CHS 2413
Pathology and Physiopathology

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Nutritional diseases

Nutritional diseases

- 1/4 of world population suffers from undernourishment, 1/4 eats too much
- western countries - high energy diet, too much fat and sugar, few fibers - related to diseases (AS, HT, DM, malignant tumors, cholelithiasis, caries, GIT disorders)
- developed countries - pediatric mortality - 10/1000 live newborns
- underdeveloped c. - >200/1000

Malnutrition

- not only in 3rd world countries! - even developed ones - poor social classes (namely children), homeless persons, lonely aged people, chronic alcoholics, patients with psychiatric disorders (anorexia nervosa, bulimia nervosa)
- primary (shortage of nutrition)
- secondary (metabolic disorders, increased requirements - growth, pregnancy, increased losses (chronic diseases)

Protein-energy malnutrition

- most frequent and most important
- dimension of epidemy (Africa - Ethiopia - up to 25% of children; 50% of all deaths are children <5Y)
- range of clinical syndromes, 2 main forms - marasmus & kwashiorkor

Kwashiorkor

- deficiency of proteins, mainly animal
- most common in Africa - children, who have been weaned too early (arrival of another child) and fed by exclusively carbohydrate diet
- kwashiorkor is more severe than marasmus - loss of visceral proteins - hypoalbuminemia - generalized edema, ascites
- skin lesions, hair changes, fatty liver, defects of immunity, secondary infections, anemia

Marasmus

- deficiency of energy (calories) - due to starving – growth retardation - arrest, loss of muscle mass, serum albumin is normal, subcutaneous fat is used as a fuel - extremities are emaciated
- anemia, immune deficiency (namely cellular immunity)

Vitamin deficiencies

- for health are necessary 45-50 compounds (9 aminoacids, 2 fatty acids, several trace elements and 13 vitamins)
- vitamin deficiency - primary (diet) or secondary (malabsorption, metabolic disorders, liver diseases)
- oversupply can be harmful as well !!!

Vitamin A

- retinol and related substances
- important for vision (visual pigment) and differentiation of some types of epithelial cells (mucus-secreting)
- main sources: liver, fish, milk, eggs, butter
- provitamins - carotenoids - vegetable sources (carrots, spinach)
- in 3rd world is hypovit. A frequent cause of blindness

changes:

- impaired vision in reduced light
- squamous metaplasia
- decreased resistance to infections

Deficiency state

- Eyes - xerophtalmia, small corneal opaque (squamous keratinizing) plaques (*Bitot's spots*), keratomalacia -> total blindness
- Respiratory tract - squamous metaplasia, pulmonary infections
- Urinary tract - pelvic keratinization -> stones
- Skin - hyperkeratosis

Vitamin D

- maintenance of normal plasma Ca and P levels, important for normal development and mineralization of bones

two sources:

- endogenous synthesis in the skin (UV light) from 7-dehydrocholesterol - 80% of needed amount
- exogenous - dietary sources (deep-sea fish, plants, grains)

Causes of hypovitaminosis

- decreased endogenous synthesis (inadequate exposure to sunlight)
- decreased absorption (dietary lack, malabsorption syndrome)
- enhanced degradation (drugs)
- impaired synthesis of metabolites (liver diseases, renal disorders)
- target resistance (congenital lack of receptors)
- phosphate depletion (renal tubular disorders, long-term use of antacids)

Deficiency state

- children - before closing of epiphyses - rickets (rachitic rosary, pigeon breast deformity, lumbar lordosis, bowing of the legs)
- adults - after closing of epiphyses - osteomalacia (impaired remodelation of bone mass, no mineralization of osteoid - microfractures (vertebral bodies, femoral necks)
- Hypervitaminosis D - hypercalcaemia - metastatic calcification, urolithiasis

