CLINICAL PHARMACOLOGY OF VITAMINS, MACRO- AND MICROELEMENTS
Vitamins - low molecular weight organic compounds that have different chemical structure and are not synthesized or are synthesized in small amount in the human organism, are not used as building material, but have marked biological effect and are necessary components of diet.

Hypovitaminosis - decrease of vitamin amount in the organism
Hypervitaminosis - increase of vitamin amount in the organism
Avitaminosis - lack of vitamin in the organism

Two types of hypo- and avitaminosis: exo- and endogenic
Classification of vitamins

**Water soluble:**
- group B
- C
- H
- P

**Fat soluble:**
- A
- D
- E
- K
- F
<table>
<thead>
<tr>
<th>Water soluble vitamins</th>
<th>Fat soluble vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form coenzymes</td>
<td>Do not form coenzymes</td>
</tr>
<tr>
<td>Do not affect membranes</td>
<td>Modulators of membranes</td>
</tr>
<tr>
<td>Do not have antioxidant properties (except vit. C)</td>
<td>Most are antioxidants</td>
</tr>
<tr>
<td>Do not affect genetic apparatus</td>
<td>Cause the expression of genes</td>
</tr>
<tr>
<td>Do not cause hypervitaminosis</td>
<td>Cause hypervitaminosis</td>
</tr>
<tr>
<td>Do not have provitamins</td>
<td>Have provitamins</td>
</tr>
</tbody>
</table>
# Water-soluble and Fat-soluble Vitamins

<table>
<thead>
<tr>
<th>Water-Soluble Vitamins: B Vitamins and Vitamin C</th>
<th>Fat-Soluble Vitamins: Vitamins A, D, E, and K</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Directly into the blood.</td>
</tr>
<tr>
<td><strong>Transport</strong></td>
<td>Travel freely.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Circulate freely in water-filled parts of the body.</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Kidneys detect and remove excess in urine.</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Possible to reach toxic levels when consumed from supplements.</td>
</tr>
<tr>
<td><strong>Requirements</strong></td>
<td>Needed in frequent doses (perhaps 1 to 3 days).</td>
</tr>
</tbody>
</table>

**NOTE:** Exceptions occur, but these differences between the water-soluble and fat-soluble vitamins are valid generalizations.
### Water-soluble Vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Coenzyme</th>
<th>Typical reaction type</th>
<th>Consequences of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine (B₁)</td>
<td>Thiamine pyrophosphate</td>
<td>Aldehyde transfer</td>
<td>Beriberi (weight loss, heart problems, neurological dysfunction)</td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>Flavin adenine dinucleotide (FAD)</td>
<td>Oxidation–reduction</td>
<td>Cheliosis and angular stomatitis (lesions of the mouth), dermatitis</td>
</tr>
<tr>
<td>Pyridoxine (B₆)</td>
<td>Pyridoxal phosphate</td>
<td>Group transfer to or from amino acids</td>
<td>Depression, confusion, convulsions</td>
</tr>
<tr>
<td>Nicotinic acid (niacin)</td>
<td>Nicotinamide adenine dinucleotide (NAD⁺)</td>
<td>Oxidation–reduction</td>
<td>Pellagra (dermatitis, depression, diarrhea)</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Coenzyme A</td>
<td>Acyl–group transfer</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Biotin</td>
<td>Biotin–lysine complexes (biocytin)</td>
<td>ATP-dependent carboxylation and carboxyl–group transfer</td>
<td>Rash about the eyebrows, muscle pain, fatigue (rare)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Tetrahydrofolate</td>
<td>Transfer of one-carbon components; thymine synthesis</td>
<td>Anemia, neural-tube defects in development</td>
</tr>
<tr>
<td>B₁₂</td>
<td>5’-Deoxyadenosyl cobalamin</td>
<td>Transfer of methyl groups; intramolecular rearrangements</td>
<td>Anemia, pernicious anemia, methylmalonic acidosis</td>
</tr>
<tr>
<td>C (ascorbic acid)</td>
<td></td>
<td>Antioxidant</td>
<td>Scurvy (swollen and bleeding gums, subdermal hemorrhages)</td>
</tr>
</tbody>
</table>
Vitamin B₁ (thyamin, antineuritic)

Consists of two rings - pyrimididine and thiazole
Is phosphorylated in liver to **TMP, TPP and TTP**

**TMP, TPP and TTP** are coenzymes of:
- pyruvate- and alpha-ketoglutarate dehydrogenase
- transketolase
In the thiamin deficiency ketoacids that are toxic for nervous system are accumulated.

