Vitamins

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Vitamins are essential organic compounds that

- the body is not capable to synthesize (excl. D, PP)
- required in small amounts for maintaining metabolic integrity

- Used for synthesis of coenzymes and signaling substances or act as antioxidants**.**
- are **neither plastic material nor energy source**
- Requirements – from micrograms to tens of milligrams per day.
  - are influenced by age, sex, and physiological conditions (pregnancy, breast-feeding, physical exercise, and nutrition).
- only a few vitamins can be stored (A, D, E, B_{12})
  - lack of vitamins quickly leads to **deficiency diseases (hypovitaminoses)**
- **hypervitaminoses** (effects of overdose) **with** toxic symptoms
  - known for vitamins A and D only.

  Normally, excess vitamins are rapidly excreted

Classification of vitamins

A character, the chemical name and the name of the pathology to be treated

Fat-soluble vitamins:

- A, retinol (antixerofthalmic).
- D; calciferol (antiricketic).
- E, tocopherols (antisteril, vitamin of fertility).
- K; naphthoquinones (antihaemorrhagic).

Water-soluble vitamins:

- B_1, thiamine (antinevritic).
- B_2, riboflavin (vitamin of growth).
- B_3, pantothenic acid (antidermatic).
- B_6, pyridoxine (antidermatic).
- B_{12}, cyanocobalamin (antianemic).
- PP, nicotinamide, nicotinic acid, niacin (antipellagric).
- Bc, folic acid (antianemic).
- H, biotin (anti-seborrhoeic).
- C, ascorbic acid (antiscurvic).
- P, rutin.

Vitamin-like compounds

group of substances, partly synthesized in the body, but possess some properties of vitamins

No specific clinical symptoms of deficiency

- B_4, choline (lipotropic factor).
- B_8, inositol (lipotropic factor).
- B_{13}, orotic acid (growth factor).
- B_{15}, pangamic acid.
- B_t, carnitine.
- N, lipoic acid.
- U (anti-ulcer).
- PABA, *para*-aminobenzoic acid.
- F (linoleic, linolenic and arachidonic acid).
- Coenzyme Q.

General plan of answer

For each vitamin	Example
Full name	B_1: thiamine
co-enzyme or other active form (if any)	thiamine pyrophosphate
enzymes (if any)	dehydrogenase complexes for α-ketoacids and transketolase
biochemical process involved	oxidative decarboxylation of α-ketoacids and transfer of active aldehyde groups
daily requirement for adult	2-3 mg
food sources	grain, yeast, meat (pork)
main symptoms of hypo-(a)vitaminosis	neurological disturbances, cardiac insuffciency, and muscular atrophy

- For self-study:
  - History of discovery and investigations of vitamins
  - causes of deficiency of vitamins

Classification of vitamins according to their biochemical function

- **coenzyme** vitamins (B_1, B_2, B_6, B_{12}, PP, K, folic acid, biotin, etc.);
- **precursors of signal molecules**, with active forms
  - having hormonal activity (D)
  - regulating protein synthesis/gene expression (A, active form - retinoic acid, plays role in growth and differentiation of cells) ;
- **antioxidant** vitamins (E, carotenes, bioflavonoids).
- **multifunctional action** (C: antioxidant and co-enzyme).

Metabolism of vitamins

vitamins cannot function in the form in which they are supplied with food.

Stages of vitamins metabolism :

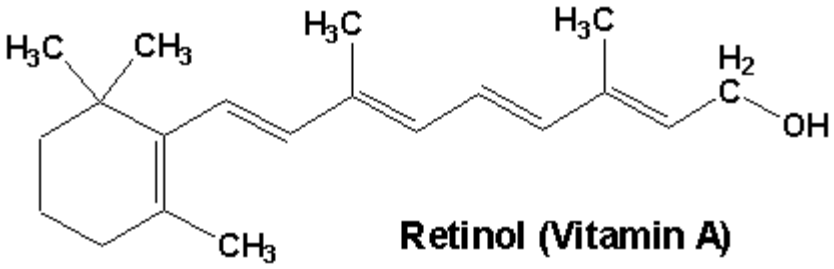
- **absorption** in the intestine with special transport systems;
- **transport** to target organ/tissue of action/depot via transport proteins;
- **conversion (biotransformation)** to active (coenzyme) form using special enzyme systems;
- **proteidization** with corresponding apo-enzyme

