Vitamins

Vitamins are chemically unrelated organic compounds that cannot be synthesized in adequate quantities by humans and, therefore, must be supplied by the diet.

The world vitamin is derived from:

vita → a latin word meaning life

Amine → because they were thought to contain amine

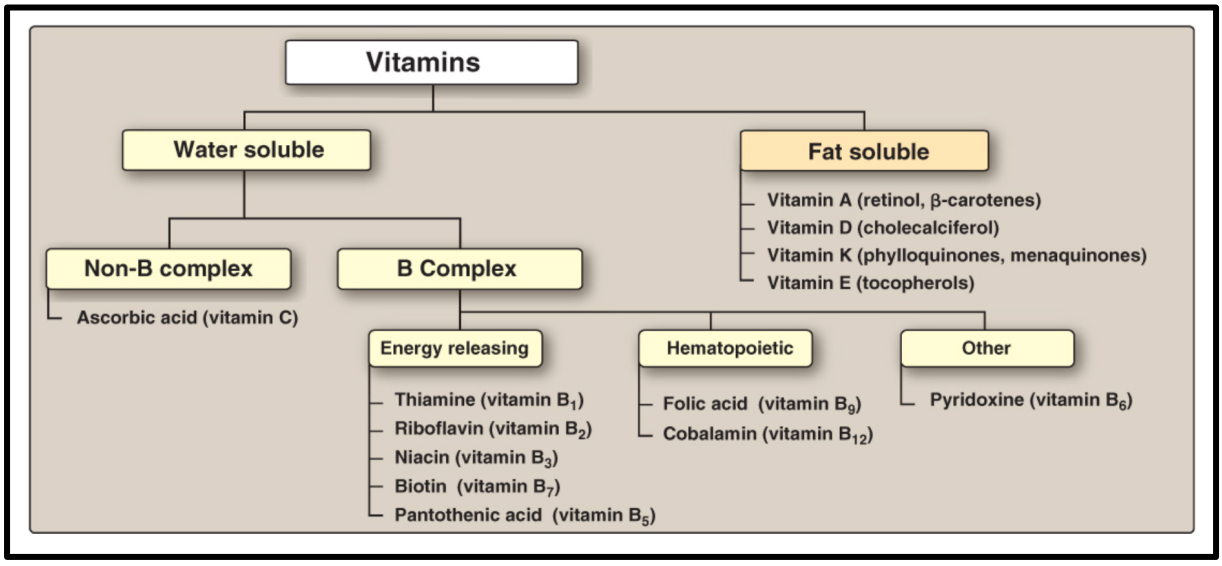
Vital amines → Vitamine → Vitamin

Since they are required in lesser amounts than the macronutrients (carbohydrate, protein, and lipid), vitamins are termed micronutrients.

Classification:

Vitamins are classified into 2 groups according to their solubilities:

1. Fat soluble vitamins: which include vitamins A, D, E and K.
2. Water soluble vitamins: which include vitamins B and C.



Fat Soluble Vitamins

Vitamin A

Two groups of nutritional compounds have vitamin A activities:

1. **Retinol, retinal and retinoic acid:** found only in foods of animal origin.
2. **Carotenes:** found in plants; they are precursors of vitamin A as they are cleaved in the intestinal mucosa to form 2 molecules of retinal by **carotene oxygenase**.

The intestinal activity of carotene dioxygenase is low (1:12), so that a relatively large proportion of ingested β-carotene may appear in the circulation unchanged. So excessive ingestion of carotene-rich food leads to Carotenaemia.

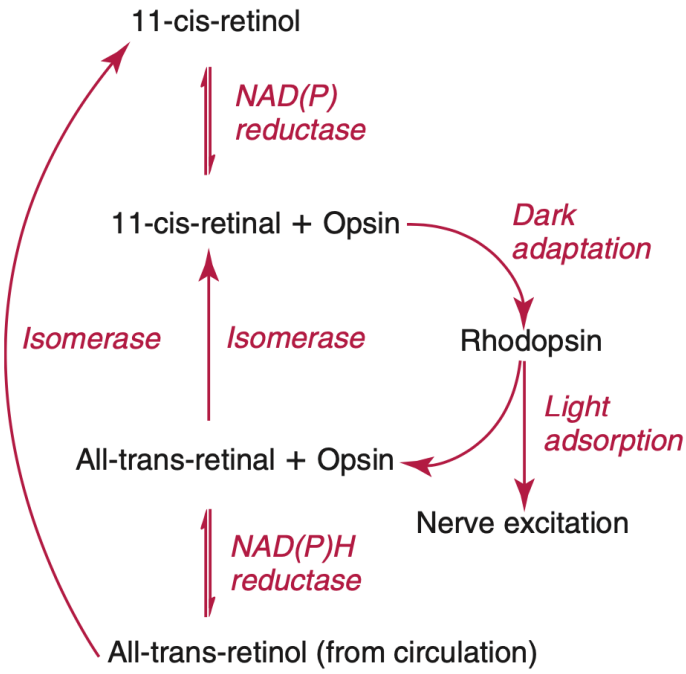
Vitamin A is stored in the liver and adipose tissue. On need, retinol is transported through blood to the extrahepatic tissue by binding to Retinol Binding Protein (RBP).

Sources:

1. Animal-derived foods, such as liver, fish oils, full cream milk, butter.
2. Yellow to orange fruits and vegetables and from green leafy vegetables; such as pumpkin, carrots, tomatoes and most green vegetables.

Functions:

1. Vision: Rhodopsin, the visual pigment of the rod cells in the retina, consists of 11-cis retinal bound to the protein opsin. When rhodopsin is exposed to light, it will be cleaved to all-trans retinal and opsin.



