WATER-SOLUBLE VITAMINS

These vitamins excess can be excreted in the urine.

Vitamin B1 - thiamine, anti-beriberi vitamin.

Thiazole, a core ring of vitamin B1, is a derivative of pyrimidine.

Its coenzyme form,TPP (thiamine pyrophosphate) is called "cocarboxylase".

TPP is aconstant compound (coenzyme) of pyruvate-DH, α-ketoglutarate-DH, decarboxylase (liase) enzymes. Decarboxylases with TPP coenzyme are involved in the metabolism of branched carbon-chain amino acids, i.e. valine, isoleucine, leucine.

TPP is coenzyme of the transketolase and forms NADPH, ribose.

Vitamin B1 avitaminosis has 3 different forms:

1) Acute, moist (edematous), that appears in cardiovascular damage

2) Chronic, dry (atrophic), in which peripheral nervous system is disturbed. In this case B1 avitaminosis results in paralysis, paresis occurs.

3) Acute, which occurs in breastfed infants. When the mother is deficient in B1 vitamin, it results in the sudden death of the child.

In Europe, avitaminosis B1 is called Wernicke's or Weiss syndrome:

Encephalopathy is called Wernicke's syndrome, while cardiovascular disorder is termed Weiss's syndrome. Not only B1, but also B2, B6, PP and C vitamins are deficient in beri-beri desease.

Avitaminosis B1 in drunks causes **Wernicke-Korsakoff** syndrome (psychosis, irreversible brain damage, memory impairment). B1 is abundant in unrefined rice, wheat, cereals, flour bran, peanuts, peas etc.

Vitamin B2 (riboflavin)

Vitamin B2 (riboflavin) is a derivative of isoalloxazine

It has a bitter taste. B2 forms coenzymes FMN & FAD.

FAD and FMN participate:

1) In dehydrogenation of substrates

2) in the acquisition of electrons and protons from intermediate carriers (NAD, NADP).

Angular stomatitis, cheilosis, glossitis, vascularization are characteristic of ariboflavinosis (vitamin B2 deficiency).

The main source of vitamin B2 is milk and dairy products.

Pantothenic acid (antidermatitis factor)

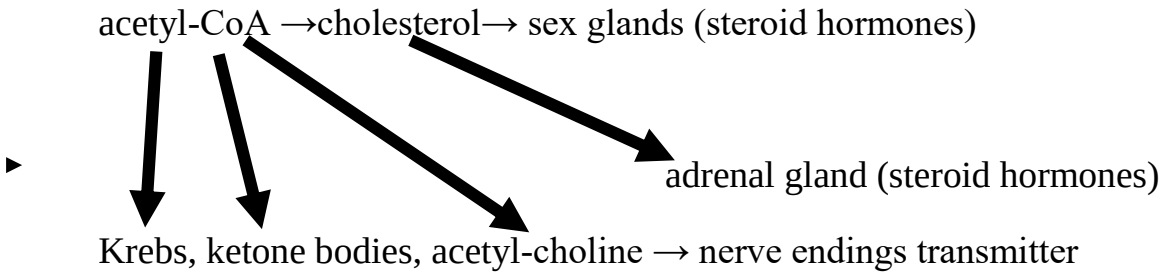
Pantothenic acid is a vitamin that comprises a non-proteinogenic amino acid, i.e. β-alanine.

Pantothenic acid is included in such enzymes as *Transferases & Liases.*

Pantothenic acid forms coenzymes: A (HS-CoA), dephospho-CoA, 4-phosphopantotein.

Pantothenic acid generates energy by forming acetyl-Co and acyl-CoA, It provides synthesis of fatty acids, cholesterol, ketone bodies, acetylcholine.

Avitaminosis of pantothenic acid is caused by its antivitamins, namely homopantotene, methylpantothenic acid. During avitaminosis, the adrenal gland (which synthesizes steroids), the gonads function, the nerves are affected. The impaired function of these glands and nervous tissue results in paresis & convulsions.