Vitamin Deficiency and Excess

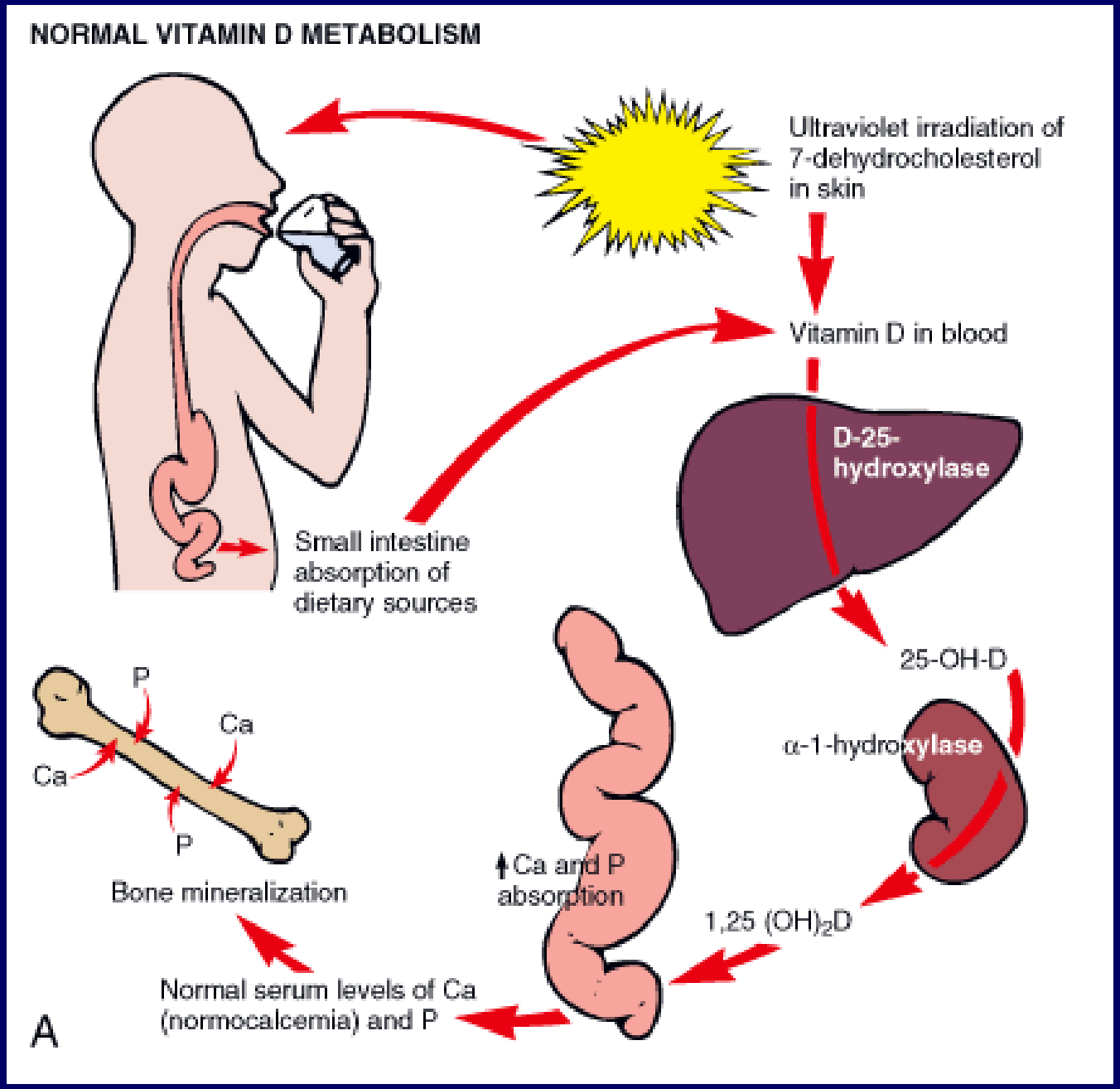
- Fat soluble vitamins
  - A, D, E, K
  - readily stored in body fat
  - poorly absorbed in digestive disorders involving malabsorbtion of fat
- Water soluble vitamins
  - remaining vitamins
  - readily excreted in urine
- Vitamin stores (fat stores longer than water)
  - vitamins B-12 and A: stores sufficient for 1 year
  - folate and thiamine may become depleted within weeks when eating a deficient diet

