Al-Mustaqbal University

جامعة المستقبل
AL MUSTAQBAL UNIVERSITY

College of Medical and Health Techniques

Medical Laboratories Techniques Departments

Biochemistry Lectures for 2nd Year Students

(2 Credit Hrs. Theory + 2 Credit Hrs. Practice / Week = 3 Credit Unit

Academic Year: 2024 - 2025

Course Organizers:

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Lecture No. 6

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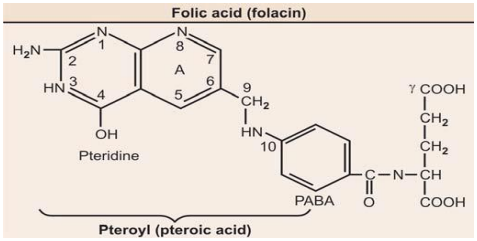
Nutrition, Vitamins and Coenzymes – Lecture 3

Folic Acid Groups (Vitamin B9)

Chemistry:

1. The designation "folic acid" is applied to a number of compounds which contain the following groups:
   a. A ***pteridine*** **nucleus** (**pyrimidine** and **pyrazine rings**)
   b. Para-aminobenzoic acid ("PABA")
   c. Glutamic acid.

There are at least three chemically related compounds of nutritional importance which occur in natural products, all may be termed ***pteroyl glutamates*** which differ only in the number of glutamic acid residues attached to **pteridine PABA complex (pteroic acid) (*Mono-glutamate, Tri-glutamate and Hepta-glutamate)*.** Pteroyl glutamic acid is liberated from these conjugates by enzymes called ***conjugases.***



Biological "Active" Forms

Active "coenzyme" form of the vitamin is the reduced **tetrahydrofolate, FH4**, see below and **Fig. 1** which obtained by addition of four hydrogens to pteridine group at 5, 6, 7 and 8 position.

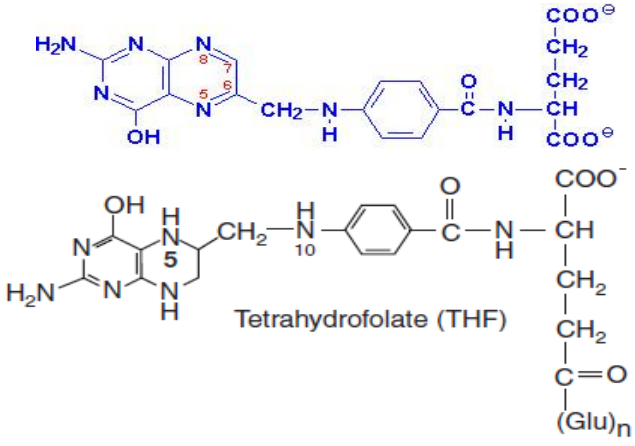
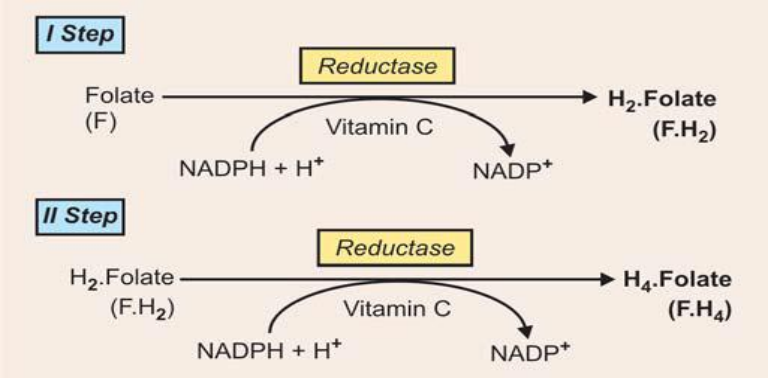


Fig. 1: Folic Acid, positions 7 & 6 carry hydrogens in dihydrofolate (DHF), positions 5-8 carry hydrogens in tetrahydrofolate (THF)

Formation of FH4: Folic acid, before functioning as a coenzyme, must be reduced in two steps. Both reactions are catalyzed by ***Folic acid***

reductases enzyme, which use NADPH as hydrogen donor. Also requires vitamin C (ascorbic acid) as cofactor as shown below:



Clinical Importance:

Some of clinically described cases of folic acid deficiency anemias may actually be due to inherited deficiency of *folic acid reductase*.