Acidosis.

Carbs are not used, energy deficit.

Organism uses lipids and proteins, loss of weight, dystrophy, growth retardation.

Catabolism prevails.

Inhibition of transketolase, inhibition of PPC, deficit of NADPH and riboses, disorders of fatty acids synthesis, steroid hormones, cholesterol, nucleic acids.
Berry-berry disease

Chronic deficiency of thiamine

Often found in
- Asian countries
- alcoholics

Two types: **dry** and **wet**

**Dry**: disseminated polyneuritis, partial paralysis, weakness and pain in the limbs, atrophy, loss of weight, impaired sensory perception

**Wet**: heart failure, edema, dystrophy of myocardium

**Wernicke-Korsakoff syndrome**: hemorrhage in CNS. Mental disorders, amnesia, encephalopathy, psychosis
Vitamin B1 (Thiamine) is found in fortified breads and cereals, fish, lean meats and milk.
Daily requirement: 1–3 mg

Preparations:
- thiamine,
- cocarboxylase

Are used in cardiac, nervous diseases, diabetes mellitus, muscle dystrophy
Vitamin $B_2$ (riboflavin, growth vitamin)

Is composed from isoallaxasine and alcohol ribitol

Flavus - yellow
Forms the coenzymes FMN and FAD

Are necessary for the action of more than 30 enzymes – oxido-reductases (oxidation-reduction reactions)

- AA deamination (oxidases of AA)
- pyruvate dehydrogenase and alpha-ketoglutarate complexes
- succinate dehydrogenase (Krebs cycle)
- fatty acids oxidation (acyl CoA dehydrogenase)
- uric acid formation (xanthine oxidase)
- electron transport in respiration chain
Hypovitaminosis – disorders of the processes of biological oxidation

**Symptoms:**

- cracks at the corners of the mouth (angular cheilitis),
- Dermatitis
- Glossitis
Ceratitis

Conjunctivitis

Blepharitis (inflammation of the eyelid margins)

Ceratitis
Blepharitis
Conjunctivitis
Anemia
Leucopenia
Food sources of Riboflavin (vitamin B2):

- Cereal
- Nuts
- Milk
- Eggs
- Green leafy vegetables
- And lean meat
Daily requirement: 1-3 mg

Partially is synthesized by the intestine microorganisms

Preparation: riboflavin
Vitamin B₃ (pantothenic acid, antidermatitic)

Coenzymes:
- coenzyme A
- phosphopantothenate

Is necessary for the action of about 80 enzymes
Processes which are inhibited in vitamin $B_3$ deficiency

- oxidative decarboxilation of pyruvate and alpha-ketoglutarate
- transport of the fatty acids residues
- synthesis of purine nucleotides
- activation of fatty acids
- phosphopantothenate is a constituent of multienzyme complex - fatty acids synthase
- cholesterol synthesis
- ketogenesis
Hypovitaminosis:
- dermatitis
- ulcers of mucosa
- spasms, paresis
- hypolipidemia
- liver steatosis
Daily requirement:
10-15 mg

Food:
liver, eggs, fish, bread

Preparation:
pantothenic acid
Vitamin B₅ (PP, nicotinic acid, nicotinamide (niacin), antipellagric)

Nature - derivative of pyridine

Form the coenzymes NAD and NADP
NAD and NADP – coenzymes of many oxidoreductases (about 100)

Take part in:
- glycolisis
- gluconeogenesis
- PPC
- FA synthesis and oxidation
- AA deamination
- Krebs cycle (3 enzymes)
- ETC
- nucleic acids formation

NADP takes part in:
- FA synthesis
- cholesterol synthesis
Hypovitaminosis – disease pellagra

**Causes:**
- malabsorption
- alcoholism
- taking of cytostatics and isoniazide for a long time
- protein starvation
- in persons who eat a lot of corn (lack of tryptophan from which B₅ can be synthesized by bacteria)
Pellagra - disease of 3 D
- dermatitis,
- diarrhea,
- dementia

Dermatitis:
- symmetrical,
- on the open areas of body,
- hyperkeratosis
Dermatitis in pellagra

Diarrhea as result of the atrophy of stomach and intestine endothelium
Glossitis, stomatitis.