Vitamin PP (nicotinamide, nicotinic acid, pellager preventive)

Vitamin PP is a derivative of pyridine. It is crystalline with sour taste. Vitamin PP does not lose its activity when heated.

Vitamin PP coenzymes are NAD & NADP.

Nicotinamide has an antilipotropic effect in large doses (decreases breakdown of lipids, which causes cumulation of lipids, especially in the liver). This effect of vitamin PP is due to its ability to increase body needs in methionine and choline. Methionine and choline are used for methylation of excess vitamin PP. As a result, the lipotropic effect of methionine and choline is weakened, and

fatty infiltration of the liver occurs. NAD and NADP are necessary for the human, because:

1) They are hydrogen carriers in oxidation-reduction reactions.

2) NAD-H and NADP-H are allosteric regulators of oxidation-reduction enzymes (especially DH). Thus, NAD(P)-H weakens the Krebs cycle when cumulated.

3) NAD is a substrate for ***DNA ligase,*** so it increases cell division and regeneration.

NAD is also the main substrate in the synthesis of poly- (ADP) ribose, thereby increasing the synthesis of nucleic acids.

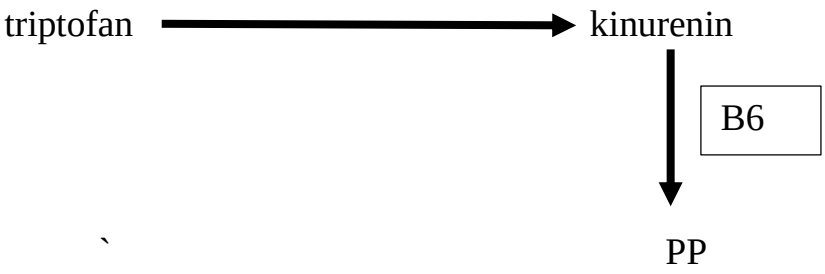
1/60 of food tryptophan is used for the synthesis of active nicotinic acid (NAD) in the body. Leucine reduces the synthesis of NAD from tryptophan, causing pellagra: when leucine level raises in the cell, PP synthesis is lowered. Pellagra is caused by a decrease in both nicotinic acid and tryptophan.

Pellager 3 is a "D" disease: dermatitis, diarrhea, dementia. PP hypovitaminosis also includes glossitis (hypertrophic inflammation of the tongue)

Vitamin PP is abundant in meat and liver. In order to absorb vitamin PP from corn, it is put in lime water.

Vitamin B6 (piridoksin, antidermatitis factor)

Vitamin B6 participates in convertion of triptofan to kinurenin:



Vitamin B6 is a derivative of pyridine. Vitamin B6 is stable: it does not decompose in 2n sulfuric acid. But it sensitive to a neutral & basic pH of environment.

Coenzymes: PALP, PAMP. Glycogen-phosphorylase contains B6. Phosphorylase (glycogen-phosphorylase) combines with more than 50% of B6 reserves.

Amintransferase, decarboxylase are also enzymes involving vitamin B6 . Reactions in which vitamin B6 participates as coenzyme are shown below:

B6

δALT → porphyrin → heme

B6

glutamate→ GABA.

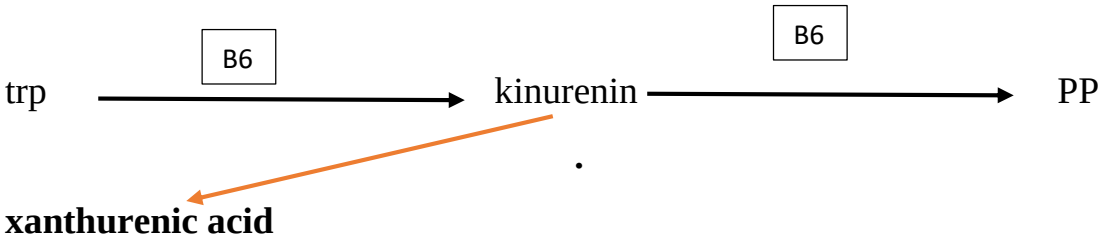
When B6 is reduced, γ-amino butyric acid is reduced, which results in epileptic seizures.