2. Epithelial cell maintenance: Vitamin A (particularly retinoic acid) is essential for normal differentiation of epithelial tissues and mucus secretion and, thus, supports the body's barrier-based defense against pathogens. Retinoic acid binds to nuclear receptors and regulates the transcription of specific genes.

3. Reproduction: Retinol and retinal are essential for normal reproduction, supporting spermatogenesis in the male and preventing fetal death in the female.

Requirement:

The RDA (Recommended Daily Allowance) for adults is 900 retinol activity equivalents (RAE) for males and 700 RAE for females. In comparison

1 RAE = 1 µg of retinol, 12 µg of β- carotene

Deficiency:

1. ***Rhodopsin deficiency:***

Night blindness (nyctalopia) is one of the earliest signs of vitamin A deficiency. Both the time taken to adapt to darkness and the ability to see in poor light are impaired.

2. *Deficient mucus secretion:*

Skin secretion is diminished and there may be hyperkeratosis of hair follicles. Dryness of the conjunctiva and cornea, caused by increased keratin synthesis leading to **xerophthalmia**.

3. Poor bone growth in the skull

4. Anaemia not responding to iron therapy.

Excess:

1. CNS: Headache, nausea
2. Liver: Hepatomegaly
3. skin: excessive dryness and hair loss (alopecia)

Vitamin D

The D vitamins are a group of sterols that have a hormone-like function. Like vitamin A, the active form of vitamin D (1,25 dihydroxycholecalciferol) binds to nuclear receptors and either stimulates or represses gene transcription.

Vitamin D is derived from:

- **Ergocalciferol (vitamin D_2),** obtained from plants in the diet.

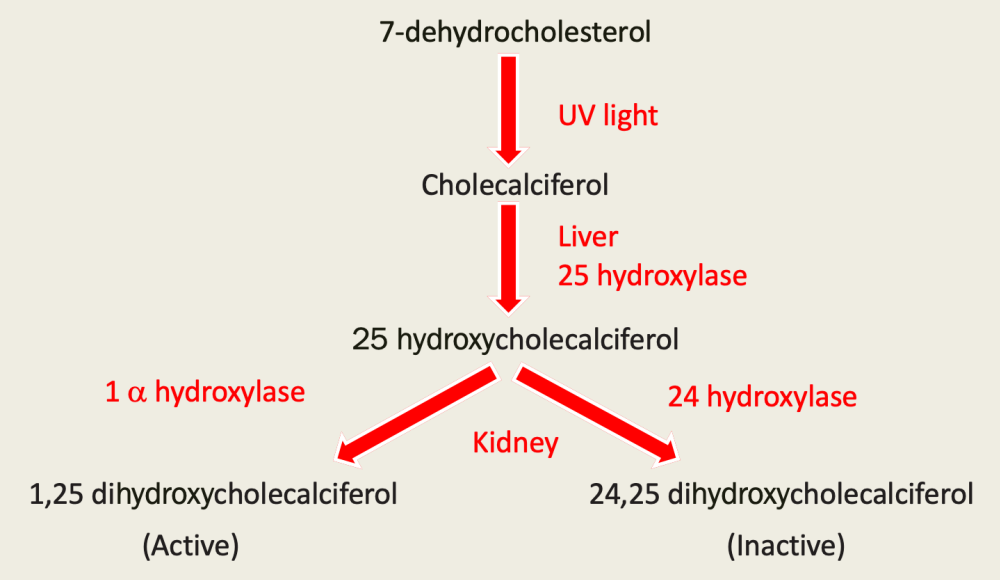
- **Cholecalciferol (vitamin D_3),** formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol (an intermediate in the synthesis of cholesterol that accumulates in the skin).

Cholecalciferol, either synthesized in the skin or from food, is not an active vitamin, it must undergo two hydroxylation:

1. In the liver: to form 25 hydroxy cholecalciferol by the action of **25 hydroxylase**.

2. In the kidney: to form 1,25 dihydroxycholecalciferol (calcitriol) by the action of **1α hydroxylase** (active form).

Or to form 24,25 dihydroxycholecalciferol by the action of **24 hydroxylase** (inactive form)



Functions:

A. The principal function of vitamin D is to maintain the plasma calcium concentration. This is performed by:

1. Increasing intestinal absorption of calcium: calcitriol enters the intestinal cells and binds to specific receptors in the cytoplasm. This complex will stimulate gene responsible for calcium-binding protein expression.

