

4- Vitamin K



Vitamin *K* Rich Foods



- Vitamin K is the generic descriptor for 2-methyl-1,4-naphthoquinone and all of its derivatives exhibiting qualitatively the biological (antihemorrhagic) activity of phylloquinone.
- It exists in three vitamer groups.
 - 1- **Phylloquinone group (K-n)**.
 - These vitamers are synthesized by green plants.
 - 2- **Menaquinone group (MK-n)**.
 - These vitamers are synthesized by bacteria.
 - 3- **Menadione (K₃)**.
 - It does not exist naturally.

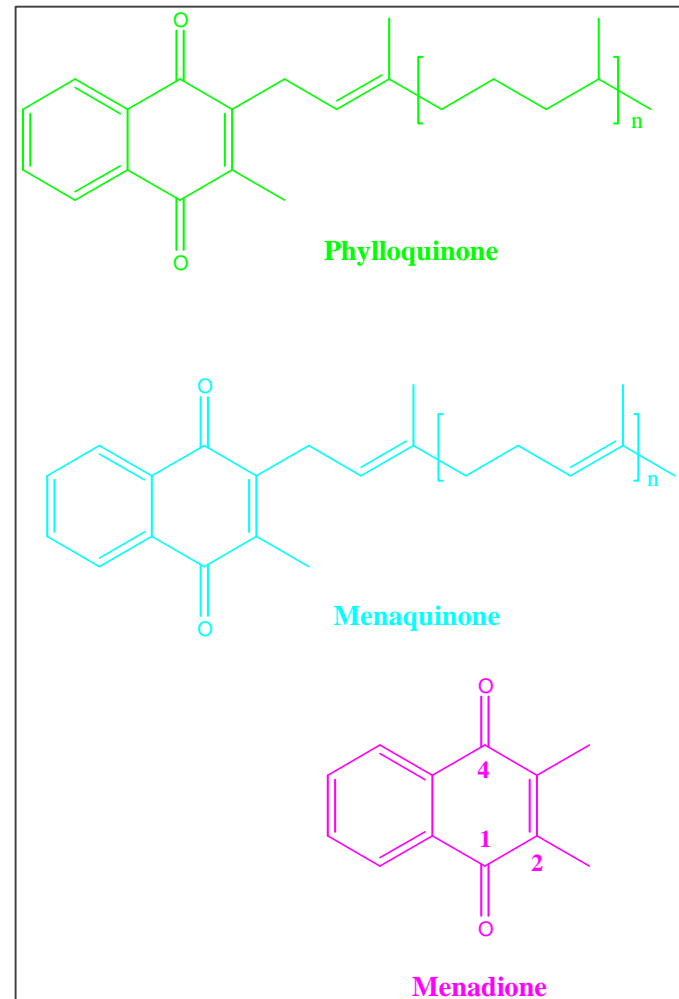
Vitamin K is a term that refers to 2-methyl-1,4-naphthoquinone (menadione)

Types

K1, Phylloquinone (Chloroplasts in plants).

K2, Menaquinone (Bacterial synthesis).

K3, Menadione (Synthetic, water soluble form & Complexed to improve stability)



Compound	Biopotency (%)
K-1	5
K-2	10
K-3	30
K-4	100
K-5	80
K-6	50
MK-2	15
MK-3	40
MK-4	100
MK-5	120
MK-6	100
MK-7	70
Menadione	40-150
Menadione sodium bisulfite complex	50-150
Menadione dimethylpyrimidinol bisulfite	100-160

Significance of vitamin K

- Vitamin K is used by plants and bacteria for electron transport and energy production.
- In animals, it is required for blood clotting and bone formation.
- Human neonates, particularly premature infants, can be at risk of hemorrhagic diseases due to limited transplacental transfer of the vitamin.



Sources of vitamin K

- Plant products such as broccoli, cabbage (الملفوف), cauliflower (الزهرة), kale (اللفت) and spinach are good sources of vitamin K.
- Beef liver and egg yolk are good animal sources.
- Normal intestinal microflora capable of synthesizing several menaquinone derivatives, which are absorbed by large intestine into the body.
- Standard clinical practice of administration of 1 mg of vitamin K (IM) at the time of birth (to prevent gradual decline in clotting factors).



Metabolism of vitamin K

1- Side-Chain Modification.