Vitamin D Metabolism

- Absorption of vitamin D in the gut or synthesis from precursors in the skin
- Binding to a plasma α1-globulin (D-binding protein) and transport to liver
- Conversion to 25-hydroxyvitamin D, 25(OH)D (calcidol) by 25-hydroxylase in the liver
- Conversion of 25(OH)D to $1,25(OH)_2$ D (calcitrol, Vitamin D3) by α1-hydroxylase in the kidney; *biologically this is the most active form of vitamin D.*

Functions of Vitamin D

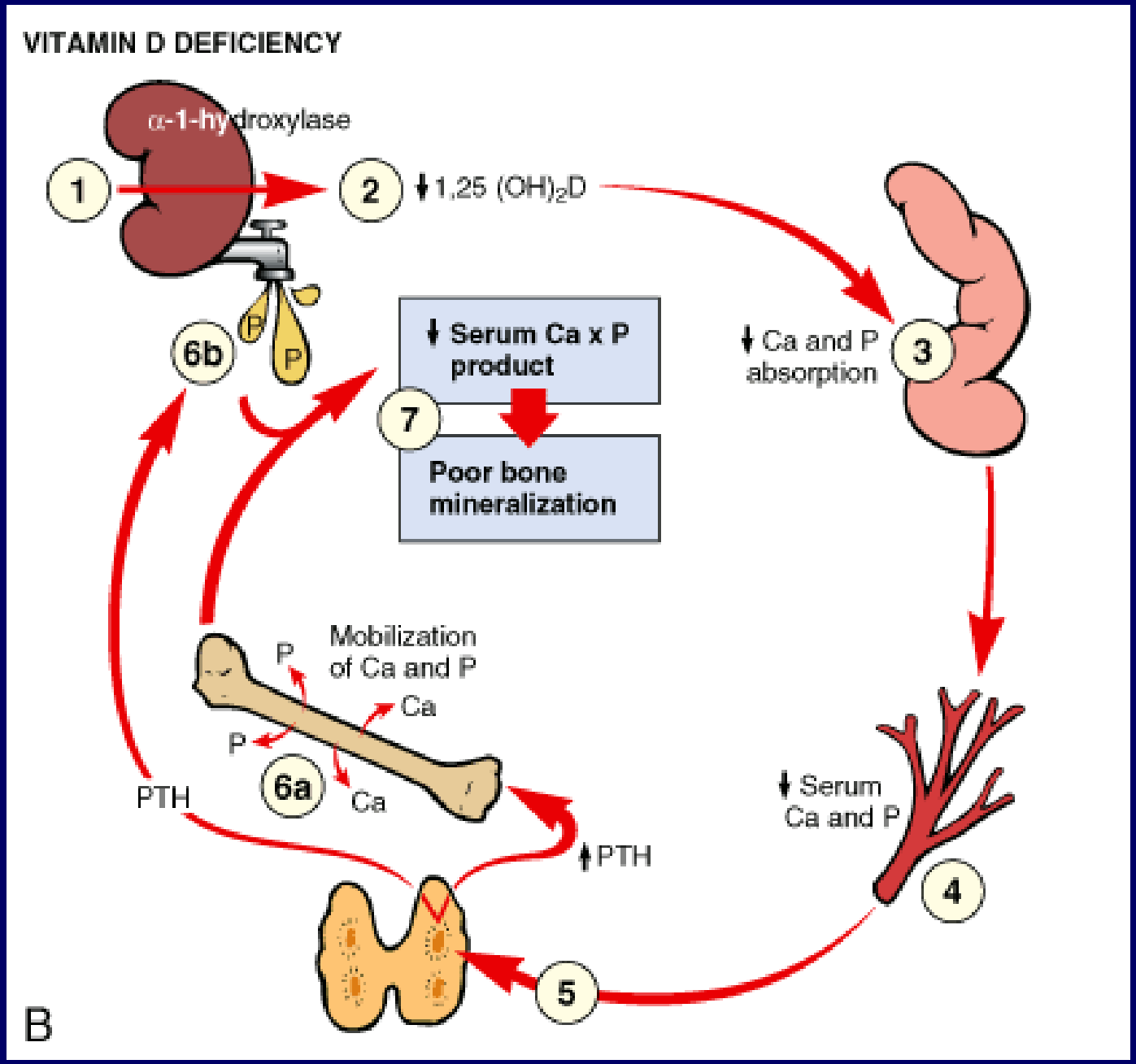
- Stimulates intestinal absorption of calcium and phosphorus
- Collaborates with PTH in the mobilization of calcium from bone
- Stimulates the PTH-dependent reabsorption of calcium in the distal renal tubules
- $1,25(OH)_2$ D, the biologically active form of vitamin D, is best regarded as a steroid hormone which acts by binding to a high-affinity receptor