Lipid-soluble vitamins

- vitamins A, D, E, and K
- can be absorbed efficiently only when there is **normal fat absorption**.
- transported in the blood in lipoproteins or attached to specific binding proteins
- belong to the **isoprenoids**

Vitamin A

- **Retinol**, presents in meat (as ester),
- provitamin (**β-carotene**), found in plants
  - converted to retinaldehyde by dioxygenase
  - (6 mg into 1 mg of retinol)
- Active forms:
  - retinaldehyde utilized in vision
  - retinoic acid acts in the control of gene expression, cell differentiation.
- Deficiency: *night blindness, xerophthalmia*
- Through **retinoid X receptors:** impairs functions of D and thyroid hormones



Retinol (Vitamin A)

Daily requirement in retinol activity equivalent (RAE)

900 – 3000 µg RAE/day for men

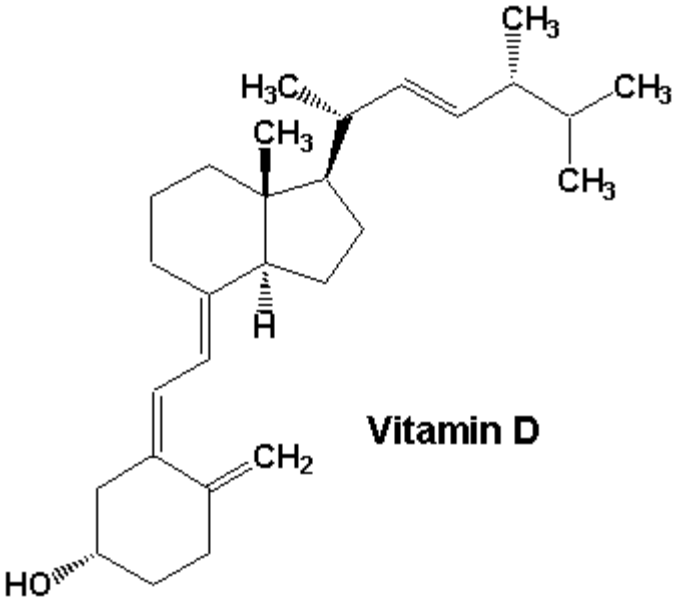
700 – 3000 µg RAE/day for women

1 µg RAE = corresponds to

- 1 µg retinol,
- 2 µg of β-carotene in oil,
- 12 µg of "dietary" beta-carotene

Vitamin D

- precursor of the hormone ***calcitriol*** *(1α,25-dihydroxycholecalciferol*) **in lever and kidney**
- regulates the Ca and P homeostasis
- Synthesized in the skin from 7-dehydrocholesterol, by a photochemical reaction
- Vitamin D-binding globulin – storage form



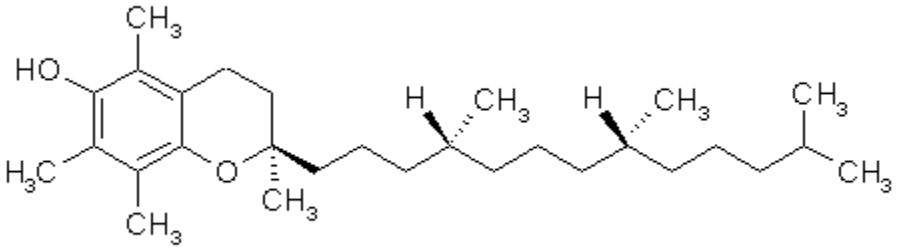
Vitamin D

• deficiencies only occur when
-**the skin** receives insufficient UV light
-**and** vitamin D is lacking in the diet

rickets in children, *osteomalacia* in adults (bone mineralization is disturbed)

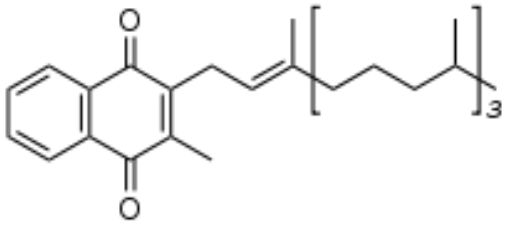
High doses: Can reduce risk of **diabetes, metabolic syndrome, cancer *(prostate, colorectal)***