Vitamin B6 participates in the metabolism of ser, tre, tri, cystationin, kinurenin, δ-ALA (δ-amino levulinic acid required for heme synthesis). Vitamin B6 is coenzyme in the synthesis of nicotinic acid from tryptophan. In B6 deficiency, the endogenous synthesis of vitamin PP is impaired.

Vitamin B6 is both lipotropic (protects liver from fats cumulation & fatty distrophy) and antilipotropic vitamin.

Hypovitaminosis B6 is characterized by angular stomatitis, chelos, glossitis (as in B2-hypovitaminosis).

Isoniazid, ftivazid, tubazid, cycloserine used in tuberculosis, and estrogens are antagonis of vitamin B6.



xanthurenic acid

Xanthurenic acid accumulates and is excreted in the absence of pyridoxine (vitamin B6) after ingestion of tryptophan. Due to this, vitamin B6 deficiency is tested with a "tryptophan load": If a patient has vitamin B6 deficiency, xanthurenic acid is detected in the urine and the kinure increases.

Folic acid (folasin, Bc, B9)

Folic acid consists of pteridine, vitamin-like substance PABT (paraamine benzoic acid) and proteinogenic amino acid (glutamic acid). Folasin, which contains only 1 glutamic acid, is called pteroil-glutamic acid.

Folic acid is resistant to temperature: melting temperature for folic acid is T = 360ºC. Folic acid is tasteless, odorless crystal difficult to dissolve in water. It is soluble in weak alkali. Folic acid is not resistant to sunlight, so it breaks downafter sunlight apply.

The coenzyme of folic acid is THFA. The reserve of folic acid is in the liver, kidneys and small intestine.

THFA serves as a **carrier** molecule for single-carbon moieties: methyl (-CH3), methylene (-CH2), methenyl (-CH =), formyl, oxymethyl, formimine, methylidine.

THFA is involved in the synthesis of choline, purines and pyrimidines. It is also involved in the formation of methionine from homocysteine. Therefore, vitamin B9 deficiency causes homocysteine-uria. Since in vitamin B9 deficiency methionine formation is decreased, fatty infiltration of the liver occurs. In vitamin B9 deficiency, Hunter glossitis & cheilosis develop. Cheilosis is painful swelling and fissuring of the lips followed by bleeding.

In vitamin B9 deficiency, blood color index increases, megalocytic anemia occurs. The color index is the ratio of the hemoglobin percentage (compared to "normal") to the red blood cell count (compared to "normal").

Vitamin B12 (cobalamin, antianemic)

Vitamin B12 is the only vitamin that contains metal ion (Co). B12 is not synthesized in animals and plants, but obtained from bacteria.

Vitamin B12 does not lose its stability when boiled for several hours in a weakly acidic environment, but is sensitive to alkali.

Vitamin B12 absorption occurs with help of gastromucoprotein, i.e. transkorrin (an internal factor of Castle).

Vitamin B12 is transported in the blood by trans-cobalamin I, trans-cobalamin II and trans-cobalamin III.

Vitamin B12 coenzymes are: a) methyl-cobalamin, that is coenzyme of ***transferases***

b) 5-DOAK (deoxy-adenosyl-cobalamin), that is coenzyme of ***isomerases*** and ***lyases.***

Reactions, that occur in the body with B12 invopvement:

a) transmethylation, in which methyl-cobalamin takes part

b) isomerization with DOAK.