Dementia as result of the chronic injury of CNS. Psychosis. Mental confusion.
Daily requirement: 14–25 mg

Is formed in the intestine (by microorganisms) and cells from tryptophan

Food: liver, meat, fish, black bread, yeast, eggs
Vitamin B₆ (pyridoxine, antidermatatic)

In the base of structure - pyridine core

Form coenzymes pyridoxal phosphate (PLP) and pyridoxamine monophosphate (PMP)
PLP and ПМФ — coenzymes of enzymes of AA metabolism:
- amino transferases
- decarboxylases
- participate in oxidation of amines
- synthesis of GABA

α-amino acid  α-keto acid  α-keto acid  α-amino acid
Hypovitaminosis
-in the using of antagonists (isoniazid, penicyllamine, L-DOPA, estrogens)
in malabsorption, alcoholism
-increased requirement in pregnancy

isoniazid

L-DOPA
Disorders of protein metabolism
- hyperaminoaciduria
- negative nitrogen balance
- dermatitis (erythema, pigmentation, edema)
- anemia (disorders of iron utilization)
- leucopenia (disorders of protein synthesis)
- growth inhibition
- convulsions, muscle spasms (GABA inhibition)
Food sources of vitamin B6 (pyridoxine) include beans, legumes, nuts, eggs, meats, fish, breads, and cereals.
Daily requirement: 2-3 mg

Is formed by intestinal bacteria

Photosensitive

Thermostable
Vitamin $\text{B}_{10}$ (folic acid, antianemic)

In the base of structure - residue of pterine, paraaminobenzoic acid, glutamic acid

Coenzyme - tetrahydrofolic acid (THFA)
**Biological role of THFA:**
- transfers methyl groups in the synthesis of AA, pyrimidine nucleotides, creatin, methionin. In deficiency - disorders of the NA and protein synthesis, inhibition of growth and cell division

**Symptoms:**
- hyperchromic megaloblastic anemia
- leucopenia
- thrombocytopenia
- glossitis, conjunctivitis, gastritis (disorders of epithelium proliferation)
- growth inhibition
- impairment of the wound healing
- immunodeficiency
Daily requirement: 200-500 mg

Is formed by intestinal bacteria

Food: bean, green leafy vegetables, lemons, mushrooms, meat, liver
There are many antivitamins of folic acid: - cytostatics (methotrexat is used for treatment of leukemia) - sulfanilamide (structural analogs of p-aminobenzoic acid, inhibit the synthesis of folic acid (purine bases, DNA, RNA in bacteria)
Vitamin $B_{12}$
(cyanocobalamin, antianemic)

Structure – tetrapyrrolic compound, Co ion, nucleotide part

Coenzymes –
-5-deoxyadenosylcobalamin
-methylcobalamin
Biological role:
- tightly connected to folic acid
- synthesis of methionine from homocysteine
- synthesis of creatin, cholin
- synthesis of phospholipids
- synthesis of purine and pyrimidine bases, nucleic acids

Symptoms:
- hyperchromic megaloblastic anemia (malignant, pernicious, Addison-Birmer disease)
- fatty dystrophy of nervous cells, neurological disorders
- cardiovascular disorders (accumulation of homocystein)
Food sources of vitamin B12:

- Eggs
- Meat
- Poultry
- Shellfish
- Milk
- Milk products
Daily requirement: 2-5 micrograms

Is not synthesized neither in plants nor in animals.
Is formed only by intestinal bacteria

Is absorbed in small intestine
Vitamin C (ascorbic acid, antiscorbutic)

**Structure** - lacton of dienol gulonic acid

**Coenzyme function** has not been established

L-ascorbic acid
Has oxidation-reduction properties

Can donate hydrogen, as result is converted to dehydroascorbic acid
Biological role:
- reduces sulhydryl groups of proteins, enzymes
- formation of serotonin
- synthesis of norepinephrine
- synthesis of steroid hormones
- formation of carnitine
- synthesis of collagen (hydroxyprolin)
- formation of THFA
- decomposition of hemoglobin
- $\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}$ - absorption in the intestine
- promote immunity defense
Hypovitaminosis - scurvy:
- hemorrhages
- loose of teeth, gums swell and bleed easily (collagen deficit)
- anemia (lack of THFA)

-pain in heart, swelling of legs, weakness, fatigue
-loss of weight
Daily requirement: 75-100 mg

Requirement is increased in infections, flue, in pregnancy

Food: rose, black currant, citrus, vegetables, fruits, needles
Using:

- anemia
- pregnancy
- for the stimulation of regeneration
- for the increase of immunity
Vitamin P (biophlavonoids, factor of permeability)

Structure - compounds having phenolic structure

Representatives:
- catechin
- rutin
- kvercetin
- hesperidin
Biological role:
- synergist of vitamin C
- protects vitamin C against oxidation
- hydroxylation of proline and lysine
- inhibit hyaluronidase
- prevent oxidation of epinephrine
- antioxidants