Tetrahydrofolate can carry one-carbon fragments attached to N-5 (formyl, formimino, or methyl groups), N^{10} (formyl group), or bridging N-5 to N-10 (methylene or methenyl groups). N^5-Formyl-tetrahydrofolate is more stable than folate and is therefore used pharmaceutically in the agent known as **folinic acid** and in the synthetic (racemic) compound **leucovorin**. Methylene, methenyl, and N^{10}-formyl tetrahydrofolates are interconvertible.

The role of N^5,N^{10}-methylene-THF in deoxy thymidine monophosphate (dTMP) synthesis the most metabolically significant function for this vitamin, also the role of vitamin B_{12} and N^5-methyl-THF in the conversion of homocysteine to methionine also can have a significant impact on the ability of cells to regenerate needed THF or FH4, figure 2.

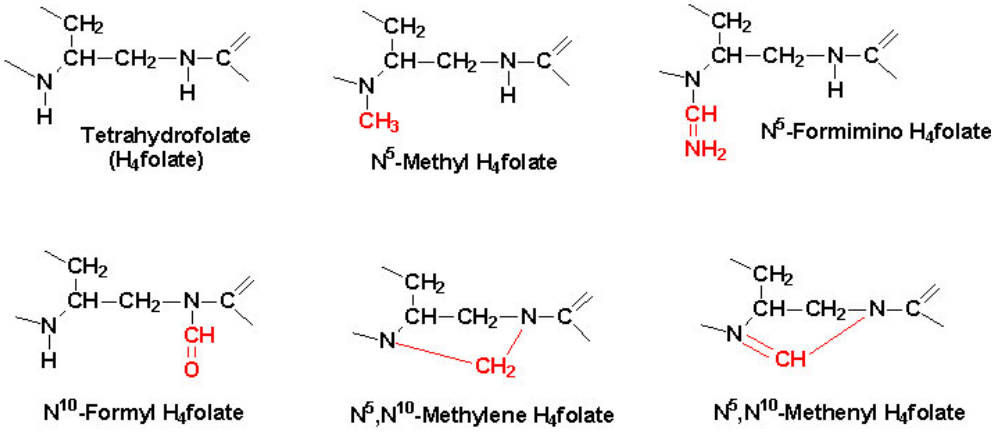


Fig. 2: Active center of tetrahydrofolate (THF).

Biosynthesis and Metabolism

Many microorganisms including those inhabiting the intestinal tract can synthesize folic acid. Some of them cannot synthesize PABA, which has to be supplied. In presence of ATP and CoA-SH, PABA reacts with glutamic

acid to form *"p-amino-benzoyl glutamic acid". The latter then reacts with a "Pterin" to produce "pteroyl monoglutamic acid or (folic acid).*

Effect of drugs: *Sulphonamide drugs and antibiotics inhibit their growth by blocking the incorporation of PABA in the synthetic pathway (by competitive inhibition), figure 3.*