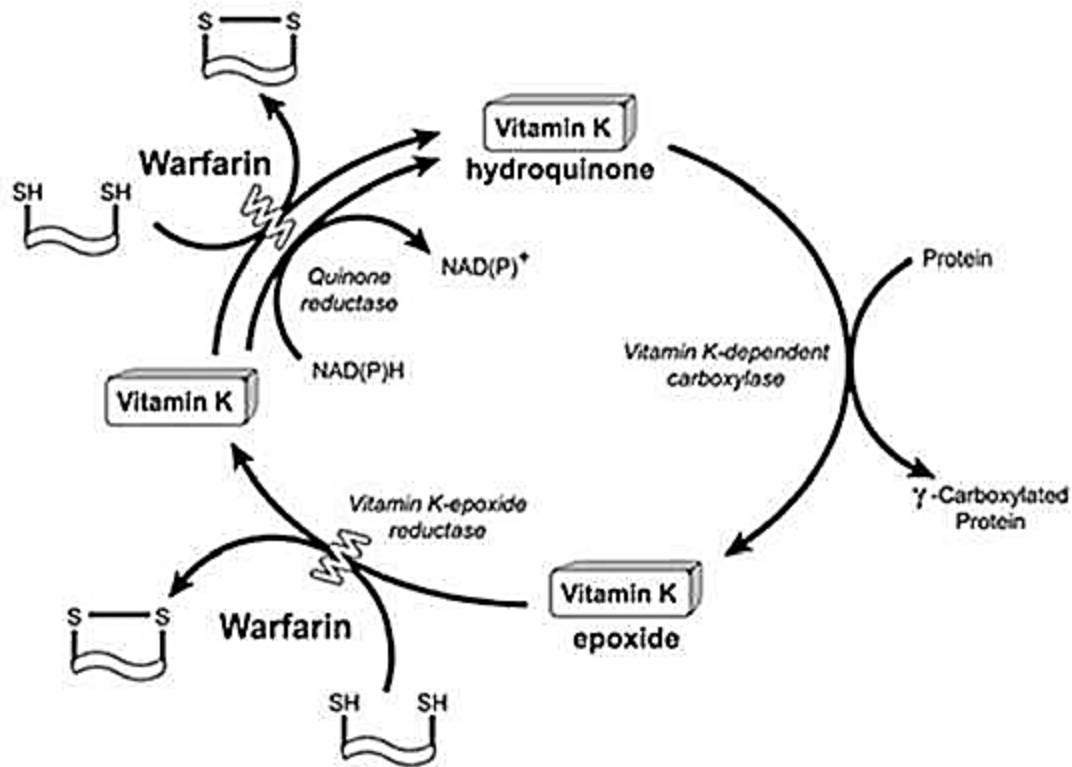
2- Catabolism.

- Menadione is rapidly metabolized and excreted primarily in urine as phosphate, sulfate and glucuronide conjugate in feces.
- Phylloquinone has shown to undergo oxidative shortening of the side chain to 5- or 7-carbon carboxylic acids, which are glucuronidated and excreted in feces.
- Menaquinone is likely metabolized in the same manner as phylloquinone.

3- Vitamin K Epoxide.

- Naphthoquinone ring of vitamin K can be altered by a hepatic microsomal enzyme to yield the 2,3-epoxide metabolite.
- It can also be altered to form 3-hydroxy-2,3-dihydrophyloquinone.
- Both metabolites are thought to be degraded metabolically before excretion to urine and feces.

4- Vitamin K-Dependent γ -Carboxylations.



The reduced form of vitamin K (hydroquinone) donates a pair of electrons to the vitamin K-dependent carboxylase (known as γ -glutamyl carboxylase), which carboxylates glutamic acid residues in specific vitamin K-dependent proteins. The resultant oxidized form of vitamin K (epoxide) is converted back to hydroquinone in a two-step reaction. The first step, which converts vitamin K epoxide to vitamin K, is catalyzed by vitamin K-epoxide reductase; the second step is catalyzed by either vitamin K-epoxide reductase or most likely by another yet-to-defined reductase. This pathway is inhibited by the vitamin K antagonist and anticoagulant drug, warfarin. The reduction of vitamin K to hydroquinone is also possibly catalyzed by a NAD(P)H-dependent reductase that is resistant to warfarin.

