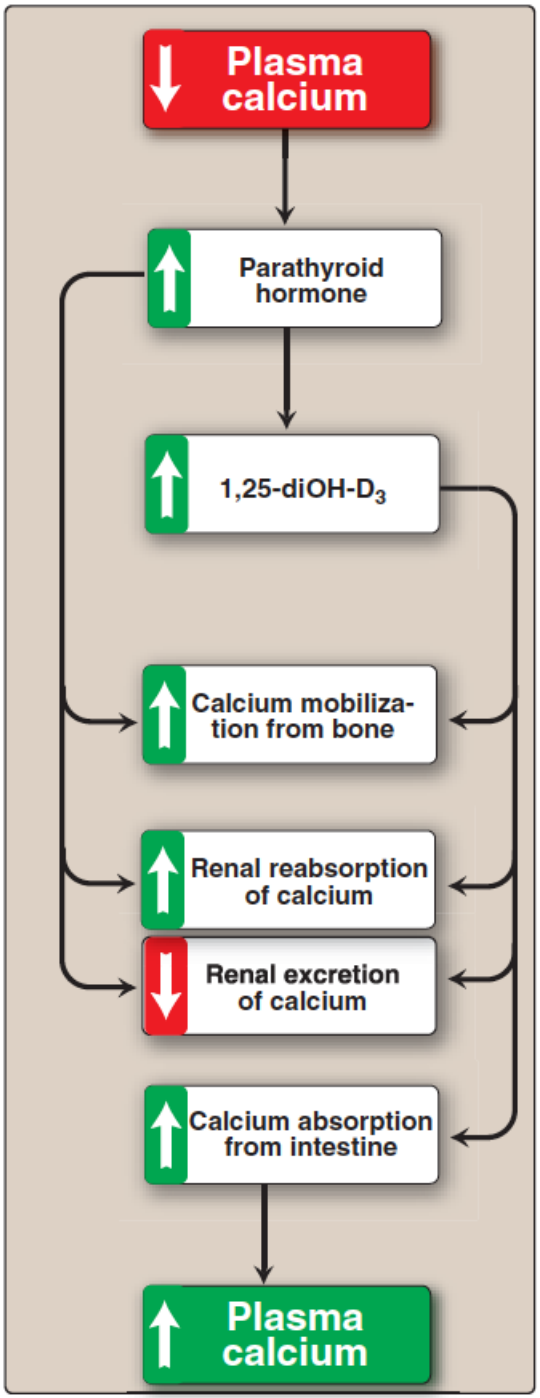
Metabolism and actions of vitamin D





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

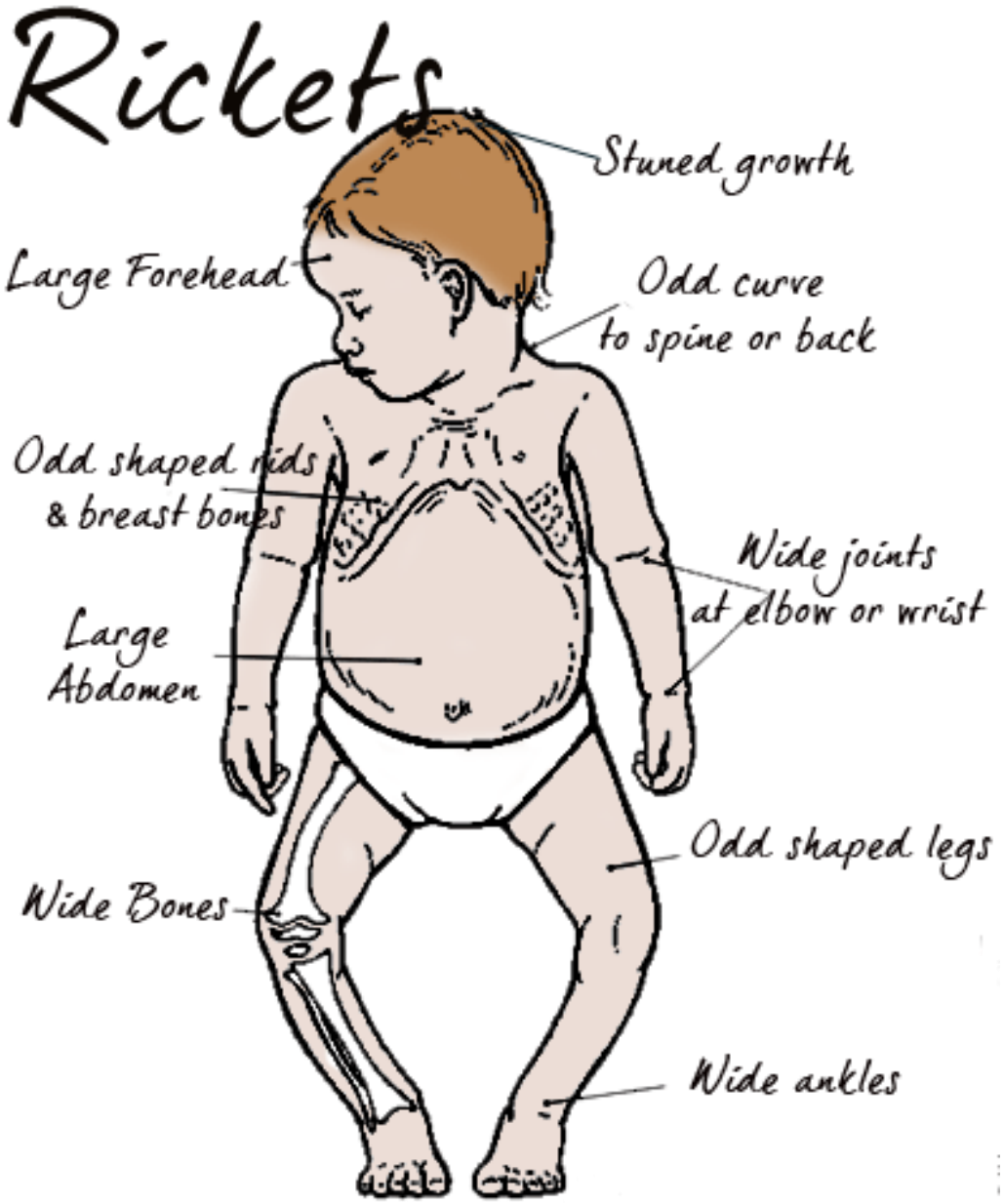
- Deficiency most common worldwide
- High prevalence in Saudi Arabia due to:
  - Low dietary intake
  - Insufficient exposure to sun
  - Lifestyle (eg. clothing esp in women)
- Circulating level of >75 nmol/L is required for beneficial health effects