B12, (B9) THFT, B6, FAD (B2) are involved in the synthesis of methionine from homocysteine:

$$\text{Homocysteine} \xrightarrow{\text{B2, B6, B9, B12.}} \text{methionine.}$$

The conversion of methyl-malonyl-CoA to succinyl-CoA and thus the breakdown of fatty acids with odd number of carbons depends on vitamin B12 availability. In vitamin B12 deficiency, methyl-malonyl-uria and homocysteine-uria occur. **Adisson-Birmer disease** is caused by avitaminosis B12. Vitamin B12 deficiency causes megaloblastic anemia. The disease is treated by giving high-dose B_{12} orally, or intramuscular injection of cyanocobalamin. Therapy must be continued throughout the lives of patients with pernicious anemia. Deficiency of vitamin B_{12} can be measured by the level of *methylmalonic acid* in blood, which is elevated in individuals with low intake or decreased absorption of the vitamin B12. When vitamin B12 decreases, THFA decreases too. In B12 deficiency like folic acid deficiency, methyl-malonic acid is found in the urine, but along with it homocysteine is also excreted.

After gastrectomy patients can not absorb the vitamin B12.

In achrestic anemia (Israel-Wilkinson syndrome), the bone marrow cannot use vitamin B12. Hunter glossitis is characteristic for B12 avitaminosis. In vitamin

B12 avitaminosis myelosis occurs, i.e. the dorzo-lateral columns of the spinal cord are damaged.

In avitaminosis B12, the color index is higher than normal: 1.3-1.8. The number of leukocytes, platelets, erythrocytes decreases.

Vitamin B12 is one of the least needed vitamins for health (2-3 mcg). Need in vitamin B12 in comparison to vitamin C is 25,000 times less.

Vitamin H (biotin)

Vitamin H - biotin is a coenzyme in carboxylation reactions, in which it serves as a carrier of activated carbon dioxide. Biotin deficiency occur at the addition of raw egg white as a source of protein to the diet. Dermatitis, glossitis, loss of appetite, and nausea are the symptoms of it.

Vitamin C (ascorbic acid)

A deficiency of ascorbic acid results in scurvy, a disease characterized by sore and spongy gums, loose teeth, fragile blood vessels, swollen joints, petechiae (spot haemorrages) and anemia. Many of the deficiency symptoms can be explained by a deficiency in the hydroxylation of collagen, resulting in defective connective tissue.

Antivitamins

Antivitamins fight vitamins, replace them in coenzyme linked spot of enzymes, and by this way disrupt the reaction. Some of them make inactive metabolites from enzymes. .

Vitamin	Antivitamins	Apply of antivitamins

K (naphthoquinone)	coumarins (trimexan, warfarin)	in thrombosis
B1	pyrithiamine, neopiritiamine	cause avitaminosis
B2	aterbin, acrixin, dichlor-ripoflavin	cause avitaminosis

Fat soluble vitamins

Vitamins are not a source of energy and do not enter cell structures. According to their *solubility*, vitamins are divided into 3 groups:

1. Fat-soluble vitamins (A, D. E, K) are not synthesized in the liver

2. Water-soluble vitamins (B group vitamins & vitamin C)

3. Vitamin-like substances - can be synthesized in the body, but should be taken with food for health.

Example of vitamers: pyridoxine, pyridoxal, pyridoxamine

Following substances are examples of provitamins: a) carotene (converted to retinol, i.e. vitamin A)

b) 7-dehydrocholesterol – it is converted to vitamin D

According to their *biological functions*, vitamins are divided into 3 groups:

1) enzyme-vitamins (B group).

2) hormone-vitamins (A and D).

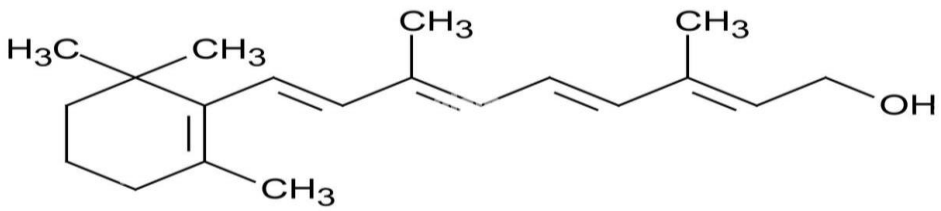
3) antioxidant or redox vitamins (A, E, C, lipoic acid)

Hypervitaminosis is characteristic to fat-soluble vitamins.