Figure 1: The vitamin K cycle

Metabolic functions of vitamin K

- Vitamin K functions in the posttranslational carboxylation of specific glutamate residues to γ -carboxyglutamate residues in at least a dozen proteins, which are referred to as vitamin K dependent.
- A- The four clotting factors; prothrombin (factor II), factor VII, IX and X.
- B- Plasma proteins C, S, Z and M.
- Protein C is an endogenous anticoagulant.
 - Protein S regulates the activity of protein C.
 - Protein Z appears to enhance the action of thrombin by promoting its association with phospholipids in cell membranes.
 - Function of Protein M is not known.

INTRINSIC PATHWAY VERSUS EXTRINSIC PATHWAY

Intrinsic pathway refers to multiple cascades of protein interactions activated by a trauma inside blood vessels

Extrinsic pathway refers to multiple cascades of protein interactions activated by damaged external surfaces

Activated by internal trauma

Activated by external trauma

Factors VIII, IX, XI, and XII are involved

Factor VII is involved

Slow

Fast

Takes about 15-20 seconds for the initiation of blood clotting

Takes about 2-6 minutes for the initiation of blood clotting

Requires ionized calcium for the activation of factor IX by factor IXa

Requires both calcium and tissue factor for the activation of factor IX by factor VIIa

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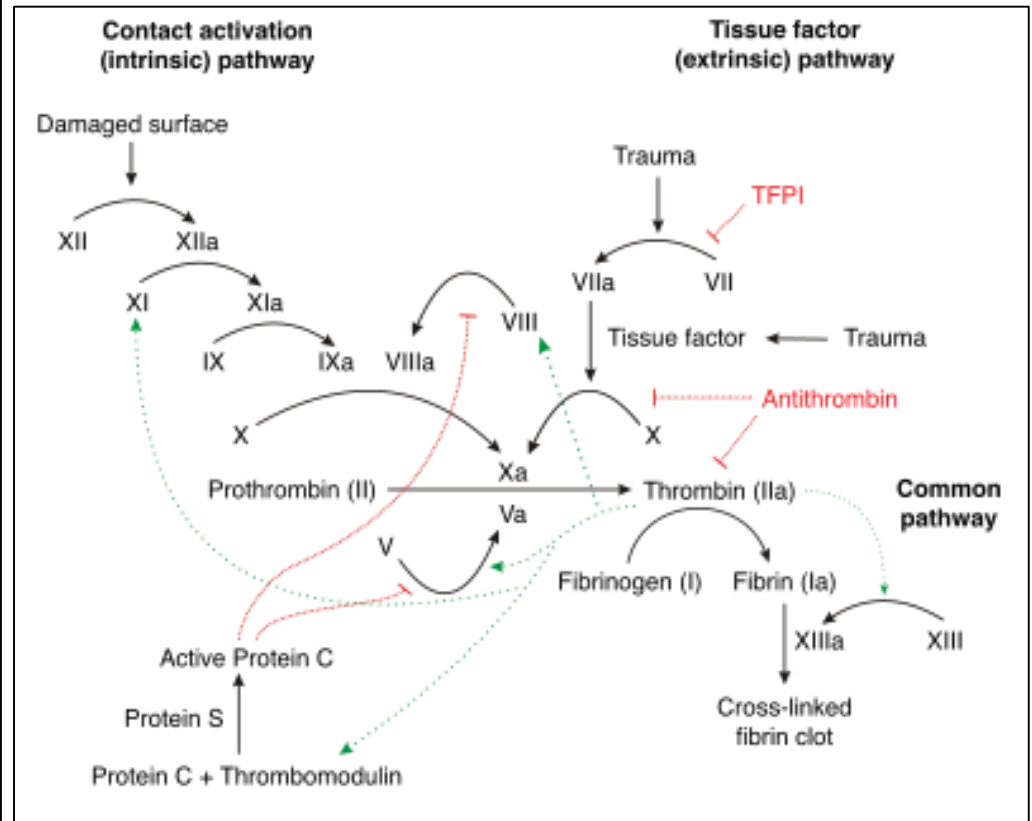


Figure 2: Coagulation cascade

C- Vitamin K-dependent proteins in calcified tissues.