Hypovitaminosis:
- petechiae
- symptoms of scurvy
Daily requirement: 50-75 mg

**Food:** pepper, citrus, black currant, rowan, buckwheat, fruits
Is used to make capillaries stronger
Vitamin H (biotin, antiseborheic)

Structure - consists of tiophen, imidazol and valeric acid

Coenzyme of carboxylase, serves as transporter of carboxylic group
- Pyruvate carboxylase - gluconeogenesis
- Acetyl-CoA carboxylase, propionyl-CoA carboxylase - lipid metabolism
Hypovitaminosis almost does not occur. Can be in malabsorption, disbacteriosi, using of large amount of eggs white (contains avidin).

Avidin – glycoprotein that irreversibly binds biotin – antivitamin

**Symptoms:**
- seborrheic dermatitis of the hair part of head
- conjunctivitis
- anemia
- depression

Seborrheic dermatitis
Daily requirement: 150-200 mg
Food: liver, soybeans, egg yolks, mushrooms, beans, onion, spinach
LIPID SOLUBLE VITAMINS
Vitamin A

Retinol. Antixerophthalmic
Active forms

- Retinol
- Retinal
- Retinoic acid
Precursors - carotenoids

- Most important - beta-carotene

- Are cleaved to retinol in liver
Dark green and yellow vegetables are good sources for carotenoids: tomatoes, carrots, apricots, parsley, corn, radish

Organism gets $\frac{1}{4}$ of vit. A from carotenoids
Biological functions of carotenoids

- Antioxidants
- Anticancer properties
Biological functions of vitamin A

- Modulator of biomembranes
  - changes the permeability
  - synthesis of membranes components
- Growth vitamin
  - stimulates the synthesis of proteins (especially in cartilages)
  - stimulates the synthesis of purine and pyrimidine nucleotides
- Participates in oxidation-reduction reactions
Biological functions of vitamin A

- Regulates the synthesis of keratin (prevents the conversion of cylindrical epithelium into horny)
- Promotes the spermatogenensis and placenta development
- Stimulates the synthesis of antibodies and phagocytosis (antiinfectious)
Biological functions of vitamin A

Regulates the hormonal status
- prevents the oxidation of vitamin C
- inhibits the synthesis of thyroxin

• Maintains the antioxidant potential of different tissues
Biological functions of vitamin A

Is responsible for the vision cycle

Night blindness - early symptom of vitamin A deficiency
Later symptoms of vitamin A deficiency

**Anemia** (vit. A is required for the synthesis of transferrin)

**Increased susceptibility to infection and cancer**

**Follicular hyperkeratosis** ("goosebumps" skin)
The most cosmetic creams contain retinol.
Xerophthalmia (progressive keratinization of cornea)
Keratomalacia (corneal ulcerations)
Bronchitis, pneumonia (metaplasia of endothelium)
Cysts in salivary glands
Cystitis, pyelonephritis (change of endothelium in nephrones)
Daily requirement: 2–3 mg

Sources of vitamin A and beta-carotene:

Vitamin A comes from animal sources such as eggs, meat and dairy products.

Beta-carotene, a precursor of vitamin A, comes from green, leafy vegetables and intensely colored fruits and vegetables.
Hypervitaminosis

• Accumulates in liver
• In overdosing in treatment, consumption a large amount of fish oil, liver of polar animals

• Symptoms:
  o bone pain
  o vomiting, diarrhea
  o liver and spleen enlargement
  o dermatitis
  o loss of hair
Vitamin D (cholecalciferol, antirickets)
Two forms of vitamin D

- Vitamin D2 - ergocalciferol
- Vitamin D3 - cholecalciferol
Both ergocalciferol and cholecalciferol are metabolized in liver.
Vit.D acts in concert with parathyroid hormone (PTH) to stimulate the production of 1,25-(OH)$_2$D.
Functions of vitamin D
regulates the Ca and P levels in the blood
• promotes absorption of Ca and P in the intestine
• promotes reabsorption of Ca in the kidneys
• high levels of serum Ca and P increase the rate of bone mineralization
• promote bone resorption (at low Ca in blood)
Functions of vitamin D affects immune system

• promotes phagocytosis

• immunomodulatory activity

• induces differentiation of immune cells
Functions of vitamin D prevents tumorgenesis

• inhibits proliferation
• inhibits angiogenesis
• induces differentiation
Functions of vitamin D