2. Reducing excretion of calcium by stimulating its reabsorption in the distal renal tubules)

3. Mobilizing bone minerals (bone resorption).

B. It is involved in insulin secretion

C. Synthesis and secretion of parathyroid and thyroid hormones.

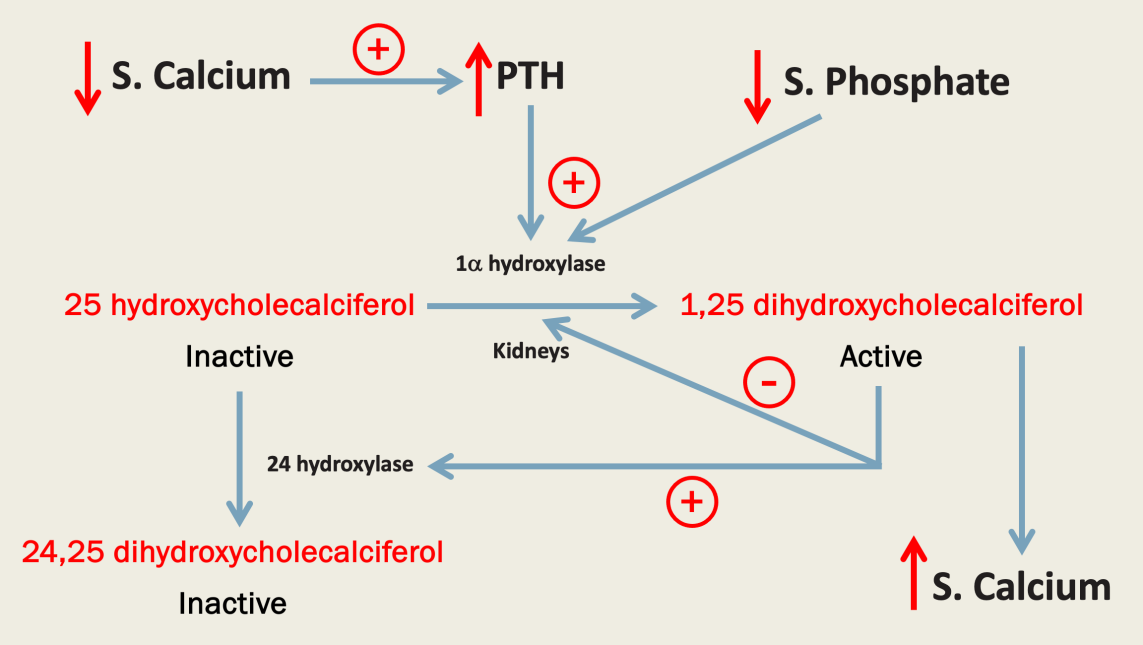
D. Inhibition of production of interleukin (Immune modulator).

Factors affecting the activation process:

1. Parathyroid hormone (PTH): A fall in plasma free ionized calcium concentration stimulates PTH secretion. The PTH enhances 1-α-hydroxylase activity and hence enhances calcitriol synthesis.

2. Phosphate level: hypophosphataemia directly stimulates calcitriol synthesis

3. Calcitriol acts to reduce its own synthesis by inducing the 24-hydroxylase and repressing the 1-hydroxylase in the kidney.



Sources and Requirement:

Vitamin D is found naturally in fatty fish, liver, and egg yolk.

The RDA (Recommended Daily Allowance) is:

- *600 IU for people aged up to 70 years*
- *800 IU for people above 70 years*

Deficiency:

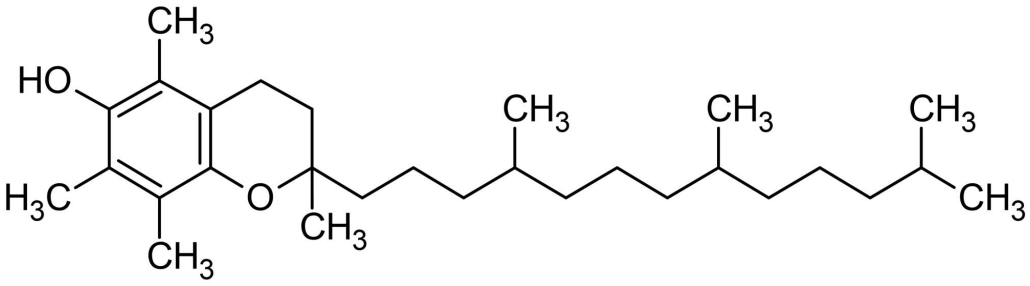
- Vitamin D deficiency causes a net demineralization of bone, resulting in:
  - *Rickets in children*
  - *Osteomalacia in adults*
- Rickets is characterized by the continued formation of the collagen matrix of bone, but incomplete mineralization results in soft, pliable bones.
- In adult, osteomalacia results from demineralization of preexisting bones increases their susceptibility to fracture.

Excess:

- Vitamin D excess causes loss of appetite, nausea, thirst, and weakness.
- Enhanced Ca^{2+} absorption and bone resorption result in hypercalcemia, which can lead to deposition of calcium salts in soft tissue (Calcinosis).

VITAMIN E

It is the collective name (nutritional term) for a group of 8 closely related lipids 4 **tocopherols** and 4 **tocotrienols**, that have biological activity similar to the naturally occuring α-tocopherol. All of which contain a substituted aromatic ring and a long isoprenoid side chain.



Much of the vitamin is normally stored in adipose tissue

Functions:

Tocopherols are biological antioxidants. The aromatic ring reacts with and destroys the most reactive forms of oxygen radicals and other free radicals, protecting unsaturated fatty acids in cell membranes and plasma lipoproteins from oxidation and preventing oxidative damage to membrane lipids, which can cause cell fragility.

The tocopheroxyl radical is relatively unreactive, and ultimately forms nonradical compounds. Commonly, the tocopheroxyl radical is reduced back to tocopherol by reaction with vitamin C from plasma.

Sources and daily requirement:

The principal sources of dietary vitamin E are oils and fats, particularly wheat germ oil and sunflower oil, grains, and nuts

The RDA for α-tocopherol is 15 mg/day for adults

5 mg/day for infants

Deficiency:

Premature and low-birth-weight infants are particularly susceptible to vitamin E deficiency because:

1. placental transfer is poor.

2. Infants have limited adipose tissue where much of the vitamin is normally stored.

Signs of deficiency include:

(1) Irritability

(2) Oedema

(3) Haemolytic anemia: anaemia reflects the shortened life span of erythrocytes with fragile membranes.

Vitamin E deficiency is rare in older children and adults.

Toxicity:

Vitamin E toxicity results only from excessive supplementation. Such supplementation is contraindicated in subjects with coagulation defects caused by vitamin K deficiency and in those receiving anticoagulant drugs. **(Why?)**

VITAMIN K

Three compounds have the biological activity of vitamin K:

1. Phylloquinone (K_1), the normal dietary source, found in green vegetables;

2. Menaquinones (K_2), synthesized by bacteria in the ileum.

3. Menadione (K_3), synthetic compounds that can be metabolized to menaquinone (K_2).

Function:

1. Vitamin K has important roles in coagulation and bone metabolism

It is needed for the posttranslational modification of prothrombin (factor II) and coagulation factors VII, IX and X which are synthesized in the liver (1972).