Hypovitaminosis means vitamin deficiency, avitaminosis - a serious vitamin deficiency or absolute absence.

Vitamin A

Vitamin A is a derivative of β-ionone.



In the retina of the eye, it is in the form of 11-cis-retinal. The product richest in this vitamin is β-carotene containing carrot, since β-carotene is split to 2 molecules of vitamin A. Vitamin A forms rhodopsin (11-cis-retinal + opsin). Sight is associated with transducin (g-protein) action.

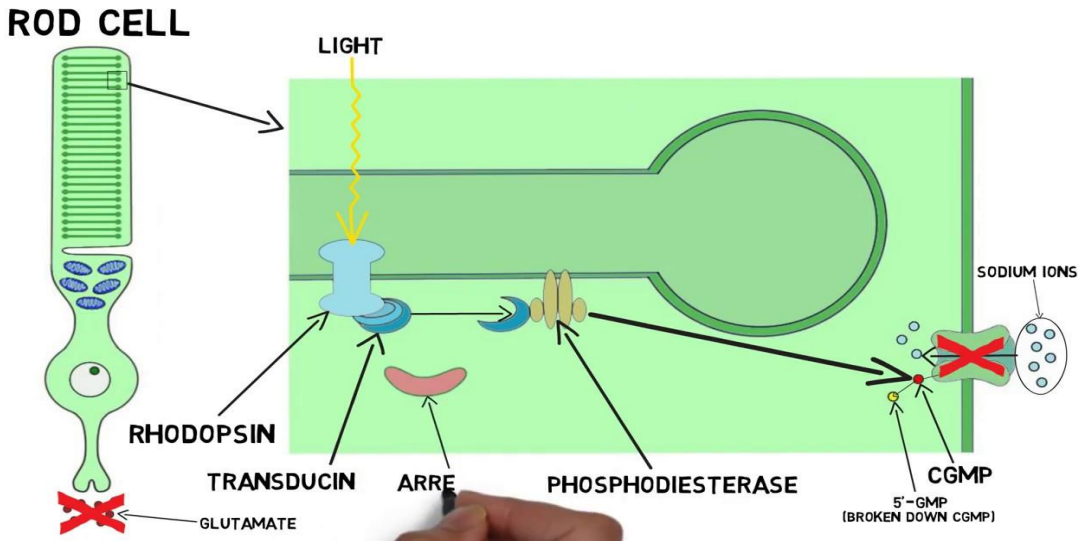


Fig.2. Organization of rhodopsin & transducing inside of rode cells

During vision, 11-cis-retinal in rhodopsin is converted to11-trans-retinal, then it fully recovers. The adaptation of eye to darkness requires 30 minutes.

Active forms of vitamin A: *retinol, retinal, retinoic acid and their esters*.

Color blindness is due to the lack of some iodopsins synthesis.

Vitamin A hypovitaminosis first causes hemeralopia, followed by xerophthalmia (dryness of the cornea) and keratomalacia (necrosis of the cornea). This is due to hyperkeratosis of the tear duct in A hypovitaminosis.