• Activates reabsorption of amino acids, especially prolin

• Activates the monosaccharides phosphorylation (glycogen synthesis)

• Promotes ATP formation
Rickets
softening of bones in children potentially leading to fractures and deformity

Causes:
• vitamin D deficiency
• lack of calcium in the diet (famine)
• severe diarrhea and vomiting
• fat malabsorption
• alcoholism
• severe liver and kidney diseases
Signs and symptoms of rickets

- Bone pain or tenderness
- Dental problems
- Muscle weakness
- Fractures (easily broken bones)
- Skeletal deformity
  - Bowed legs (genu varum)
  - Knock-knees (genu valgum) or "windswept knees"
  - Cranial, spinal, and pelvic deformities
- Hypocalcemia
- Tetany (uncontrolled muscle spasms)
- Craniotabes (soft skull)
- Widening of wrist (due to metaphysial cartilage hyperplasia)
Knock knee deformity (genu valgum)

Windswept deformity
Dietary sources

Vitamin D

Daily requirement: 12-25 micrograms

The body itself makes vitamin D when it is exposed to the sun.

Cheese, butter, margarine, fortified milk, fish and fortified cereals are food sources of vitamin D.
Hypervitaminosis

- Increase of Ca and P in blood
- Demineralization of bones
- Calcification of inner organs
- Renal stones
Vitamin E

Tocopherols and tocotrienols. Antisterile
• Group of tocopherols and tocotrienols
• Most active - alpha-tocopherol
Biological role

• Most potent antioxidant
• Active scavenger of free oxygen and nitrogen radicals
• Protects vit. A from oxidation
• Prevents oxidation of Se
• Stabilizes the cell membranes
• Increases the resistance of membranes to oxidation and toxic effects
• Improves cellular respiration stabilizing ubiquinone
• Prevents **oxidation of LDL**
• Reduces risk of **atherosclerosis**
• Regulates transcription
• Maintains normal immune function
• Inhibits cholesterol biosynthesis
Hypovitaminosis

• **Causes:** malabsorption, famine

• **Symptoms:**
  - Activation of FRO
  - Increase of membrane permeability
  - Hemolysis of erythrocytes
  - Deficit of ATP
  - Muscle dystrophy (creatinuria)
  - Demyelization of nerves (CNS changes)
  - Disorders of reproductive function (atrophy of testis, azoospermia, inability to implantation)
Daily requirement: 20-50 mg

Vitamin E is found in corn, nuts, olives, green, leafy vegetables, vegetable oils and wheat germ, but food alone cannot provide a beneficial amount of vitamin E, and supplements may be helpful.
Using:

• Cardiovascular diseases
• Stimulation of immunity
• Tumors
• Miscarriages
Vitamin K
Quinone derivatives
Antihemorrhagic
K1, phyloquinone (in green vegetables)
K2, menaquinone (is synthesized by intestinal bacteria)
Biological functions
• Stimulates the synthesis of coagulation factors in liver
• Increases the resistance of capillaries
• Stimulates the synthesis of albumins, pepsin, trypsis, lipase, amilase
• Increases the peristalsis of intestine
• Inhibits free radical oxidation
Hypovitaminosis

Causes:
• Lipids malabsorption (lack of bile acids)
• Disbacteriosi (vit. K is synthesized by intestinal microflora)
• Taking of antivitamins (dicumaryl)

\[
\text{dicumaryl}
\]
Hypovitaminosis

Symptoms:
• Hemorrhages (subcutaneous, intramuscular, into inner organs)
• Increased coagulation time
Daily requirement: 0.2-0.3 mg

Food sources of vitamin K include cabbage, cauliflower, spinach and other green, leafy vegetables, as well as cereals.
Vikasol

- Water soluble analog of vit. K
- Is used to stop bleeding
- Can be administered parenterally
Vitamin F
Polyunsaturated fatty acids
Antisclerotic
Linoleic acid
Linolenic acid
Arachidonic acid
Biological functions

- Participate in the organism growth and development
- Components of phospholipids (cell membranes)
- Regeneration of skin epithelium
- Synthesis of prostaglandins
- Decrease cholesterol level
- Increase the organism resistance
Hypovitaminosis

Causes:
• Growth retardation
• Dermatitis
• Dry skin
• Exema
• Atherosclerosis
Daily requirement: 10-15 g
Minerals

• minerals are elements of the periodic table
• more than 25 have been isolated
• 21 elements have been shown to be essential (excluding C,H, and O)
• minerals make up about 4 to 5% of body weight (for a 70 kg individual: 2.8 kg)
• many minerals are found in ionic form (others as ligands or covalent compounds)
Minerals