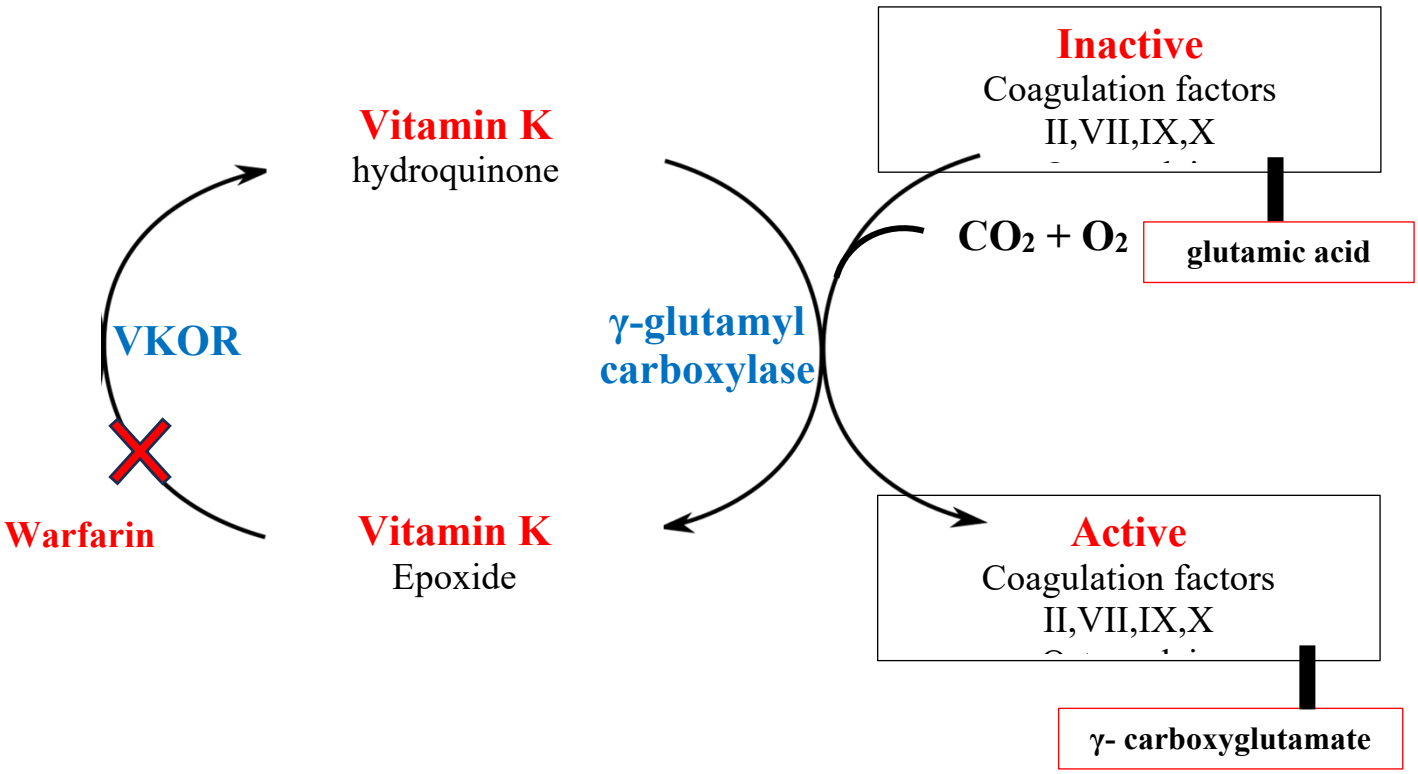
Formation of the functional versions of these factors requires the vitamin K–dependent carboxylation of several glutamic acid residues to γ-carboxyglutamate. The carboxylation reaction requires γ-glutamyl carboxylase, O_2, CO_2, and the hydroquinone form of vitamin K which gets oxidized to the epoxide form.

Regeneration of the functional hydroquinone form of vitamin K requires vitamin K epoxide reductase (VKOR), which converts the epoxide form of vitamin K back to hydroquinone form.

Warfarin, a synthetic analog of vitamin K, inhibits VKOR so inhibits vitamin K epoxide reductase regeneration.

Q: Vitamin K is given to patients with bleeding due to warfarin overdose?

2. Vitamin K is also involved in bone mineralization: Proteins that contain γ-carboxyglutamate are also abundant in bone tissue such as osteocalcin so it is involved in bone synthesis.



Deficiency:

Vitamin K deficiency in the adult is uncommon, the risk is increased with:

1. Fat malabsorption states such as bile duct obstruction, chronic pancreatitis and liver disease.

2. Use of drugs that interfere with vitamin K metabolism, such as warfarin and cephalosporin.

3. Prolong use of antibiotics.

Hemorrhagic disease of the newborn can develop readily because of:

1. Poor placental transfer of vitamin K, (2) hepatic immaturity leading to inadequate synthesis of coagulation proteins.

Toxicity:

The use of high doses of naturally occurring vitamin K (K_1 and K_2) appears to have no known toxic effect; however, menadione (K_3) treatment can lead to the formation of erythrocyte cytoplasmic inclusions known as Heinz bodies and hemolytic anemia.

WATER SOLUBLE VITAMINS

VITAMIN C

The active form of vitamin C is ascorbic acid. It is thermolabile.

Most animals make large amounts of vitamin C, converting glucose to ascorbate in four enzymatic steps. Humans and some animals such as gorillas, guinea pigs, and fruit bats have lost the last enzyme in this pathway (L-gulonolactone oxidase) and must obtain ascorbate in their diet.

Functions:

1. Its main function is as a reducing agent. Vitamin C is a coenzyme in hydroxylation reactions:

a. Hydroxylation of proline and lysine in collagen synthesis, as a cofactor for protocollagen hydroxylase.

b. Hydroxylation of dopamine to norepinephrine in epinephrine synthesis.