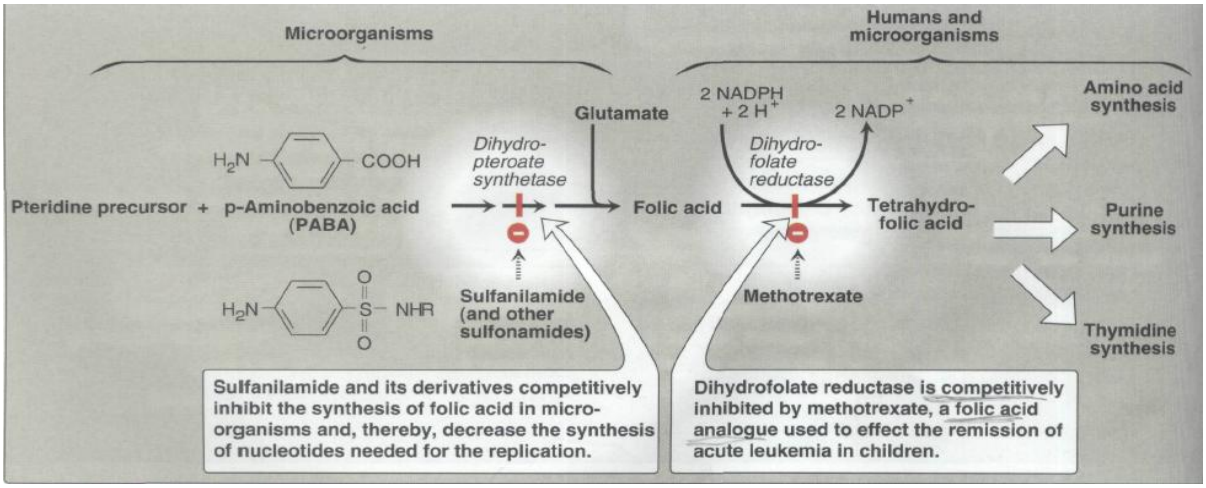


Fig. 3: Folic acid, activation and biochemical roles

Transport: Transported in blood as methyl tetrahydrofolate **bound to a specific protein.**

Plasma level: In normal individuals, it varies from 3 to 21 ng/ml.

Excretion

a. **Urine:** 2 to 5 µg/day. This is much increased after an oral dose of folate if the tissues are saturated.
b. **Feces:** 20% of the ingested folates that remains unabsorbed + 60 to 90 µg in the bile that is not reabsorbed + some unabsorbed synthesis of folate by bacterial flora of intestine.

Occurrence and Food Sources: Widely distributed in nature being present in many animal and plant tissues and in microorganisms. Particularly abundant in liver, yeast, kidney and green leafy vegetables. Spinach, meat, fish, wheat are a good source. Fair sources: milk, fruits.

Metabolic Role ("one-carbon" Metabolism)

The folic acid coenzymes are specifically concerned with metabolic reactions involving the transfer and utilization of the one carbon moiety (C1). **One carbon moiety (C1)** may be either **Methyl ($-CH_3$), formyl (–CHO), formate (HCOOH), formimino group (–CH=NH) or hydroxymethyl.**

Clinical Significance:

Folic acid (antagonists): Several antagonists to this vitamin has been found out. They are of much clinical interest: On account of their ability to inhibit cell division and multiplication, **they have been used in treatment of conditions where there is unrestricted cell growth,** e.g. **Leukemias,** and **malignant growths.**

Example of Folic acid antagonists are:

1. **Amethopterin or methotrexate:** It is 4-amino-10 methyl folate. Methotrexate inhibits "dihydrofolate reductase" and has been used as anticancer drug.
2. **Trimethoprim:** Inhibits dihydrofolate reductase and formation FH4 is decreased. The drug has been used as antibacterial agent.

Recommended dietary daily allowance:

Adults: 400 to 500 µg daily, Infants: 50 µg, children: 100 to 300 µg, requirement must be increases in pregnancy and lactation. Pregnant women: 800 µg , Lactating women: 600 µg

Clinical Significance of Folate Deficiency:

Folate deficiency results in complications nearly identical to those described for vitamin B_{12} deficiency. The most pronounced effect of folate deficiency on cellular processes is upon DNA synthesis. The result is megaloblastic anemia as for vitamin B_{12} deficiency. The inability to synthesize DNA during erythrocyte maturation leads to abnormally large erythrocytes termed macrocytic anemia.

Poor dietary habits as those of chronic alcoholics can lead to folate deficiency. The predominant causes of folate deficiency in non-alcoholics are impaired absorption or metabolism or an increased demand for the vitamin. The predominant condition requiring an increase in the daily intake of folate is pregnancy. This is due to an increased number of rapidly proliferating cells present in the blood. The need for folate will nearly double by the third trimester of pregnancy. Certain drugs such as anticonvulsants and oral contraceptives can impair the absorption of folate. Anticonvulsants also increase the rate of folate metabolism.