NORMAL VITAMIN D METABOLISM
Ultraviolet irradiation of 7-dehydrocholesterol in skin
Vitamin D in blood
D-25-hydroxylase
25-OH-D
α-1-hydroxylase
1,25 $(OH)_2D$
Ca and P absorption
Small intestine absorption of dietary sources
Normal serum levels of Ca (normocalcemia) and P
Bone mineralization
P
Ca
Ca
P
A

Vitamin D Deficiency

- Holick et al (2005) reported the results of a large North American study that assessed the vitamin D status of postmenopausal women receiving therapy to treat or prevent osteoporosis
- 52% of 1536 women had inadequate [25(OH)D] levels (<30 ng/mL)
- 36% and 18% had levels less than 25 and 20 ng/mL, respectively.

Holick MF et al: J Clin Endocrinol Metab 90:3215, 2005


VITAMIN D DEFICIENCY
α-1-hydroxylase
1
2
↓1,25 (OH)2D
3
↓ Ca and P absorption
4
↓ Serum Ca and P
5
↑PTH
6a
Mobilization of Ca and P
P
Ca
P
Ca
PTH
6b
P
P
7
↓ Serum Ca x P product
Poor bone mineralization
B

Vitamin D Deficiency

- Childhood: Rickets
  - epiphyses are open
  - cartilage overgrowth
- Adults: osteomalacia
  - bone matrix is not calcified
  - vs osteoporosis (matrix reduced)

ADULTS→

←CHILDREN (RICKETS)

OSTEOMALACIA

1) Bone fractures that happen with very little injury
2) Muscle weakness
3) Widespread bone pain, especially in the hips

Vitamin K

- required cofactor for synthesis of clotting factors VII, IX, X

Causes of hypovitaminosis:

- fat malabsorption syndromes
- destruction of endogenous vit. K synthesizing flora (broad spectrum ATB)
- neonatal period (low reserve, no bacterial flora)
- diffuse liver disease
- iatrogenic decrease (warfarin)

Deficiency state

- bleeding diathesis (e.g. hemorrhagic disease of the newborn - intracranial bleeding, any site - skin, umbilicus, viscera)
- adults - hematomas, hematuria, melena, ecchymoses, bleeding from the gums

Vitamins B

- coenzymes
- major source - grains, rice, vegetables, fish, meat, yeast, seed oils
- in deficiency - involved mainly highly metabolic active tissues with short cell-turnover period (skin, oral mucosa, stomach, bone marrow, neural system)

Vitamin B1 (thiamine)

- widely available in the diet - nonpolished rice, grains
- avitaminosis in 3rd world - in severe malnutrition
- avitaminosis in developed countries - in chronic alcoholics (25%!) (malnutrition, decreased absorption from the gut)
- affected peripheral nerves, heart, brain
- dry beri-beri (polyneuropathy) - degeneration of myelin sheaths and axons (motoric, sensoric and vegetative)
- wet beri-beri (cardiovascular syndrome) - dilatation, right heart failure, peripheral edema
- Wernicke-Korsakoff syndrome - ophthalmoplegia, nystagmus, ataxia of gait and stance, confusion, apathy, amnesia, psychosis

Vitamin B2 (riboflavin)

- avitaminosis associated with changes at the angles of the mouth (cheilosis or cheilitis), glossitis, ocular (keratitis) and skin changes (nasolabial dermatitis), bone marrow (erythroid hypoplasia - anemia)

Niacin (nicotinic acid)

Deficiency state:

- pellagra (rough skin) - 3 Ds
- dermatitis - neck - chronic inflamm., fissures, depigmentation, hyperpigmentation
- diarrhea - atrophy of columnar epithelium of GIT mucosa, inflammation and subsequent ulceration
- dementia - degeneration of the neurons of the brain