2. It is required for the maintenance of normal connective tissue as well as for wound healing.

3. Facilitates the absorption of dietary nonheme iron from the intestine by reduction of the ferric form (Fe^{+3}) to the ferrous form (Fe^{+2})

4. It works, in synchrony with vitamin E, as water-soluble antioxidant.

5. Carnitine biosynthesis.

6. Degradation of tyrosine.

7. Synthesis of adrenal hormones.

8. Bile acids formation.

Sources and requirement:

Ascorbate is found in fruit, particularly citrus fruits, and vegetables.

At intakes above about 100 mg/day, the body's capacity to metabolize vitamin C is saturated, and any further intake is excreted in the urine.

RDA is 30-50mg/day.

Deficiency:

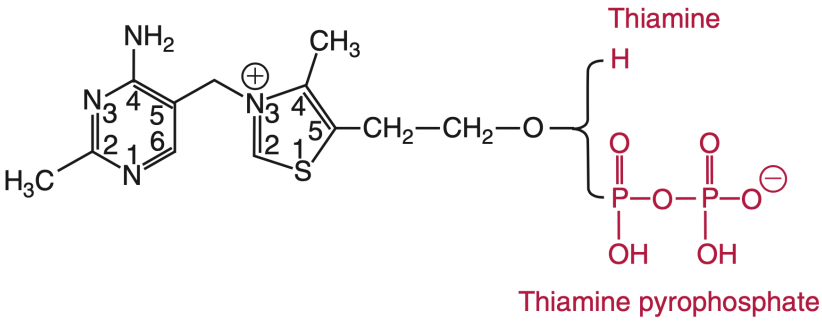
Deficiency of ascorbate causes scurvy, a disease characterized by spongy gums, loose teeth, fragile blood vessels (causing bleeding tendency), swollen joints, bone changes, and fatigue.

Deficiency of bone matrix causing osteoporosis and poor healing of fractures. The enzyme procollagen hydroxylase is mediated by vitamin C and is important for the intracellular matrix.

Anaemia, possibly due to impaired erythropoiesis and poor iron absorption.

VITAMIN B_1 (THIAMIN) (THIAMINE)

The structure of *thiamine* is a pyrimidine ring, bearing an amino group, linked by a methylene bridge to a thiazole ring. The thiazole has a primary alcohol side chain which can be phosphorylated to produce thiamine pyrophosphate.Thiamine pyrophosphate (TPP) is the biologically active form of the vitamin.



Thiamine pyrophosphate

Functions:

1. Thiamine pyrophosphate is an essential cofactor for transketolase in the pentose–phosphate pathway.

2. It serves in the oxidative decarboxylation of α-keto acids, which plays a key role in energy metabolism of most cells particularly in the CNS, which include:

a. Pyruvate dehydrogenase in carbohydrate metabolism.

b. α-ketoglutarate dehydrogenase in the citric acid cycle.

c. branched-chain keto acid dehydrogenase involved in the metabolism of leucine, isoleucine, and valine.

Sources:

Small amounts of thiamine and its phosphates are present in most plant and animal tissues, but more abundant sources include unrefined cereal grains, liver, heart, kidney.

Deficiency:

Deficiency is most common in alcoholics and in patients with anorexia nervosa due to decrease intake or those ingesting raw fish which contains thiaminases.

Three distinct syndromes:

1. A chronic peripheral neuritis called beriberi, which is found in 2 forms:

a. Peripheral neuropathy → Dry beriberi

b. Heart failure and oedema → Wet beriberi

2. Acute pernicious beriberi (Shoshin beriberi), in which heart failure and metabolic abnormalities (lactic acidosis) predominate, without peripheral neuritis.

3. Wernicke encephalopathy with Korsakoff psychosis, which is associated with alcohol and narcotic abuse.

VITAMIN B_2 (Riboflavin)

Sources:

Riboflavin is found in large amounts in yeasts and germinating plants such as peas and beans

Function:

Riboflavin is present in many naturally occurring flavoproteins, in most of which it is incorporated in the form of flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD). Both FMN and FAD are reversible electron carriers in biological oxidation systems, which are, in turn, oxidized by cytochromes.

Deficiency:

Although riboflavin is centrally involved in lipid and carbohydrate metabolism, and deficiency occurs in many countries, it is not fatal, because riboflavin released by the catabolism of enzymes is rapidly incorporated into newly synthesized enzymes.

Tough, scaly skin, especially on the face (dermatitis), cheilosis (red, swollen, cracked lips), angular stomatitis, swollen, tender, red tongue that is described as magenta colored.

VITAMIN B_3 (Niacin) (Nicotinic acid)

It is a substituted pyridine derivative. Nicotinamide is a nicotinic acid that contains an amide instead of a carboxyl group.

Functions:

Nicotinamide is the active constituent of nicotinamide adenine dinucleotide (NAD^+) and its phosphate ($NADP^+$), which are important cofactors in oxidation– reduction reactions.

The NAD^+ and $NADP^+$ and their reduced forms (NADH and NADPH) are essential for glycolysis and oxidative phosphorylation, and for many synthetic processes.

Sources:

Nicotinamide can be formed in the body from nicotinic acid. Nicotinic acid can also be synthesized in humans from tryptophan with the use of vitamin B_6 as a coenzyme, 60 mg of tryptophan is equivalent to 1 mg of dietary niacin.

Both substances are plentiful in animal and plant foods. Niacin is found in unrefined and enriched grains and cereal, milk, meats and liver.

Deficiency:

A deficiency of niacin causes pellagra, a disease involving the skin, gastrointestinal tract, and CNS. The symptoms of pellagra progress through the three Ds:

Dermatitis, sunburn-like erythema, especially severe in areas exposed to the sun

Diarrhea, is due to widespread inflammation of the mucosal membranes of the GIT

Dementia, with delusions.