Supplements of 400 µg/day of folate begun before conception result in a significant reduction in the incidence of neural tube defects as found in **spina bifida.**

Cyanocobalamin or Vitamin B_{12}:

Structure of vitamin B_{12}, Fig. 4:

1. Central portion of the molecule consists of four reduced and extensively substituted **pyrrole rings**, surrounding a **single cobalt atom (Co)** called as **Corrin Ring *system which*** is similar to porphyrins.
2. A ***cyanide*** group is coordinately bound to the cobalt atom and then is called as ***cyanocobalamine.***

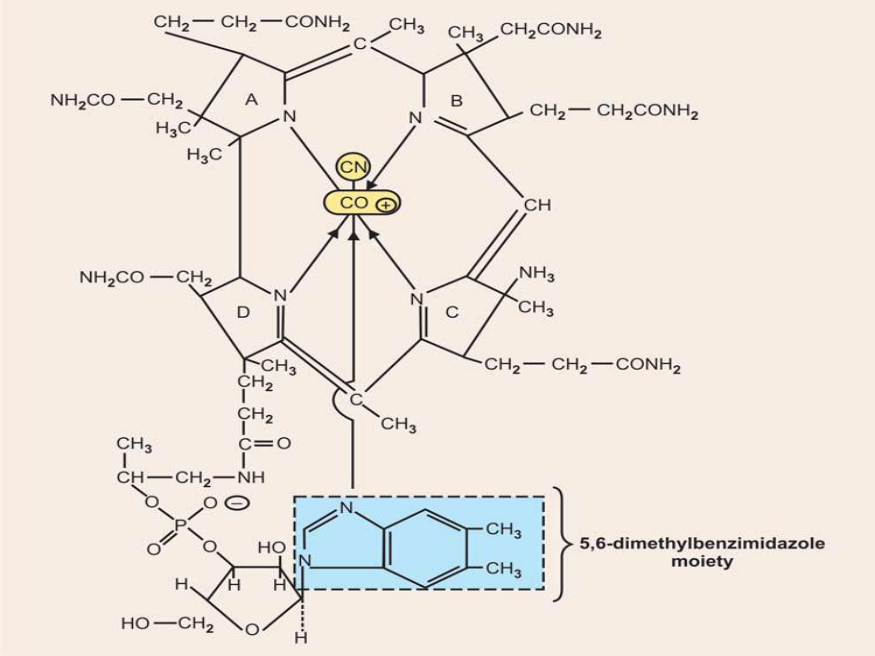


Fig. 4: Chemical structure of vitamin B_{12}

Varieties of Vitamin B_{12}

1. When cyanide is bound to cobalt atom it is called as ***cyanocobalamine***, but if cyanide group is removed, then it is called as ***cobalamine.***
2. The –OH group, NO_2 and SO_4^{-2} may replace cyanide group forming:
   a. **Hydroxycobalamine (B_{12a}) which is more useful therapeutically.**
   b. **Nitritocobalamine (B_{12c})**
   c. **Sulphatocobalamine**
3. Biologic actions of these derivatives are similar to cobalamine, but ***hydroxycobalamine (B_{12a}) is superior as:***
   a. It is more active in enzyme systems
   b. It is retained longer in the body when given orally.

Metabolism

Absorption and Excretion

1. **Vitamin B_{12} is absorbed from Ileum;** for its proper absorption it requires the presence of HCl, and ***Intrinsic factor*** (IF), a constituent of normal gastric juice.
2. **Intrinsic factor (IF).** It is secreted by parietal cells, it is a **glycoprotein**, a constituent of gastric mucoproteins. In addition to amino acids, contain hexoses, hexosamines and sialic acid. **Note:** ***Atrophy of stomach fundus and a lack of free HCl (achlorhydria) is usually associated with pernicious anemia, caused by B_{12} deficiency (B_{12} is called antipernicious anemia vitamin).***

Normal serum level of B_{12}: Normal serum level varies from 0.008 to 0.42 µg/dl. (Average = 0.02 µg/dl).

Excretion: Normally there is no urinary excretion. But following parenteral administration there is urinary excretion up to 0.3 µg/day.

Storage: Main storage site is **liver. A man on normal non-vegetarian diet may store several mg (about 4 mg).** As storage is high, development of deficiency state takes long time.