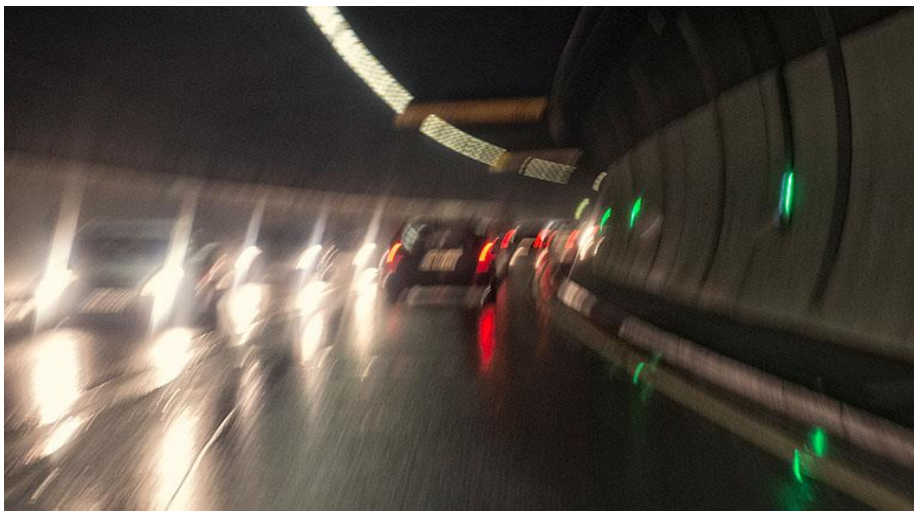


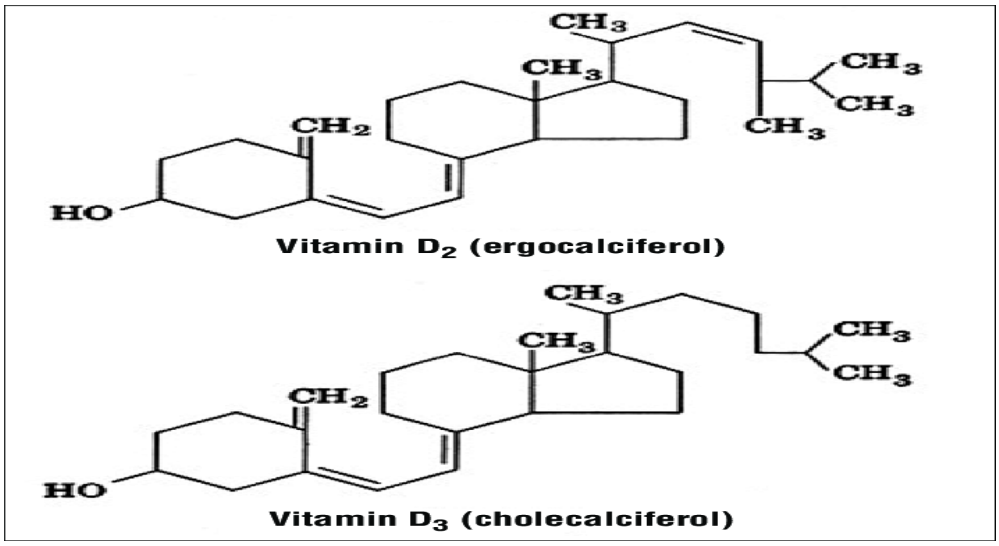
Fig.1. Such looks the external world at hemeralopia

Vitamin A hypervitaminosis results in xanthosis termed wrong Jaundice (carotenodermia). Unlike true jaundice characterized by scleral icterus, the color of the mucous membranes and sclera in wrong Jaundice is normal.

When vitamin F and E are sufficient, they protect vitamin A.

Vitamin D (calciferol, antirachitic)

Vitamin D is a derivative of sterin. D Vitamers are ergocalciferol (D_2) and cholecalciferol (D_3). Vitamin D is formed when UV radiation is applied to the skin. D_3 is more active than D_2.



Along with vitamin A, E, K, vitamin D is absorbed from the small intestine with the bile acids and passes into chylomicrons. Vitamin D combines with transcalciferin in the liver. Vitamin D is converted in the liver to 25-hydroxy, i.e. 25 (OH) calciferol. 25 (OH) -calciferol is delivered to the kidneys, where it is converted to 1,25-dihydrocalciferol, i.e. 1.25 (OH) calciferol. 1.25 is called *calcitriol.*

The parathyroid hormone (PTH) increases the synthesis of calcitriol by renal induction of ***Calciferol-1-hydroxylase***. This enzyme works with help of vitamin C. Since calcitriol is a hormone, vitamin D is considered an exogenous prohormone. Calcitriol facilitates:

- Intestinal absorption of calcium and phosphate
- Kidney reabsorption of calcium and phosphate

- Stimulates the deposition (mineralization) of calcium and phosphate in the bones. However, when the level of Ca in the blood decreases, calcitriol demineralizes the bone to maintain normal level of Ca ions in the blood.