Vitamin B12 (cyanocobalamine)

- deficiency in strict vegetarians or in chronic atrophic gastritis - pernicious anemia (lack of synthesis of intrinsic factor in gastric mucosa due to autoimmune inflammation with severe destruction of corporal glands)
- in deficiency - megaloblastic anemia (decreased number of RBC, increased size; hypersegmentation of neutrophilic leucocytes) and demyelinization of spinal cord and peripheral nerves = neuroanemic syndrome

Vitamin C (ascorbic acid)

- fruits and vegetables - not synthesized endogenously
- involved in metabolism of collagen and basic intercellular matrix - involvement of vessel walls - increased fragility - bleeding
- deficiency in adults - scurvy
- deficiency in children - Möller-Barlow disease - subperiostal hematomas

Scurvy

- sailors, travelers, today elderly persons, homeless people, etc.
- petechial skin bleeding, ecchymoses, epistaxis, melena, intraarticular bleeding
- gingival swelling, hemorrhages, secondary bacterial infection - periodontitis
- hyperkeratotic papular rash
- impaired wound healing, defective osteoid - pathologic fractures
- anemia

Hypervitaminosis C

- mega doses of vit. C (several grams/day) - no effect in prevention or in treatment
- excretion into urine - urolithiasis
- hyperacidity in stomach - mucosal erosions

Vitamin K

- Clotting factors VII, IX, and X and prothrombin (II) all require carboxylation of glutamate residues for functional activity
  - anticoagulant coumadin is a Vitamin K antagonist
- Activation of anticoagulant proteins C and S also requires glutamate carboxylation
- Sources
  - endogenous intestinal bacterial flora
  - diet

Vitamin K Deficiency

- Causes
  - fat malabsorption
  - reduced gut bacterial flora
    - administration of wide specturm antibiotics
    - neonatal period before gut is colonized
  - liver disease with reduced recycling of vitamin K
- Effects of vitamin K deficiency
  - bleeding diathesis
  - estimated 3% prevalence of vitamin K-dependent bleeding diathesis among neonates warrants routine prophylactic vitamin K therapy for all newborns

Trace elements

- 14 anorganic elements - Fe, Cu, Co, I, Zn, Se, Mn, Mo, Cr, F, Si, Ni, Sn (tin), Va
- activity in enzymes
- primary deficiency - only I (thyroid gland - goiter)
- secondary deficiency:
- Zn - skin lesions, neurological and psychiatric syndromes, growth retardation, hypogonadism in males
- Cu - anemia, impaired synthesis of connective tissue matrix
- Se - China - Keshan disease - dilated cardiomyopathy

Obesity

- epidemy in the USA, frequent in many western countries
- 20% of world population
- disorder of energetic balance - food derived energy chronically exceeds energy expenditure, excess calories are stored as fat
- some genetic predispositions (multifactorial disease)

Results

- hypertension - 3x more frequent (in young adults 20-44Y - 6x!!!)
- DM type II. - 3x more frequent
- hypercholesterolemia - AS - MI
- more frequent malignant tumors - colon ca, breast ca, gallbladder ca, endometrial ca
- respiratory insuficiency in chronic bronchitis - *Pickwick syndrome* - pulmonary hypertension - cor pulmonale
- cholelithiasis (gallstones) - 6x more frequent + ca

Diet and cancer

- not completely clear - no clear evidence, that diet can cause or prevent from ca
- most frequently accused:
- red meat, animal fat, cholesterol, refined sugar, chemical additives
- assumption of WHO - 1/3 of all ca - nutrition
- oral cavity, pharynx, esophagus - alcohol, smoking of cigarettes
- colorectal ca - increased intake of fat, reduced intake of fibers
- liver ca - aphlatoxin (nuts, grains) - cirrhosis - hepatocellular ca
- breast ca - fat intake (in USA - 10% of females - increasing incidence)

NUTRITION & DISEASE

- Food Safety
  - Additives
  - Contaminants
- Nutritional Deficiencies
  - Vitamins
  - Minerals
- Obesity
- Diet and Disease
- Chemoprevention of Cancer