Biological "Active" Forms of B_{12}

1. Biologically active forms are **cobamide coenzymes,** act as coenzyme with various enzymes.
2. Cobamide coenzyme do not contain the "cyano" group attached to cobalt but instead there is an **Adenine Nucleoside** (5'–deoxyadenosine) which is linked to cobalt by a C →CO bond.

Two clinically significant reactions in the body that require vitamin B_{12} as a cofactor. During the catabolism of fatty acids with an odd number of carbon atoms the resultant propionyl-CoA is converted to succinyl-CoA for oxidation in the TCA cycle.

$$\text{L-Methyl Malonyl-CoA} \xrightarrow[\text{Isomerase}]{B_{12}\text{ coenzyme}} \text{Succinyl-CoA}$$

Normal healthy individuals excrete less than <2 mg/day which is not detectable.

In B_{12} deficiency: Methyl malonic acid accumulates and excretion of methyl malonic acid in urine is increased. **Methyl malonic aciduria is a sensitive index for B_{12} deficiency.**

The second reaction requiring vitamin B_{12} catalyzes the conversion of homocysteine to methionine and is catalyzed by methionine synthase. This requires tetrahydrofolate (FH4) as a $–CH_3$ carrier.

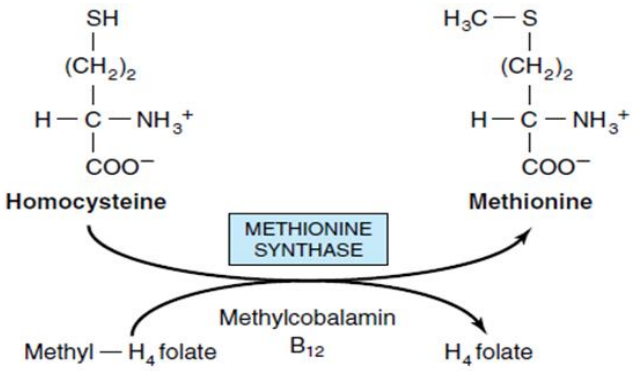


Fig. 5: Homocysteinuria and the folate trap. Vitamin B_{12} deficiency leads to inhibition of methionine synthase activity causing homocysteinuria and the trapping of folate as methyltetrahydrofolate.

In B_{12} deficiency, lead to ***diminished synthesis of thymidylate and DNA. Increased folate levels are observed in plasma and the activity of the enzyme* homocysteine methyl transferase *is low.***

Vitamin B_{12} Deficiency:

Pernicious anemia is a megaloblastic anemia arises when vitamin B_{12} deficiency blocks the metabolism of folic acid, leading to functional folate deficiency. This impairs erythropoiesis, causing immature precursors of erythrocytes to be released into the circulation (megaloblastic anemia). The commonest cause of pernicious anemia is failure of the absorption of vitamin B_{12} rather than dietary deficiency. This can be due to failure of intrinsic factor secretion caused by autoimmune disease of parietal cells or to generation of anti-intrinsic factor antibodies.

Occurrence and Sources of Vitamin B_{12}. *It is present in foods of animal origin only and is not present in foods of vegetable sources.* In nature it is obtained via synthesis by bacteria in soil, water and animal intestine. Good and rich animal sources are: liver, eggs, fish, meat, kidney. Fair sources are; milk, and dairy products.

Daily Requirements

a. In normal adults: 3 µg/day
b. Infants: 0.3 µg/day
c. Children: 1 to 2 µg/day
d. In pregnancy and lactation: Requirement is increased to about 4 µg/day.
e. In pernicious anemia: 0.5 to 1.0 µgm/day given parenterally will maintain in complete hematologic and neurologic remissions.

Vitamin C or (Ascorbic Acid).

Vitamin C is a non-B-complex water-soluble vitamin and must be supplied by the diet. Naturally occurring vitamin C is L-ascorbic acid.