- Osteoblasts synthesize three vitamin K-dependent proteins; osteocalcin, matrix Gla protein and protein S.
- Matrix Gla protein is also synthesized in most soft tissue and protein S is made by hepatocytes, megakaryocytes and endothelial cells.
- Osteocalcin is believed to function in the regulation of incorporation of calcium phosphates into bone.
- Its synthesis is inhibited by warfarin and is stimulated by $1,25\text{-(OH)}_2\text{-D}_3$.

- Matrix Gla protein has unclear metabolic function and it has been suggested it may serve in the clearance of extracellular calcium to protect against calcification of soft tissues and to assist in calcification of bone matrix.
- Protein S is also believed it may have activity in bone in addition to its role in the regulation of clotting.
- Gas 6 (Growth Arrest Specific gene 6) is found in nervous system, heart, lungs, stomach, kidneys and cartilage.
- It appears to be a cellular growth regulation factor with cell-signaling activities although the exact mechanism is not known.

Recommended Daily Allowance (RDA)

- 120 $\mu\text{g}/\text{day}$ for males.
- 90 $\mu\text{g}/\text{day}$ for females.
- 30 $\mu\text{g}/\text{day}$ for children.

Vitamin K deficiency

- Vitamin K deficiency is rare.
- It can happen due to factors:
- Causes lipid malabsorption such as diseases of GIT, biliary stasis, liver disease, cystic fibrosis and celiac disease.
- Interferes with the microbial synthesis of vitamin K
LIKE neonate with relatively sterile GIT and patients treated with antibiotics.

- Neonates are at special risk of vitamin K deficiency and lead to condition called **Vitamin K Deficiency Bleeding (VKDB)**, due to:
 - 1- Placental transport of the vitamin is poor.
 - 2- The neonatal intestine is sterile for the first few days of life.
 - 3- Hepatic biosynthesis of the clotting factors is inadequate in the young infant.
 - 4- Human milk is an inadequate source of vitamin K.

Vitamin K toxicity

- Phylloquinones and menaquinones are nontoxic.
- Menadione can be toxic, producing fatal anemia, hyperbilirubinemia and severe jaundice.
- It interferes with the function of glutathione.
- The toxic dose is three times the required dose for normal physiological function.
- The basis of menadione toxicity appears to be oxidative stress.



II- Water soluble vitamins

**WATER
SOLUBLE**

ViTAMiNS



II- Water soluble vitamins

Definition

Vitamins that essential to human health and function, that dissolve in water, they are not stored in the body and are easily excreted. They must, therefore, be consumed regularly as foods or supplements to maintain health.

Water-Soluble Vitamins

9 Water-soluble vitamins = 8B's and 1C!

- B1 = Thiamin
- B2 = Riboflavin
- B3 = Niacin
- B5 = Pantothenic Acid
- B6 = Pyridoxine
- B7 = Biotin
- B9 = Folate
- B12 = Cobalamin

Easily destroyed by **heat**, **light**, and **oxidation**

They function as coenzymes that help the body obtain energy from food.

▪ **Coenzyme**, Any of a number of freely diffusing **organic compounds** that function as **cofactors** with **enzymes** in promoting a variety of metabolic reactions.

▪ **Examples:**

- **nicotinamide adenine dinucleotide** (NAD), which accepts hydrogen (and gives it up in another reaction),
- **ATP**, which gives up phosphate groups while transferring **chemical energy** (and reacquires phosphate in another reaction).

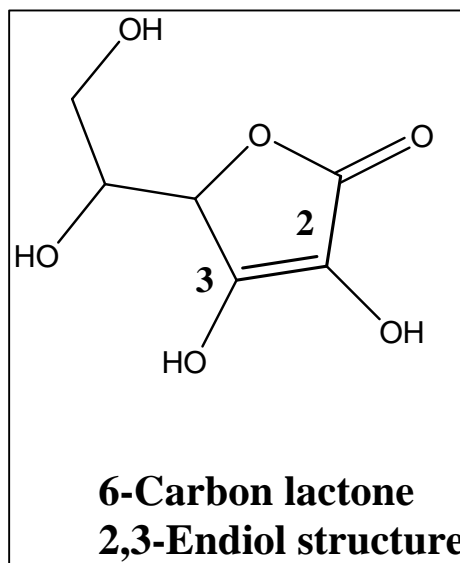
Most of the B vitamins (**vitamin B complex**) are coenzymes and are essential in facilitating the transfer of atoms or groups of atoms between molecules in the formation of carbohydrates, fats, and proteins.