VITAMIN B_5 (Pantothenic acid)

Pantothenic acid is a component of CoA, which functions in the transfer of acyl groups, ex: succinyl CoA, fatty acyl CoA, and acetyl CoA.

Sources and requirement:

Eggs, liver, and yeast are the most important sources. No RDA has been established.

Deficiency:

Its deficiency is not well characterized in humans.

VITAMIN B_7 (Biotin)

Biotin is a coenzyme in carboxylation reactions, in which it serves as a carrier of activated carbon dioxide (CO_2) for the mechanism of biotin-dependent carboxylations.

Biotin also has a role in regulation of the cell cycle, acting via the biotinylating nuclear proteins.

Deficiency:

Biotin deficiency does not occur naturally because:

1. The vitamin is widely distributed in food.

2. A large percentage of the biotin requirement in humans is supplied by intestinal bacteria.

But raw egg white to the diet as a source of protein can induce symptoms of biotin deficiency. (Why?)

Raw egg white contains the glycoprotein avidin, which tightly binds to biotin and prevents its absorption from the intestine.

VITAMIN B_6 (Pyridoxine)

Vitamin B_6 is a collective term for pyridoxine, pyridoxal, and pyridoxamine. All derivatives of pyridine.

They are precursors of the biologically active coenzyme, pyridoxal phosphate.

Sources and requirement:

Pyridoxine is found primarily in plants, whereas pyridoxal and pyridoxamine are found in foods obtained from animals.

RDA is 0.5 mg/day for children

1.5 mg/day for adults

Functions:

Pyridoxal phosphate acts as coenzyme:

1. That catalyzes reactions involving amino acids.

2. That synthesize of dopamine and serotonin.

3. A cofactor for **glycogen phosphorylase** (80% of the body's total vitamin B_6 is pyridoxal phosphate in muscle, associated with glycogen phosphorylase).

4. It is important in steroid hormone action. Pyridoxal phosphate removes the hormone-receptor complex from DNA binding, terminating the action of the hormones.

Deficiency:

Dietary deficiencies of pyridoxine is rare but have been observed in:

1. Alcoholism.

2. Women taking oral contraceptives.

3. Patients with tuberculosis using Isoniazid, as it can induce a vitamin B_6 deficiency by forming an inactive derivative (hydrazones) with pyridoxal phosphate.

Toxicity

Vitamin B_6 is the only water-soluble vitamin with significant toxicity.

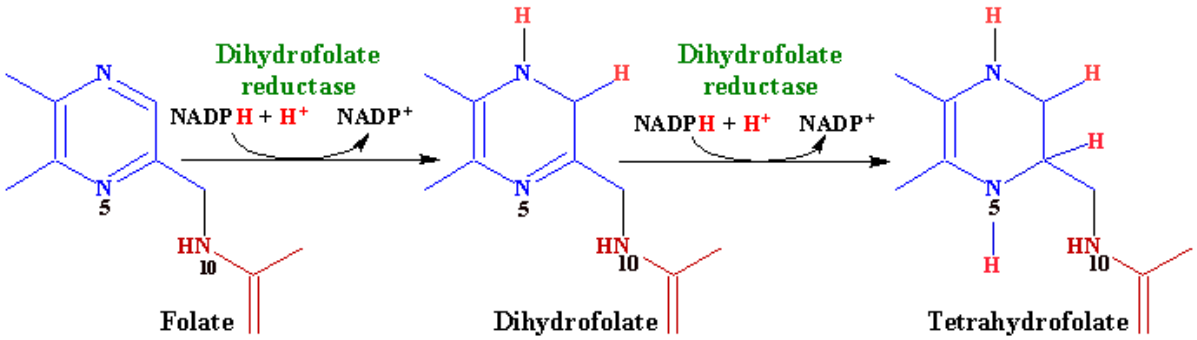
Neurologic symptoms (sensory neuropathy) occur at intakes above 500 mg/day and can lead to irreversible sensory nerve damage even after withdrawal.

FOLIC ACID (Folate) (B_9)

The folate molecule is synthesized from pterin pyrophosphate, para-aminobenzoic acid (PABA), and glutamate. Animals can't synthesize folate and therefore must obtain folate from their diet. All plants and fungi can synthesize it.

Functions:

Tetrahydrofolate (THF), the reduced, coenzyme form of folate. All of the biological functions of folic acid are performed by THF and its methylated derivatives.



THF receives one-carbon fragments (a methyl group, methylene group, or formyl group) from donors such as serine, glycine, and histidine to form 5,10-Methyl THF and then:

1. Used in the synthesis of thymidine (and incorporation into DNA).

2. Oxidized to formyl-THF for use in the synthesis of purines (precursors of RNA and DNA).

3. Reduced to 5-MTHF, which is necessary for the methylation of homocysteine to methionine.

Sources and requirement:

Folate is present in green vegetables and some meats. It is easily destroyed during cooking.

RDA is 400 µg/day for adults

600 µg/day for pregnant and lactating women

Deficiency:

Folic acid deficiency is probably the most common vitamin deficiency.

Causes include:

1. Insufficient dietary intake.

2. Increase demand such as during pregnancy.

3. Administration of antifolate drugs (ex: methotrexate)

4. Alcohol consumption, possibly by interference with folate transport.

Since folate deficiency limits cell division due to decrease in DNA synthesis. Highly multiplying tissues will be first affected such as bone marrow leading megaloblastic anaemia, hypersegmented polymorphs WBC.

Drugs that inhibit dihydrofolate reductase

Methotrexate, a cytotoxic drug, is an analogue of folate which inhibits dihydrofolate reductase, and therefore inhibits DNA synthesis.