Vitamin E (tocopherols, tocotrienols)



- occurs only in plants
- located in the membranes and plasma
- **antioxidant, chain-braking anti-radical**
- protects unsaturated lipids against free radicals
- tocopheroxyl radical is reduced back to tocopherol by reaction with **vitamin C**
- **10 mg/day** for adults
- **Deficiency:** caused by abnormalities in dietary fat absorption, not dietary
  - **Neuromuscular and neurological problems**
  - **Hemolytic anemia** – due to oxidative damage to red blood cells
  - **Retinopathy**
  - **Impairment of the immune response**

Vitamin K (K_1: phylloquinone, K_2: metaquinone)

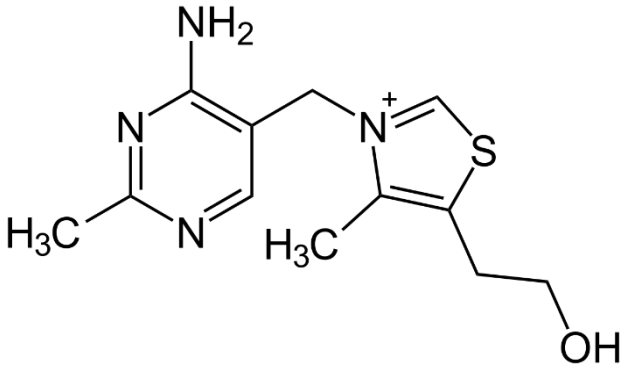


- K_1 is made by plants, found in highest amounts in **green leafy vegetables**
- Animals may also convert K_1 to K_2
- Bacteria: K_1 and K_2

- carboxylating Glu residues of blood coagulation factors VII, IX, X, proteins C and S in the liver **(cofactor of gamma-glutamyl carboxylase)**
- Reduction to coenzyme is inhibited by **coumarins** (prevent reduction of vit. K epoxide)

- Requirement: 70 µg/day
- Deficiency: bleeding

B_1 (Thiamin)

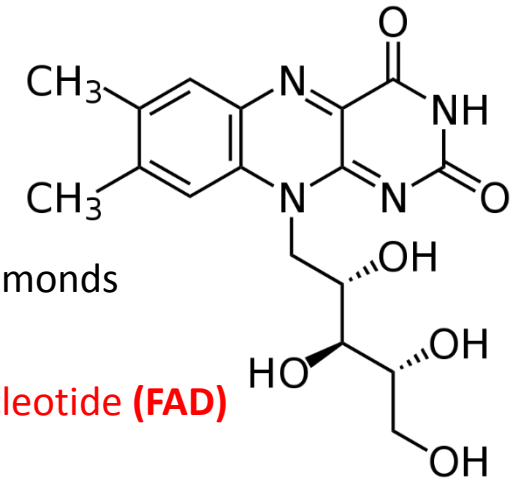


- Key role in carbohydrate metabolism
- Active forms:
  - Thiamine diphosphate - TPP **(coenzyme)**
  - Thiamine triphosphate (neuroactive form, Cl^- channels in neurons)

- TPP is a **coenzyme** of
  - pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase **and**
  - branched-chain α-keto acid dehydrogenase – oxidative decarboxylation and conjugation with coenzyme A
  - Transketolase - transfer of two-carbon units
  - pyruvate decarboxylase (in yeast)

- Food sources: whole grains, legumes, and some meats and fish.
- Dietary requirement: 1.2 mg/day
- Deficiency: beriberi and Wernicke encephalopathy.