1- Vitamin C



Vitamin C

- It is the generic descriptor for all compounds exhibiting qualitatively the biological activity of ascorbic acid.
- Ascorbic acid is the trivial name for the compound 2,3-didehydro-L-threo-hexano-1,4-lactone.



Significance of vitamin C

- Many species synthesize ascorbic acid human is not of them.
- It is the major water soluble antioxidant in plasma.
- It enhances the iron bioavailability.
- Vitamin C deficiency resulted in a disease called **scurvy**.

Sources of vitamin C

- Vitamin C is widely distributed in both plants and animals foods as both ascorbic acid and dehydroascorbic acid.
- Most of the vitamin is lost upon storage, oxygen and cooking.
- Ascorbic acid is available as ascorbic acid sulfate and phosphate in commercial products.
- Good dietary sources of ascorbic acid include **citrus fruits, tomatoes, strawberries, and other fresh fruits and vegetables.**



Metabolic functions of vitamin C

- It acts as powerful antioxidant and radical scavenger.
- High concentration of vitamin C acts as prooxidant in the presence of metal ions.

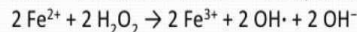
Pro Oxidants

- Pro-oxidants are chemicals that **induce oxidative stress**, either by generating reactive oxygen species or by inhibiting antioxidant systems
- The oxidative stress produced by these chemicals can **damage cells and tissues**
- Some substances can serve as either antioxidants or pro-oxidants, depending on conditions

Pro-oxidant activities

Antioxidants that are reducing agents can also act as pro-oxidants.

For example, vitamin C has antioxidant activity when it reduces oxidizing substances such as hydrogen peroxide, however, it will also reduce metal ions that generate free radicals through the Fenton reaction.



- It functions as cofactor for at least eight enzymes, three involved in lysine/proline hydroxylations (collagen synthesis), two required in carnitine biosynthesis, two in the biosynthesis of hormones (norepinephrine, peptide hormones) and one in the metabolism of tyrosine.

Enzymes that require ascorbic acid as a co-factor

I- Collagen synthesis:

- a- Prolyl-4-hydroxylase
- b- Prolyl-3-hydroxylase
- c- Lysine hydroxylase

II- Catecholamine synthesis:

- a- Dopamine β -monooxygenase

III- Carnitine synthesis:

- a- γ -Butyrobetaine-2-oxoglutarate 4- dioxygenase
- b- Trimethyllysine-2-oxoglutarate dioxygenase

IV- Tyrosine metabolism:

- a- 4-Hydroxyphenylpyruvate dioxygenase

V- Peptide hormone processing:

- a- Peptidyl glycine- α -amidating monooxygenase

Recommended Daily Allowance (RDA)

- 100 mg/day for men 19 years of age and up.
- 80 mg/day for women 19 years of age and up.

Vitamin C deficiency

- It results in scurvy (collagen degeneration).
- The disease is manifested by edema, hemorrhage in skin, mucous membranes, bleeding gums, fatigue and pains in the legs.
- Marginal deficiency can be caused by low dietary intake or factors like smoking, stress, chronic diseases and diabetes.



Uses of vitamin C

- For the treatment of the deficiency.
- It is used as prophylaxis in treatment of common cold to certain individuals.

Toxicity of vitamin C

- It is low even at high doses of the vitamin.
- Patients with hemochromatosis should avoid taking vitamin C supplements.
- Megadoses of vitamin C produce **gastrointestinal disturbances and diarrhea.**

2- Vitamin B complex



Definition

- ❖ A group of **water-soluble vitamins** that characteristically serve as components of coenzymes.
- ❖ **Plants** and many **microorganisms** can manufacture B vitamins but dietary sources are essential for most animals.
- ❖ Heat and light tend to destroy B vitamins.
- ❖ The vitamin B complex consists of **12** related substances.
 - Eight of them are considered essential vitamins because they are needed to be included in the diet.
 - Four of them are not essential because the body can synthesize them.