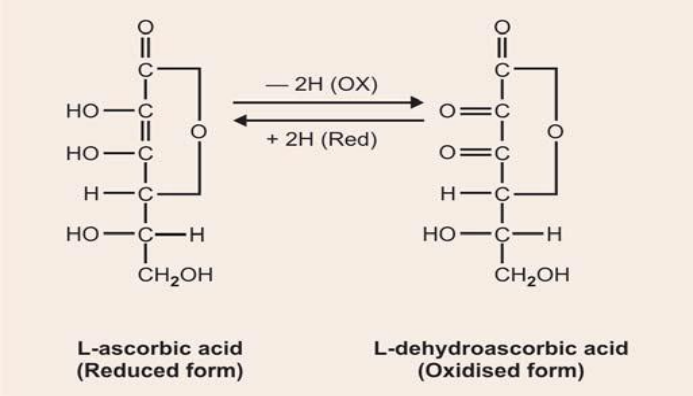
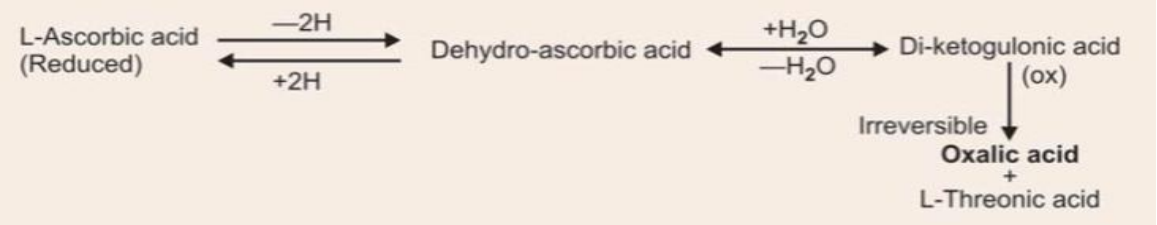


Fig. 6: Vitamin C or Ascorbic Acid

Chemistry

1. Ascorbic acid is an ***enediol-lactone*** of an acid with a configuration similar to that of the sugar L-glucose, Fig.6.
2. ***Strong reducing property: Depends on the liberation of the H-atoms from the enediol –OH groups, on C2 and C3;*** the ascorbic

acid being oxidized to dehydroascorbic acid, e.g. by air, H_2O_2, $FeCl_3$, methylene blue, ferricyanide, 2:6-dichlorophenol indophenol, etc.



Metabolism: Absorption, distribution and excretion

1. It is absorbed readily from the small intestine and subcutaneous tissues. It is widely distributed throughout the body. Some tissues contain high concentrations as compared to others.
2. **Normal human blood plasma:** It contains approximately 0.6 to 1.5 mg of ascorbic acid per 100 ml. The vitamin exists in the body largely in the 'reduced' form, with reversible equilibrium with a relatively small amount of "dehydro-ascorbic acid" (oxidized form). ***Both forms are physiologically and metabolically active.***
3. Under normal dietary intake (of 75 to 100 mg), 50 - 75% are converted to inactive compounds, 25 - 50% is excreted in urine as such.
4. It is also secreted in milk.
5. **Metabolites.** In human beings, the chief terminal metabolites being, ***oxalic acid*** and diketogulonic acid, which are excreted in urine. ***Conversion of ascorbic acid to oxalate in man may account for the major part of the endogenous urinary oxalate.***

Occurrence and food sources: Widely distributed in plants and animal tissues. In animal tissues, no storage, contains small amount, but highest concentration in metabolically highly 'active' organs, e.g. adrenal cortex, corpus luteum, liver, etc.

Dietary sources: These are chiefly leafy vegetable sources with **citrous fruits**—orange/lemon/lime. Considerable amount of vitamin C activity is lost during cooking, processing and storage, because of its water-solubility and its irreversible oxidative degradation to inactive compounds.

Metabolic Role and Functions:

1. ***Role in Cellular Oxidation-Reduction.***
2. ***Role in Collagen Synthesis:*** ***Hydroxyproline and hydroxylysine are important constituents of mature collagen fibers.*** They are hydroxylated by corresponding ***hydroxylases*** in presence of vitamin C, Fe^{++} and molecular O_2. **In scurvy,** failure of these hydroxylation may lead to a rapid destruction of the collagen intermediates.