B_2 (Riboflavin)

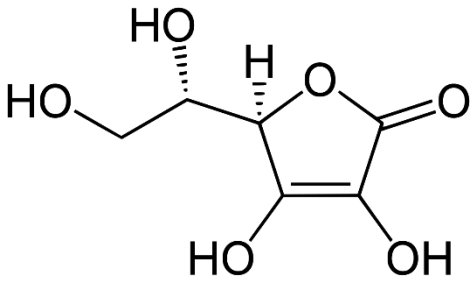


- Food sources: eggs, green vegetables, milk, meat, mushrooms, and almonds
- Coenzyme forms: Flavin mononucleotide **(FMN)**, flavin adenine dinucleotide **(FAD)**
- In ETC: FMN in Complex I and FAD in Complex II
- FAD is required for the production of pyridoxic acid from pyridoxal (vitamin B_6) by pyridoxine 5'-phosphate oxidase
- Oxidative decarboxylation of pyruvate, α-ketoglutarate requires FAD in the E3 portion of their dehydrogenase complexes
- Fatty acyl CoA dehydrogenase requires FAD in fatty acid β-oxidation
- FAD is required to convert retinol to retinoic acid via cytosolic retinal dehydrogenase
- Synthesis of an active form of folate (5-methyl-TH_4) from 5,10-methylene-TH_4 by methylenetetrahydrofolate reductase is $FADH_2$ dependent
- FAD is required by kynurenine 3-monooxygenase to convert tryptophan to niacin (vitamin PP)

Dietary requirement: 1.8 mg/day for women and 2.5 mg/day for men

Deficiency: angular stomatitis, cheilosis, anemia (interference with iron absorption), in pregnancy - birth defects (congenital heart defects, limb deformities).

Vitamin C



- Food source: citrus fruits, kiwifruit, guava, broccoli, Brussels sprouts, bell peppers and strawberries. Prolonged storage or cooking may reduce vitamin C content.

Human lacks the L-Gulono-γ-lactone oxidase so unable to synthesize vitamin C.

- Daily requirements: 75-90 mg/day
- Deficiency: scurvy.
- **C** - water-soluble antioxidant, maintains vitamin E and many metal cofactors in the reduced state

  and has specific roles in the

  – copper-containing hydroxylases **(synthesis of catecholamines)**
  – iron-containing hydroxylases **(proline** and **lysine hydroxylases)** – modification of procollagen, blood clotting, synthesis of carnitine

Vitamin C (cont.)

Vitamin C is a powerful reducing agent capable of rapidly scavenging a number of reactive oxygen species **(ROS)**.

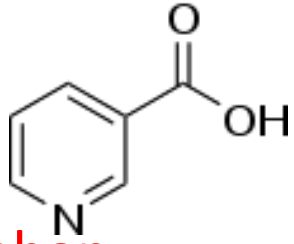
Vitamin C functions **as a cofactor** for enzymes:

- Three groups of enzymes (prolyl-3-hydroxylases, prolyl-4-hydroxylases, and lysyl hydroxylases) that are required for the hydroxylation of proline and lysine in the synthesis of collagen. Hydroxylation allows the collagen molecule to assume its triple helix structure, and thus **vitamin C is essential to the development and maintenance of scar tissue, blood vessels, and cartilage.**

  The role of vitamin C is to oxidize prolyl hydroxylase and lysyl hydroxylase from Fe^{2+} to Fe^{3+} and to reduce it from Fe^{3+} to Fe^{2+}.

- Two enzymes (ε-N-trimethyl-L-lysine hydroxylase and γ-butyrobetaine hydroxylase) of synthesis of carnitine.
- Hypoxia-inducible factor-proline dioxygenase enzymes
- synthesis and catabolism of tyrosine
- Dopamine beta-hydroxylase - biosynthesis of norepinephrine from dopamine

Niacin (PP)



- Can be synthesized by plants and animals from tryptophan.
- highest contents in meat, poultry, red fish (tuna and salmon), lesser amounts in nuts, legumes and seeds.
- Coenzyme form:

  Nicotinamide is a component of the coenzymes nicotinamide adenine dinucleotide **(NAD^+)** and nicotinamide adenine dinucleotide phosphate **($NADP^+$)**

Daily requirements: 14 mg/day for adult women, 16 mg/day for adult men

Deficiency: pellagra - can be caused by deficiency of both Tryptophan **and** niacin or:

- Hartnup disease: defect in membrane transporter for tryptophan
- Carcinoid syndrome – overproduction of serotonin by liver tumor or enterochromaffin cells (using up tryptophan)

Additional functions
Water-soluble vitamins participate:

- **B_6** as pyridoxal phosphate (PALP) is the coenzyme
  - in amino acid metabolism, including the transaminases,
  - **and** of glycogen phosphorylase
- **Biotin** is the coenzyme for carboxylase enzymes

  and has a role in regulation of the cell cycle (biotinylation of key nuclear proteins)
- **B_{12}** and **folic acid** take part in providing one-carbon residues for DNA synthesis. Conversion of CH_3-FH_4 to FH_4 requires B_{12}!
- **PP:** NAD^+ is a source of ADP-ribose for ADP-ribosylation of proteins and polyADP-ribosylation of nucleoproteins in the **DNA repair.**

Water-soluble vitamins - deficiencies

PP

- Vitamin deficiency only occurs when PP and tryptophan are **simultaneously lacking** in the diet
  - 60 mg of tryptophan in diet is equivalent to 1 mg of PP

Folate

- disturbances in nucleotide biosynthesis and cell proliferation
- deficiency: megaloblastic anemia, impaired phospholipid synthesis and amino acid metabolism
- Sign of deficiency – **hyperhomocystienemia**

B_{12}

- Not in plant products! (synthetized by flora)
- Deficiency is due to an absence of **intrinsic factor -** resorption disturbance.
- Clinical signs same as for **folate deficiency**
- Sign of deficiency – **methylmalonic aciduria**

C

- Iron- **(Pro, Lys, Asp)** and copper- **(dopamine, peptidylglycine)** containing hydroxylases
- deficiency: skin changes, fragility of blood capillaries, gum decay, tooth loss, and bone fracture - attributed to **deficient collagen synthesis**
- increased intakes may be beneficial:

  enhances the absorption of iron

Application of vitamins in clinics

- Prevention of hypovitaminosis due to
  - low intake of vitamins from food
  - Increased vitamin requirements (stress, exposure to harmful environmental factors, pregnancy)
- reducing the risk of colds, cardiovascular, cancer and other diseases
- Treatment of primary (food) vitamin deficiencies
- Treatment of metabolic disorders (incl. congenital) and secondary vitamin deficiencies due to:

  - pathological processes
  - surgeries
  - drug therapy
  - dietary restrictions
- The use vitamins in **high doses** for treatment of diseases

High doses of vitamins

- Vitamin A - prevention of infertility, increased tissue regeneration, to stimulate the growth and development of children.
- Vitamin C – enhances absorption of inorganic ions (Fe)
- Vitamin D - rickets and treatment of skin diseases, prevention of colon cancer.
- Vitamin K - for bleeding associated with a decrease in blood clotting.
- Vitamin E – protection of pregnancy and threatened abortion, liver disease, muscle atrophy, congenital disorders of erythrocyte membranes in the newborn.
- Vitamin B_1 - diabetes mellitus (to improve digestion of carbohydrates), inflammation of the peripheral nerves and lesions of the nervous system, heart and muscles.
- Vitamin B_2 - dermatitis, poorly healing wounds and ulcers, keratitis, conjunctivitis, liver damage.
- Pantothenic acid - skin and hair diseases, hepatitis, myocardium dystrophy.
- Vitamin PP - dermatitis, lesions of peripheral nerves, myocardium dystrophy.
- Vitamin B_6 - polyneuritis, dermatitis, toxemia of pregnancy, hepatitis.

Intervitamin relationships

- C and E – in trapping free radicals
- B_{12} and folic acid – in DNA synthesis
- A and D in Ca^{2+} homeostasis

Assessing the vitamin status

- direct monitoring in biological fluids
- B_6 – PALP effect in vitro on erythrocyte transaminases
- B_1 – TDP effect
- C - excretion after loading
- by level of metabolites in blood/urine (for folate - homocysteine, for B_1 - pyruvate)

Antivitamins

substances causing reduction or complete loss of biological activity of vitamins by:

- destruction of vitamin or its binding molecule to inactive forms
  - egg white protein **avidin** forms insoluble complex with **biotin** and prevents biotin absorption in intestine
  - thiaminase destroys **thiamine** (B_1)
  - lipooxydase oxidates **carotene**
- replacing coenzyme in the active sites of enzyme (structural analogs of vitamins or coenzymes)
  - sulfonamines (structural analogs of PABA)
  - coumarins (antivitamins K)
  - hydrazide of isonicotinic acid (antivitamin PP)