Although these vitamins are chemically different, they are **grouped together** because they are **found with one another in the same foods**.

a- Vitamin B₁

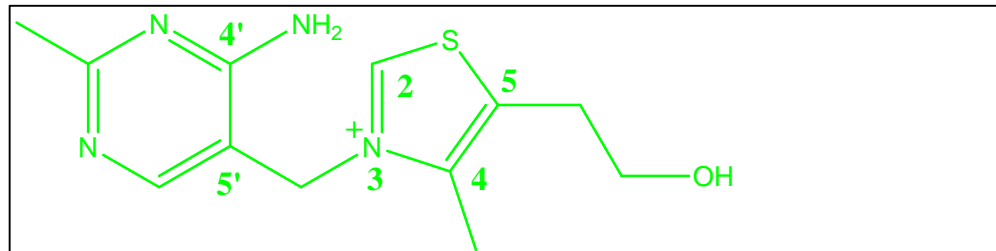
(Thiamine)

Vitamin **B-1**



Vitamin B₁

- It is called thiamin or aneurine.
- It is the trivial name of the compound 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium.



Conjoined pyrimidine and thiazole

Thiazole ring contains a quaternary nitrogen, open C-2 and phosphorylated alkyl group on C-5

Amino group on C-4' of the pyrimidine ring

- Free thiamin is unstable because of its quaternary nitrogen.
- Hydrochloride and mononitrate forms are used in commerce.
- Thiamin hydrochloride is very soluble in water (1 g/ml) and therefore, very suitable for parenteral administration.
- The mononitrate form is more stable, but it is less soluble in water (27 mg/ml) and it is used in dry pharmaceutical preparations and food supplements.

Significance of thiamin

- Thiamin is essential in carbohydrate metabolism and neural function.
- Severe thiamin deficiency results in the nerve and heart disease beriberi.
- Thiamin deficiency was prevalent among people dependent on polished rice
- Almost one fourth of world population depends on this food source.
- Some foods contain thiamin antagonists.