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

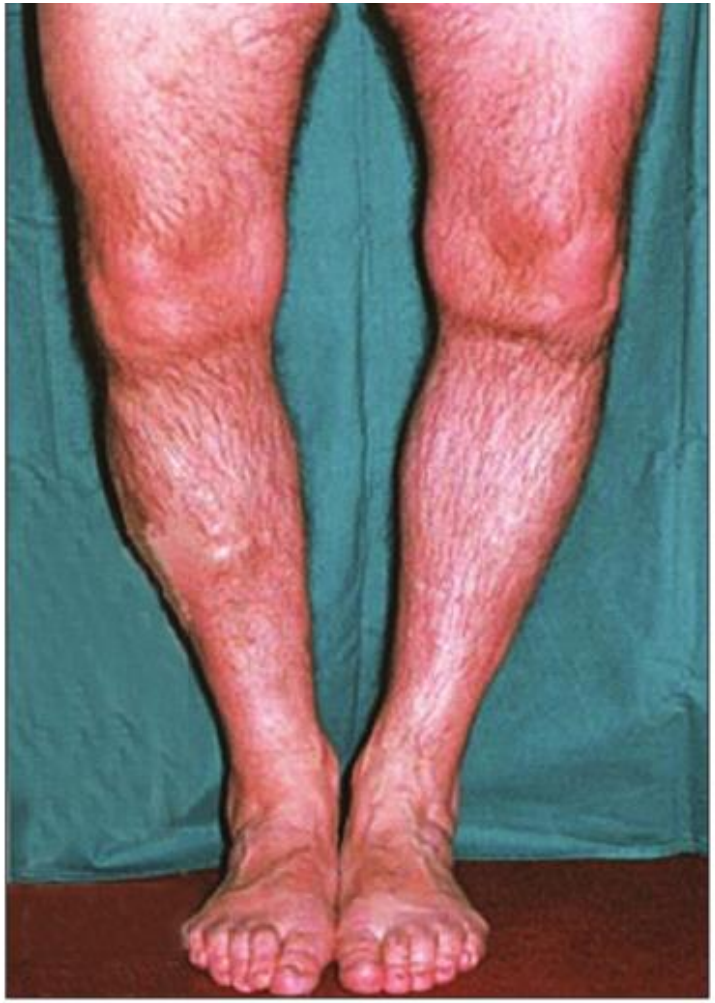


Figure 28.25
Bowed legs of middle-aged man with osteomalacia, a nutritional vitamin D deficiency that results in demineralization of the skeleton.

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)

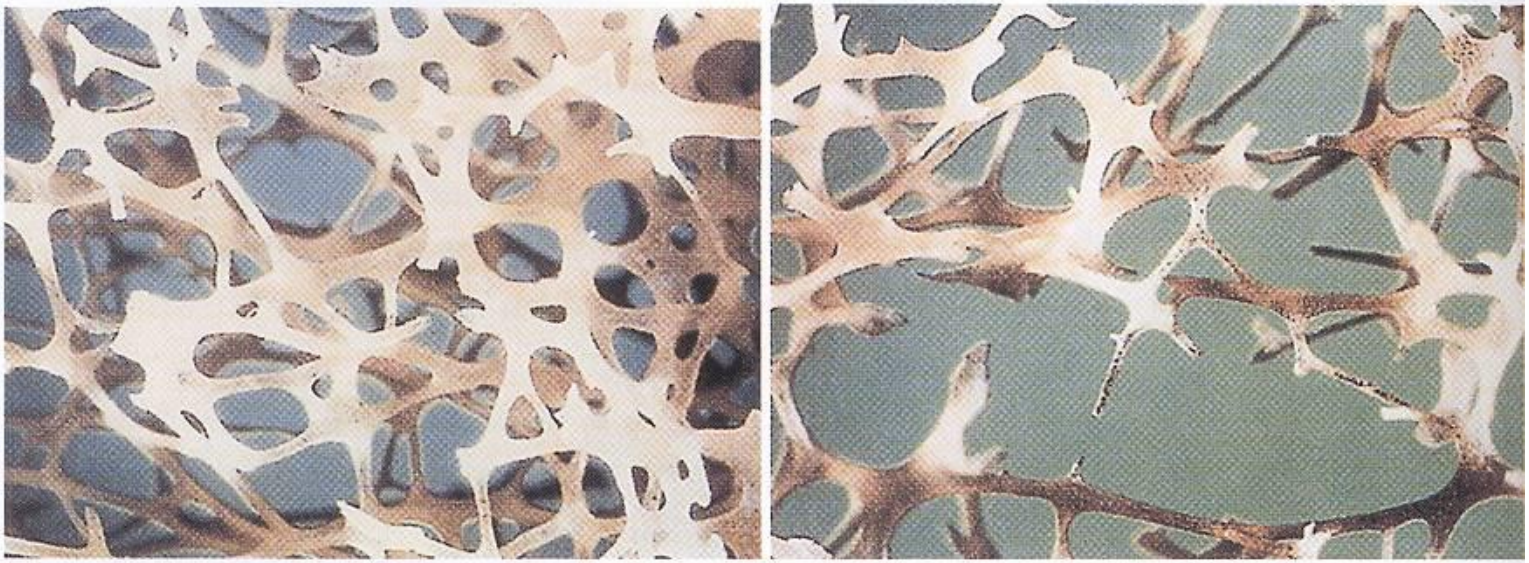
- Rare types of rickets due to genetic disorders
- Causing vitamin D deficiency mainly because of genetic defects in:
  - Vitamin D synthesis
  - Vitamin D receptor (no hormone action)