• Two categories:
  • macrominerals > 0.005%
  • microminerals < 0.005%

• macrominerals are essential at levels of 100mg or more per day for human adults

• microminerals are often referred to as trace elements
Functions of minerals

• provide a suitable medium for cellular activity
  – permeability of membranes
  – irritability of muscles and nerve cells
• play a primary role in osmotic phenomenon
• involved in acid base-balance
• confer rigidity and hardness to certain tissues (bones and teeth)
• become part of specialized compounds
# Macronutrients

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Content <em>(g)</em></th>
<th>Major source</th>
<th>Daily requirement <em>(g)</em></th>
<th>Functions/Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroelements (daily requirement &gt;100 mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>100</td>
<td>Table salt</td>
<td>1.1-3.3</td>
<td>Osmoregulation, membrane potential, mineral metabolism</td>
</tr>
<tr>
<td>K</td>
<td>150</td>
<td>Vegetables, fruit, cereals</td>
<td>1.9-5.6</td>
<td>Membrane potential, mineral metabolism</td>
</tr>
<tr>
<td>Ca</td>
<td>1300</td>
<td>Milk, milk products</td>
<td>0.8</td>
<td>Bone formation, blood clotting, signal molecule</td>
</tr>
<tr>
<td>Mg</td>
<td>20</td>
<td>Green vegetables</td>
<td>0.35</td>
<td>Bone formation, cofactor for enzymes</td>
</tr>
<tr>
<td>Cl</td>
<td>100</td>
<td>Table salt</td>
<td>1.7-5.1</td>
<td>Mineral metabolism</td>
</tr>
<tr>
<td>P</td>
<td>650</td>
<td>Meat, milk, cereals, vegetables</td>
<td>0.8</td>
<td>Bone formation, energy metabolism, nucleic acid metabolism</td>
</tr>
<tr>
<td>S</td>
<td>200</td>
<td>S-containing amino acids (Cys and Met)</td>
<td>0.2</td>
<td>Lipid and carbohydrate metabolism, conjugate formation</td>
</tr>
</tbody>
</table>
• The important microelements in human nutrition are zinc, copper, selenium, chromium, molybdenum, manganese, iodine, and iron. Although they only represent a small fraction of the human body’s total mineral content, they play important roles in various metabolic routes.

• Preterm babies can present with deficiencies, even without clinical signs, due to low concentrations of the elements at birth because these minerals are only incorporated in the last trimester of pregnancy.
Micronutrients

- Iron (Fe)
- Copper (Cu)
- Zinc (Zn)
- Boron (B)
- Molybdenum (Mo)
- Manganese (Mn)
# Micronutrients

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Content <em>(g)</em></th>
<th>Major source</th>
<th>Daily requirement <em>(g)</em></th>
<th>Functions/Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microelements (trace elements)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe</td>
<td>4-5</td>
<td>Meat, liver, eggs, vegetables, potatoes, cereals</td>
<td>10</td>
<td>Hemoglobin, myoglobin, cytochromes, Fe/S clusters</td>
</tr>
<tr>
<td>Zn</td>
<td>2-3</td>
<td>Meat, liver, cereals</td>
<td>15</td>
<td>Zinc enzymes</td>
</tr>
<tr>
<td>Mn</td>
<td>0.02</td>
<td>Found in many foodstuffs</td>
<td>2-5</td>
<td>Enzymes</td>
</tr>
<tr>
<td>Cu</td>
<td>0.1-0.2</td>
<td>Meat, vegetables, fruit, fish</td>
<td>2-3</td>
<td>Oxidases</td>
</tr>
<tr>
<td>Co</td>
<td>&lt;0.01</td>
<td>Meat</td>
<td>Traces</td>
<td>Vitamin B₁₂</td>
</tr>
<tr>
<td>Cr</td>
<td>&lt;0.01</td>
<td></td>
<td>0.05-0.2</td>
<td>Not clear</td>
</tr>
<tr>
<td>Mo</td>
<td>0.02</td>
<td>Cereals, nuts, legumes</td>
<td>0.15-0.5</td>
<td>Redox enzymes</td>
</tr>
<tr>
<td>Se</td>
<td></td>
<td>Vegetables, meat</td>
<td>0.05-0.2</td>
<td>Selenium enzymes</td>
</tr>
<tr>
<td>I</td>
<td>0.03</td>
<td>Seafood, iodized salt, drinking water</td>
<td>0.15</td>
<td>Thyroxin</td>
</tr>
<tr>
<td><strong>Requirement not known</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>Drinking water (fluoridated), tea, milk</td>
<td>0.0015-0.004</td>
<td>Bones, dental enamel</td>
</tr>
</tbody>
</table>
Zinc supplements
Zinc