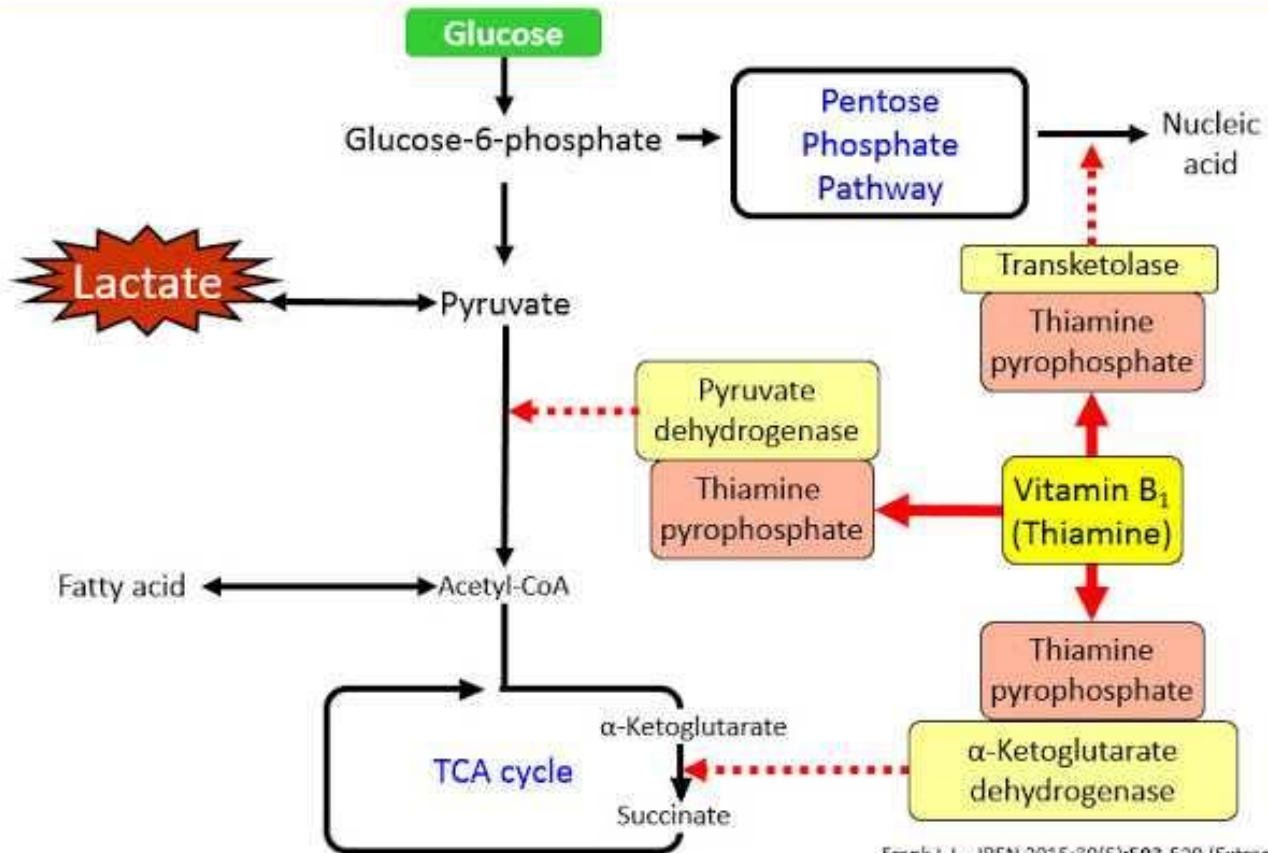
Source of thiamin

- Thiamin available in free form in plant products such as **oatmeal, whole grain and brown rice**.
- Brewer's yeast and liver are good sources of thiamin.
- In animal tissues, thiamin occurs in phosphorylated forms.
- The vitamin is stable under acidic conditions and frozen storage.
- It is destroyed by heat, oxidation, radiation and alkaline conditions.

Metabolic function of thiamin

- It is available as free thiamin, TMP, TPP & TTP.
- The metabolically functional form of thiamin is thiamin pyrophosphate (TPP) (also called cocarboxylase).
- It works as cofactor for the cleavage of C-C bond of α -keto acids and α -keto sugars to yield products transferred to acceptor.
- It is clear that thiamin has a vital role in nerve function, but the biochemical nature of that role is still unclear.

Enzymes in which thiamine serves as a cofactor in carbohydrate metabolism



Evidences

- Neurological signs of thiamin deficiency.
- Thiamin has been identified in the brain.
- Nervous stimulation by either electrical or chemical means resulted in the release of thiamin.
- Irradiation with UV light at wavelengths absorbed by thiamin destroys the electrical potential of nerve fibers in a manner corrected by thiamin treatment.

Recommended Daily Allowance (RDA)

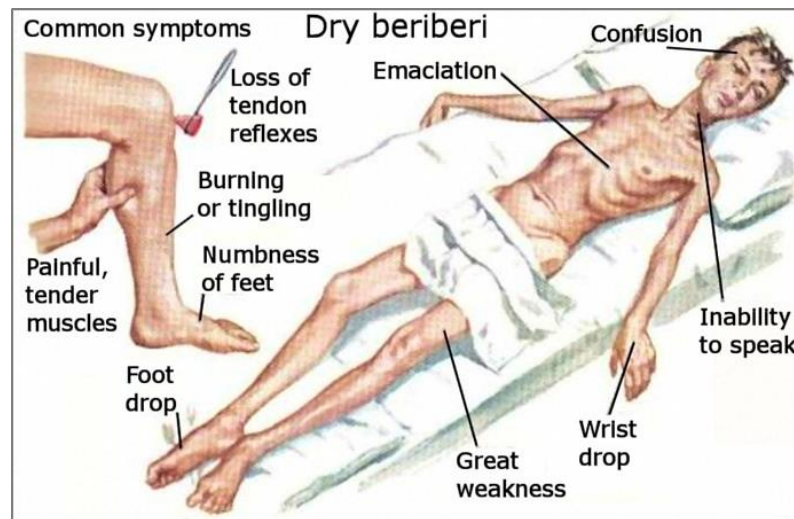
- 1.2 mg/day to men from 14 years of age.
- 1.1 mg/day for women from 14 years of age.
- 1.4 mg/day for Pregnant women and breastfeeding.

Thiamin deficiency

- The classical syndrome resulting from thiamin deficiency is beriberi.
- The general symptoms of beriberi are anorexia, cardiac enlargement, lassitude, muscular weakness, paresthesia, loss of knee and ankle jerk responses and dyspnea on exertion.
- Beriberi occurs in three clinical types:
 - 1- Dry or neuritic beriberi.
 - 2- Wet or edematous beriberi.
 - 3- Infantile or acute beriberi.