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.**

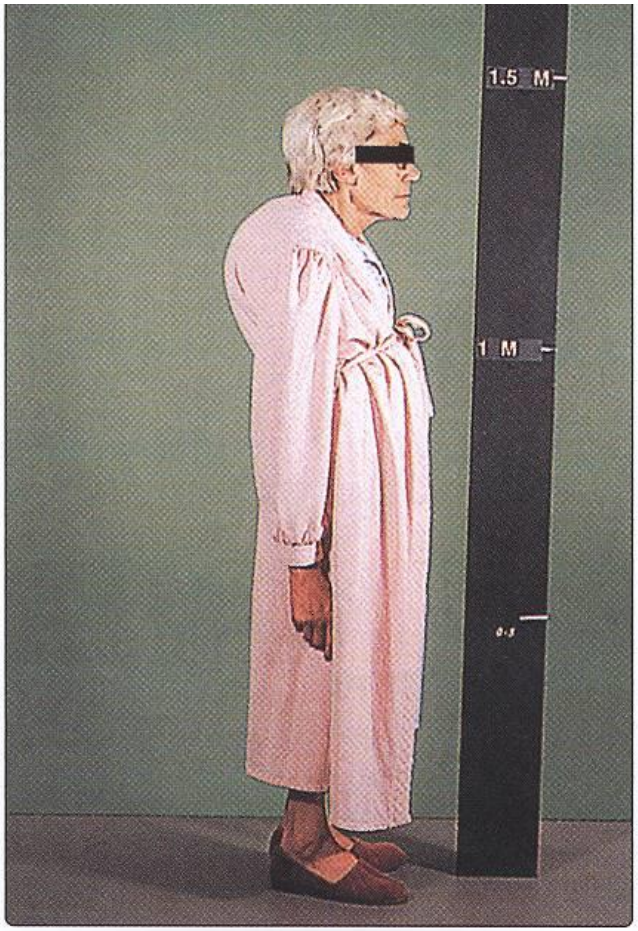


Fig. 3 **Elderly woman with so-called 'Dowager's hump' from collapsed vertebrae due to osteoporosis.**

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

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

Prevalence of vitamin D deficiency in Saudi adults.

Alsuwadia AO1, Farag YM, Al Sayyari AA, Mousa DH, Alhejaili FF, Al-Harbi AS, Housawi AA, Mittal BV, Singh

To determine the prevalence of vitamin D deficiency in healthy Saudi adults.

METHODS:

A cross-sectional study carried out as part of the screening and early evaluation of kidney disease project. Vitamin D was measured in subjects recruited at 2 screening camps in Riyadh, Saudi Arabia, between March to May 2008. Subjects from the 2 large commercial centers in Riyadh aged ≥18 years and Saudi nationals were invited.

RESULTS:

The study sample comprised of 488 subjects. The mean age of the subjects was 37.43 (11.32) years, of which 50.2% (n=245) were males. Twenty-nine percent of subjects were in the vitamin D deficiency group, 22.7% were in the relative insufficiency group, and 47.5% had normal levels of 25-hydroxy vitamin D. We observed that female gender was an independent predictor of vitamin D deficiency or insufficiency (odds ratio [OR]: 2.992; 95% confidence intervals [CI] 2.069-4.327). Anemia was also a predictor for vitamin D deficiency or insufficiency (OR: 3.16; 95% CI 2.02-4.92). Age was positively correlated with vitamin D levels (Pearson correlation=0.183, p<0.000).

CONCLUSION:

Vitamin D deficiency is common in healthy Saudi adults. This is more pronounced in females and in the younger age groups. Wearing of traditional clothes, deliberate avoidance of the sun, and inadequate dietary intake are likely to be the principal causes of low vitamin D levels.

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.