• Biological roles
  – Involved in many enzymes (over 20 metalloenzymes)
    • Carbonic anhydrase
    • Carboxypeptidase A
      – Four types of proteases
        » Serine
        » Cysteine
        » Aspartic acid
        » Zinc
    • ACE (angiotensin I converting enzyme)
    • RNA and DNA polymerases
Zinc

• zinc absorption appears to be dependent on a transport protein, metallothionein
• deficiencies include poor growth, delayed wound healing, impairment of sexual development and decreased taste acuit
• zinc is present in gustin, a salivary polypeptide that is necessary for the development of taste buds
Zinc

• severe zinc deficiency is seen primarily in alcoholics (especially if they have developed cirrhosis), patients with chronic renal disease or severe malabsorption diseases
• occasionally seen in patients on long term total parenteral nutrition (TPN) – patient develop a dermatitis
• zinc is occasionally used therapeutically to promote wound healing and may be of some use in treating gastric ulcers
Zinc Deficiency
Iron (Fe)

• 2 types of body iron
  – heme iron
    • hemoglobin, myoglobin, catalases, peroxidases, cytochromes (a, b and c – involved in electron transport), cytochrome P450 (involved in drug metabolism)
  – non-heme iron
    • ferritin, hemosiderin, hemofuscin, transferrin, ferroflavoproteins, aromatic amino acid hydroxylases

• food iron is also classified as heme and non-heme
Food iron

**heme iron**
- meats
- poultry
- fish

20-23% of heme-iron is absorbable

**non-heme iron**
- vegetables
- fruits
- legumes
- nuts
- breads and cereals

only ~ 3% on non heme iron is absorbed
Diagnosis of iron deficiency

• hematology (microcytic hypochromic cells)
• low serum iron
• low serum ferritin (indicates low body stores)
  • in some conditions (inflammation, hepatitis) ferritin may be high
• low hemosiderin
• high total iron binding capacity (TIBC)
Iron Deficiency
ANEMIA - DEFINITION

- REDUCTION OF HEMOGLOBIN CONCENTRATION BELOW REFERENCE VALUE
BLOOD PARAMETERS

- Hemoglobin concentration (Hg)
  - F: 7.2 –10; M: 7.8-11.3 mmol Fe/l (12-18 g/dl)

- Erythrocytes count (RBC)
  - F: 4.5-5.5; M: 4.5-6 \times 10^{12}/l (4-6 \times 10^6 /\mu l)

- Hematocrit (Hct)
  - F: 37-47; M: 40-54; (37-54%)

- Platelet count (Plt)
  - 150 – 450 \times 10^3/\mu l (150-450 \times 10^9/l)

- Leukocytes count (WBC)
  - 4-10 \times 10^9/l (4-10 \times 10^3/ \mu l)
Erythrocytes parameters

- Mean corpuscular volume (MCV)
  - N: 80-100 fl
- RDW (Red cell Distribution Width)
- Mean corpuscular hemoglobin (MCH)
  - N: 27-34 pg
- Mean corpuscular hemoglobin concentration (MCHC)
  - N: 310 – 370 g/IRBC (31-37 g/dl)
Reticulocytes

- RET: 0,5-2%
- ARC: 25-75x 10⁹/l
- CRC
- RPI
IRON DEFICIENCY ANEMIA

• IRON METABOLISM
  – ABSORPTION IN DUODENUM
  – TRANSFERRIN TRANSPORTS IRON TO THE CELLS
  – FERRITIN AND HEMOSYDERIN STORE IRON

• 10% of daily iron is absorbed
• Most body iron is present in hemoglobin in circulating red cells
• The macrophages of the reticuloendothelial system store iron released from hemoglobin as ferritin and hemosiderin
• Small loss of iron each day in urine, faeces, skin and nails and in menstruating females as blood (1-2 mg daily)
IRON METABOLISM

• Iron concentration (Fe)
  • N: 50-150 µg/dl
• Total Iron Binding Capacity
  • N: 250-450 µg/dl
• Transferrin saturation
• Transferrin receptor concentration
• Ferritin concentration
  • N: 50-300 µg/l
IRON DEFICIENCY ANEMIA