1- Dry or neuritic beriberi

- It occurs in adults.
- It is characterized by atrophy of the legs with accompanying peripheral neuritis.
- It usually does not have cardiac involvement.

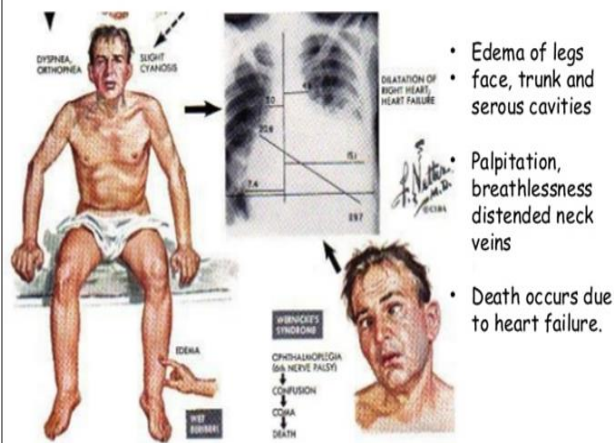


2- Wet or edematous beriberi

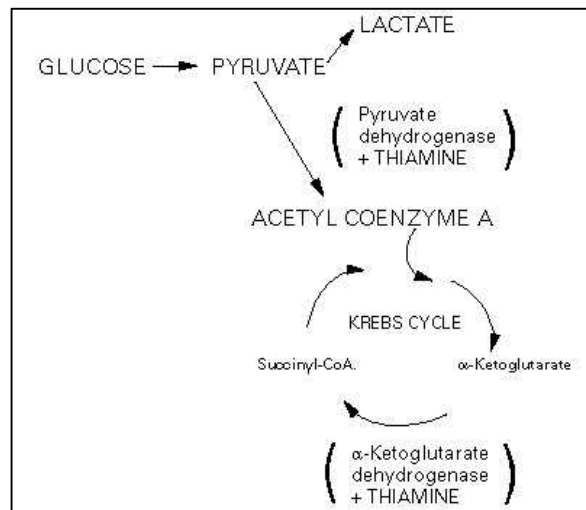
- It involves cardiac hypertrophy and edema.
- It can vary from chronic to acute.
- It is characterized by high elevation of lactic acid concentration in the blood.

Deficiency Manifestations of Thiamine

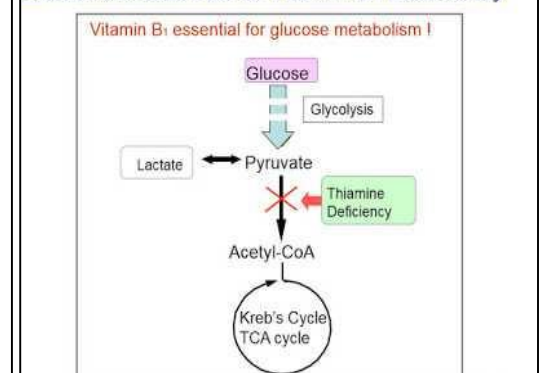
• B. Wet beriberi: cardiac beriberi



- Edema of legs, face, trunk and serous cavities
- Palpitation, breathlessness, distended neck veins
- Death occurs due to heart failure.



Lactic Acidosis due to Vitamin B₁ Deficiency



3- Infantile or acute beriberi

- It occurs in breast-fed infants of thiamin deficient mothers.
- It has a rapid onset, with death due to heart failure within a few hours.
- The infants are anorectic and milk is regurgitated.
- The mothers of these infants may show no signs of thiamin deficiency.

❖Symptoms of Infantile beriberi:

1. Restlessness
2. Sleeplessness
3. Anorexia
4. Vomiting
5. Convulsions
6. Edema
7. Tachycardia , Bouts of screaming due to cardiac dilatation
8. Aponia (absences or loss of voice)
9. If not treated ,death



Thiamin toxicity

- Little information is available concerning the toxic potential of thiamin.
- Parenteral doses of thiamin hydrochloride at 100x the RDA have been found to produce headache, convulsions, weakness, paralysis, cardiac arrhythmia and allergic reactions.