The dihydrofolate reductases of some bacteria and parasites differ from the human enzyme; enabling inhibitors of these enzymes can be used as antibacterial (trimethoprim) and antimalarial drugs (pyrimethamine).

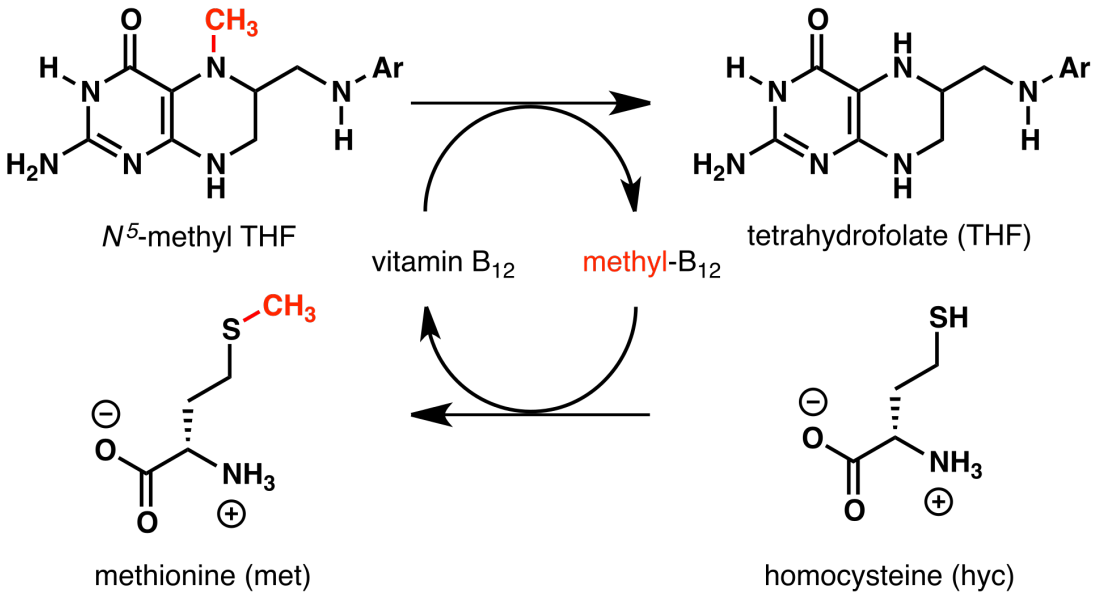
VITAMIN B_{12} (Cobalamin)

Cobalamin contains a corrin ring (tetrapyrrole ring) system with cobalt holding in the center of the corrin ring.

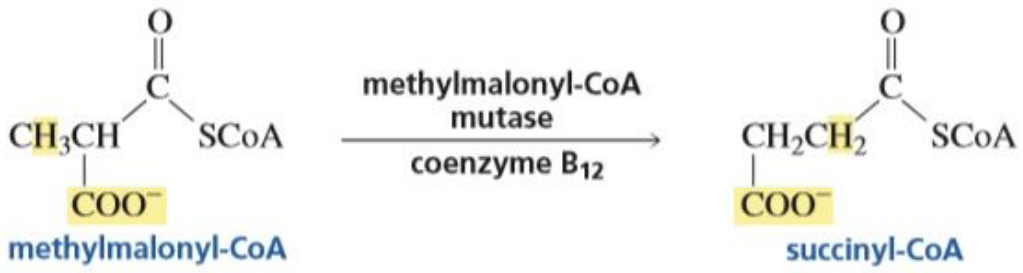
Functions:

Vitamin B_{12} is required in humans for two essential enzymatic reactions:

1. The remethylation of homocysteine to methionine **(Methylcobalamin)**.



2. The isomerization of methylmalonyl coenzyme A (CoA), which is produced during the degradation of some amino acids (isoleucine, valine, threonine, and methionine) and fatty acids (FA) with odd numbers of carbon atoms **(Adenosylcobalamin)**.



Sources and requirement:

Vitamin B_{12} is synthesized only by microorganisms. It is not present in plants.

Animals obtain the vitamin preformed from their intestinal microbiota or by eating foods derived from other animals. Cobalamin is present in appreciable amounts in liver, red meat, fish, eggs and dairy products (animal sources).

The RDA is 2 to 5 µg /day.

Absorption:

Vitamin B_{12} is tightly bound to proteins in food and must be released from food by the acidic environment of the stomach.