D hypovitaminosis leads to richets, a condition that affects bone development in children. This state causes bone pain, poor growth, short stature. Imperfect mineralization due to Ca insufficiency results in soft, weak bone tissue leading to bone deformities. Adults can experience a similar condition termed osteomalacia (soft bones). So, in the elderly, hypovitaminosis D causes osteomalacia and osteoporosis.

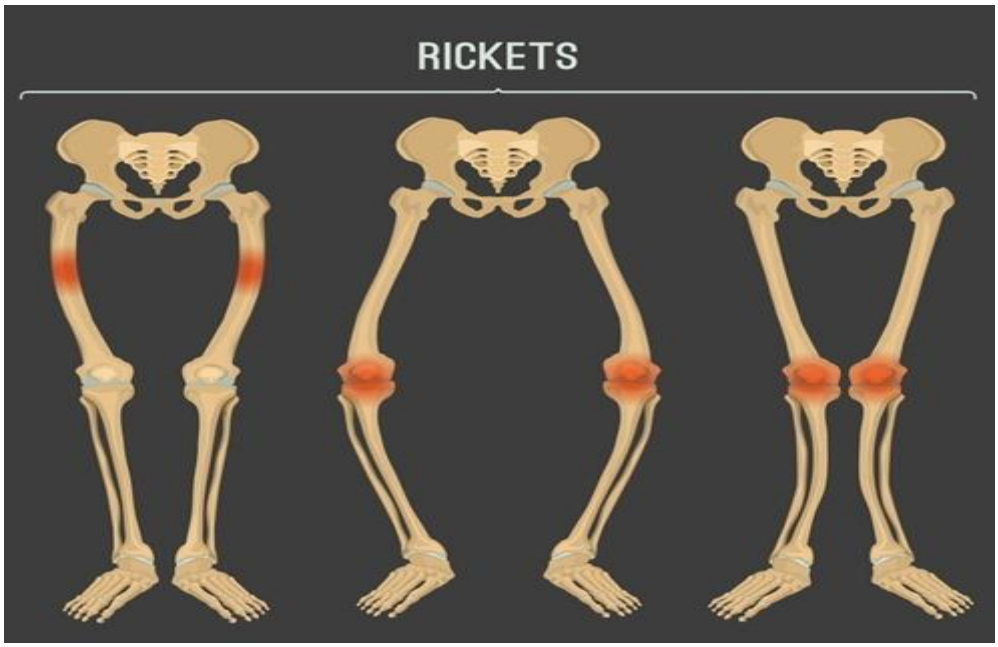


Fig.1. Osteomalacia in rickets

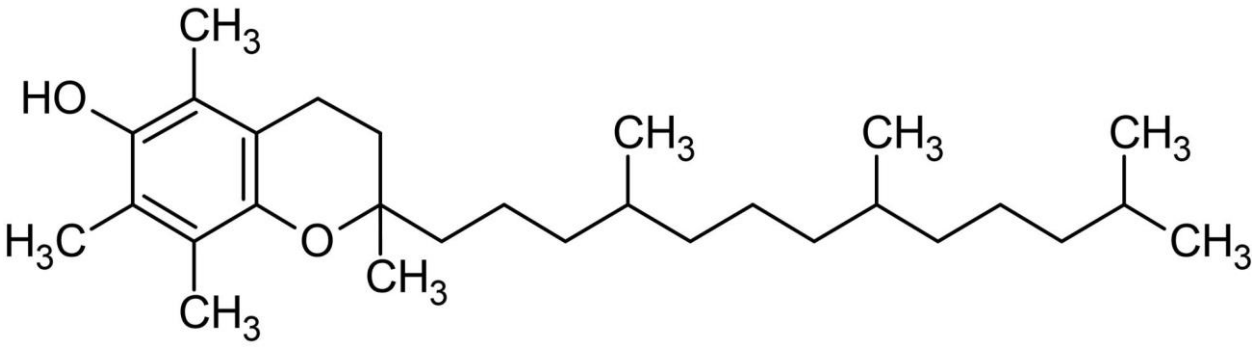
Scheme of hypercalcemia in rickets

Low vitamin D levels → Ca^{2+} decreases in the blood → low Ca^{2+} level increases parathyroid hormone secretion → Parathormone resorbs bone (washes Ca^{2+} out of the bone) → Ca^{2+} passes into the blood. It increases Ca^{2+} ions in the blood - hypercalcemia occurs.

Changes observed during rickets: the child becomes irritable, fontanelles do not grow together, the skull softens, enlargement of the abdomen occurs.

Vitamin E (tocopherol)

Vitamin E (tocopherol) is a derivative of tocol.