• ETIOLOGY:
  • CHRONIC BLEEDING
    » MENORRHAGIA
    » PEPTIC ULCER
    » STOMACH CANCER
    » ULCERATIVE COLITIS
    » INTESTINAL CANCER
    » HAEMORRHOIDS
  • DECREASED IRON INTAKE
  • INCREASED IRON REQUIREMENT (JUVENILE AGE, PREGNANCY, LACTATION)
IRON DEFICIENCY - STAGES

• Prelatent
  – reduction in iron stores without reduced serum iron levels
    • Hb (N), MCV (N), iron absorption (↑), transferin saturation (N), serum ferritin (↓), marrow iron (↓)

• Latent
  – iron stores are exhausted, but the blood hemoglobin level remains normal
    • Hb (N), MCV (N), TIBC (↑), serum ferritin (↓), transferrin saturation (↓), marrow iron (absent)

• Iron deficiency anemia
  – blood hemoglobin concentration falls below the lower limit of normal
    • Hb (↓), MCV (↓), TIBC (↑), serum ferritin (↓), transferrin saturation (↓), marrow iron (absent)
IRON DEFICIENCY ANEMIA

• GENERAL ANEMIA’S SYMPTOMS:
  – FATIGABILITY
  – DIZZENES
  – HEADACHE
  – SCOTOMAS
  – IRRITABILITY
  – ROARING
  – PALPITATION
  – CHD, CHF
CHARACTERISTICS SYMPTOMS

- GLOSSITIS, STOMATITIS
- DYSPHAGIA (Plummer-Vinson syndrome)
- ATROPHIC GASTRITIS
- DRY, PALE SKIN
- SPOON SHAPED NAILS, KOILONYCHIA,
- BLUE SCLERAES
- HAIR LOSS
- PICA (APETITE FOR NON FOOD SUBSTANCES SUCH AS AN ICE, CLAY)
- SPLENOMEGALY (10%)
- INCREASED PLATELET COUNT
BLOOD AND BONE MARROW SMEAR

• BLOOD:
  – microcytosis, hipochromia, anulocytes, anisocytosis poikilocytosis

• BONE MARROW
  – high cellularity
  – mild to moderate erythroid hyperplasia (25-35%; N 16 – 18%)
  – polychromatic and pyknotic cytoplasm of erythroblasts is vacuolated and irregular in outline (micronormoblastic erythropoiesis)
  – absence of stainable iron
Management

• History and physical examination is sufficient to exclude serious disease (e.g. pregnant or lactating women, adolescents)
  - CURE ANEMIA

• History and/or physical examination is insufficient (e.g. old men, postmenopausal women)
  - FIND ETIOLOGY OF ANEMIA AND CURE (CAUSAL TREATMENT)
    • Benzidine test
    • Gastroscopy
    • Colonoscopy
    • Gynaecological examination
ORAL IRON ABSORPTION TEST

1. baseline serum iron level
2. 200 - 400 mg of elemental iron orally
3. serum iron level 2-4 hours after ingestion
IRON DEFICIENCY ANEMIA CURE

• ORAL
  – 200 mg of iron daily 1 hour before meal (e.g. 100 mg twice daily)
  – How long?
    • 14 days + (Hg required level – Hg current level) x 4
  – half of the dose - 6 – 9 months to restore iron reserve
  – Absorption
    • is enhanced: vit C, meat, orange juice, fish
    • is inhibited: cereals, tea, milk
IRON DEFICIENCY ANEMIA CURE

• PARENTERAL IRON SUBSTITUTION
  – Bad oral iron tolerance (nausea, diarrhoea)
  – Negative oral iron absorption test
  – Necessity of quick management (CHD, CHF)
  – 50 - 100 mg daily
  – I.v only in hospital (risk of anaphilactic shock)
  – I.m in outpatient department
  – iron to be injected (mg) = (15 - Hb/g%/) x body weight (kg) x 3
Calcium (Ca)

• function of calcium:
  – structural unit of bones and teeth
  – contraction and relaxation of muscles
  – stabilizes nervous tissue
    • low calcium --- irritable nerves --- tetany
    • high calcium --- depresses the nervous irritability
  – required for blood clotting
  – activates various enzymes (glycogen phosphorylase kinase, salivary and pancreatic amylase)
Ca Deficiency  Rickets
Iodine Deficiency
Iodine

- Iodine is necessary for the formation of thyroid hormones (T-4 and T-3)
- Deficiency of iodine is manifested by a goiter (enlargement of the thyroid gland)
- Salt water fish and seaweeds are a good source of iodine
- To prevent the development of endemic goiter, tablet salt has been spiked with sodium iodide