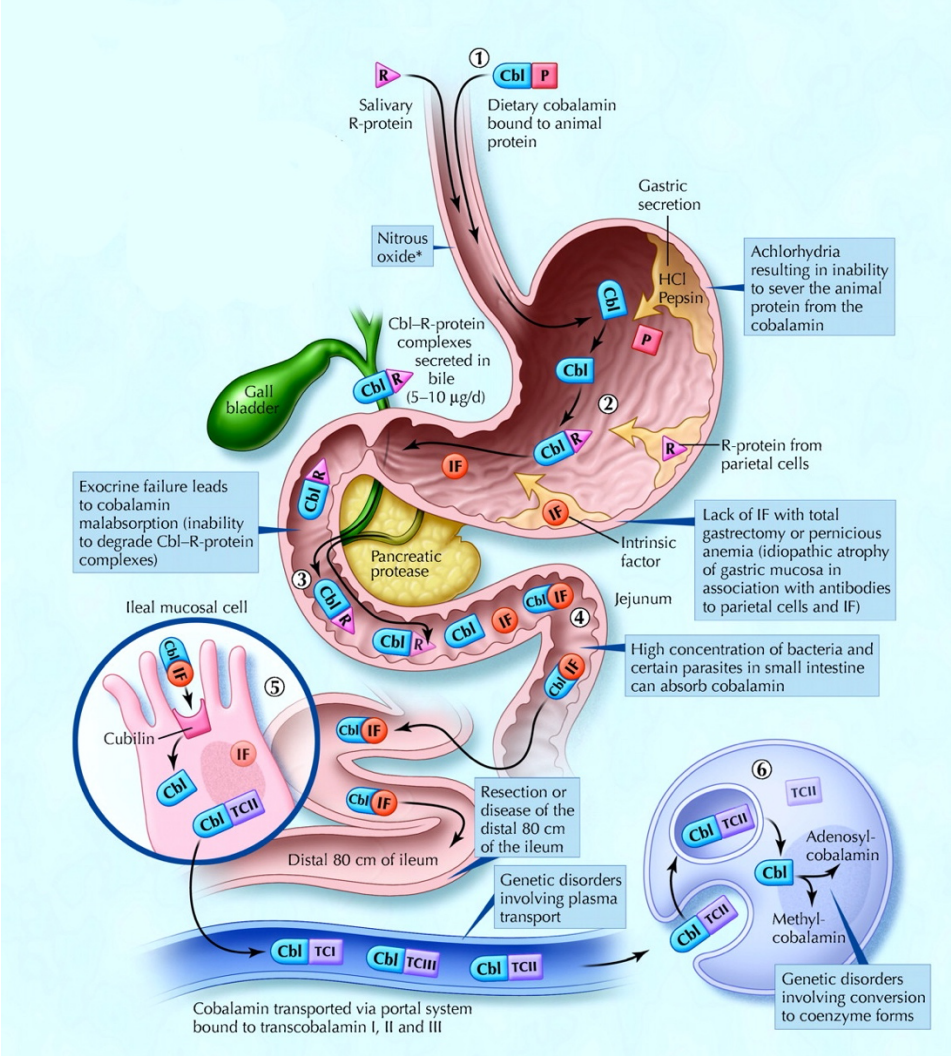
Free B_{12} then binds to a glycoprotein (R-protein or haptocorrin) and the complex moves into the duodenum.

B_{12} is released from the R-protein by pancreatic enzymes and binds to another glycoprotein, intrinsic factor (IF) which is produced by the parietal cells of the stomach.

The cobalamin–IF complex travels through the intestine and binds to a receptor (cubilin) on the surface of mucosal cells in the distal ileum.

The cobalamin is transported into the mucosal cell and then into the general circulation, where it is carried by its binding protein (transcobalamin).

B_{12} is taken up and stored in the liver.



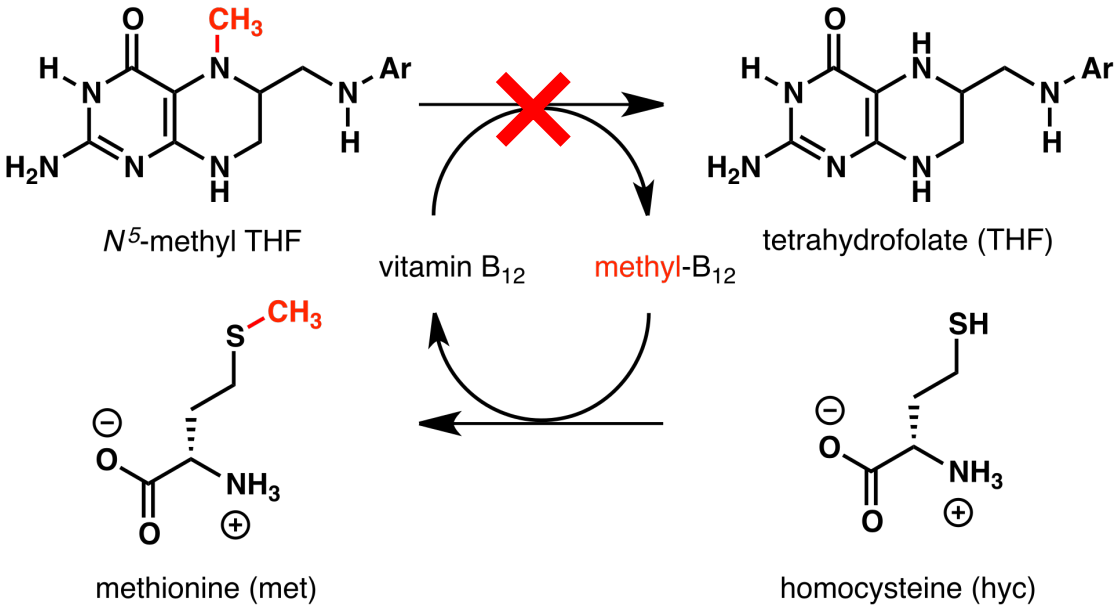
Deficiency:

In contrast to other water-soluble vitamins, significant amounts (2 to 5 mg) of vitamin B_{12} are stored in the body so it may take several years for the clinical symptoms of B_{12} deficiency to develop as a result of decreased intake of the vitamin.

Malabsorption of cobalamin in the elderly is most often due to reduced secretion of gastric acid (hypochlorhydria and achlorhydria) or in patients who have had a partial or total gastrectomy.

When cobalamin is deficient, unusual (branched) FA accumulate and become incorporated into cell membranes, including those of the CNS. This may account for some of the neurologic manifestations of vitamin B_{12} deficiency. The CNS effects are irreversible.

The hematologic effects of vitamin B_{12} deficiency are indistinguishable from those of folate deficiency. Vitamin B_{12} deficiency causes functional folate deficiency called the "**Folate Trap**" leading to megaloblastic anaemia.



Pernicious anemia: This disease is most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of IF. Pernicious anemia arises when vitamin B_{12} deficiency impairs the metabolism of folic acid.

There is irreversible degeneration of the spinal cord in pernicious anemia, as a result of failure of methylation of one arginine residue in myelin basic protein resulting in methionine deficiency in the CNS **(CNS demyelination)**.