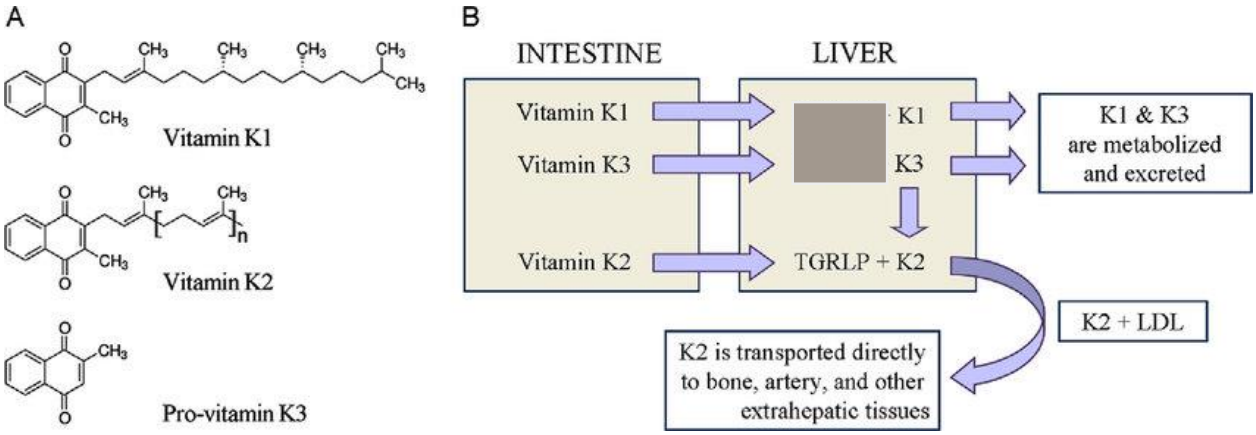


It occurs in the nature in the form of α, β, γ, δ-tocopherol and 8-methyltocotrienol. Tocopherol protects vitamin A and increases its activity. Vitamin E deficiency causes hemolytic anemia in premature babies. In vitamin E deficiency, muscle glycogen, myosin, trace elements are reduced.

Vitamin K

Vitamin K is a derivative of quinone.

K1-phylloxinone, K2-menaxinone and K3-menadion are distinquished.



Vikasol is a synthetic derivative of vitamin K that is soluble in water. Vitamin K prevents bleeding.

Vitamin K stimulates the synthesis of factors II, VII, IX, X of blood coagulation in the blood. Vitamin K helps γ-carboxylation of glutamic acid in these listed plasma coagulation factors. It also helps γ-carboxylation of osteocalcin in bone.

Vitamin K deficiency causes bleeding and hemorrhage in the joints, retina, nosebleeds and melena (blood in the stool). Dicoumarin and warfarin are

anticoagulants that reduce prothrombin level resulting in reduce of coagulation. These drugs are used in thrombosis, thromboembolism treatment.