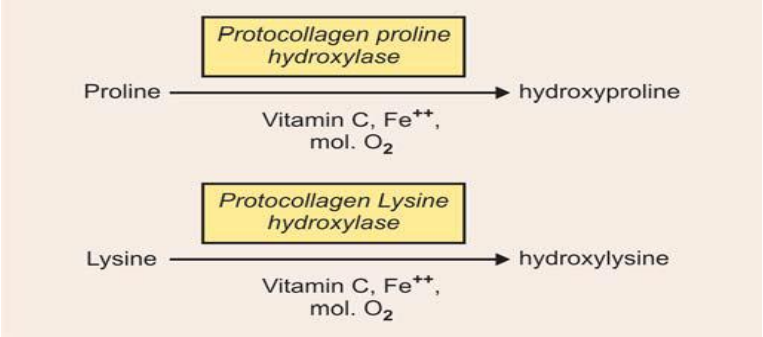


Fig. 7: Hydroxylation of proline and lysine.

3. ***Role in Tryptophan Metabolism:*** Vitamin C is required as a cofactor in the pathway of biosynthesis of serotonin.
4. ***Formation of Ferritin:*** Ascorbic acid is necessary for the formation of tissue "ferritin".
5. ***Absorption of Fe***
   - ***a.*** Ascorbic acid in food helps in the absorption of Fe by converting the inorganic ferric iron to the ferrous form.
   - ***b.*** Also helps in mobilization of Fe from its storage form 'Ferritin'.
6. ***Role in Formation of Catecholamines:*** Vitamin C is required as a coenzyme with the enzyme *dopamine hydroxylase* which catalyzes the conversion of dopamine to norepinephrine.
7. ***Effect on Cholesterol Level.*** Relation of ascorbic acid with hypo-cholesterolemia in man has been reported which stimulate cholesterol catabolism.

Clinical Aspects:

Scurvy: In the humans, its deficiency produces a disease called **Scurvy**. **The main defect is a failure to deposit intercellular cement substance.**

a. **Capillaries are fragile** and there is tendency to hemorrhages:
b. **Wound healing is delayed** due to deficient formation of collagen.
c. **Poor dentine formation** in children, leading to poor teeth formation.
d. In severe scurvy, may lead to secondary infection and loosening and falling of teeth.
e. Anemia may be associated which is **hypochromic microcytic type.**

Requirement:

A daily intake of about 100 mg is quite adequate in normal adults. The requirement is increased in presence of infections. Official recommended minimal daily intakes are:

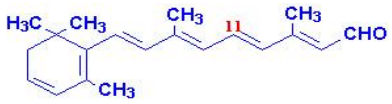
a. Infants: 30 mg per day
b. Adults: 75 mg per day
c. Adolescence: 80 mg per day
d. Pregnant women: 100 mg per day
e. Lactating women: 150 mg per day

Fat-Soluble Vitamins:

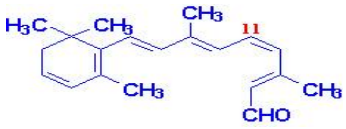
Vitamin A:

All three compounds of vitamin A contain as common structural unit, see the structure below:

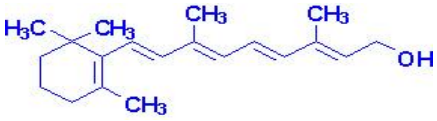
i. vitamin A alcohol or **retinol**
ii. vitamin A aldehyde or **retinal** (also called **retinene**)
iii. vitamin A acid or **retinoic acid**.



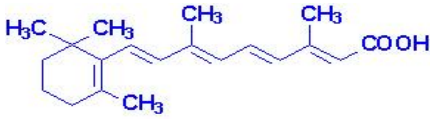
All-trans - retinal



11-cis – retinal



Retinol



Retinoic acid

Fig. 8: Various forms of vitamin A

These forms are sometimes referred to as ***retinoids***. Vitamin A is a derivative of certain carotenoids which are hydrocarbon (polyene) pigments (yellow, red). These are widely distributed in the nature. These are called as ***"Provitamins A"*** and are α, β, and γ**-carotenes as shown in Fig. 9**.

Two moles of vitamin A are formed by symmetrical oxidative cleavage of β***-carotene while only one mole of vitamin A is obtained from*** α ***and*** γ***-carotenes or cryptoxanthine.***

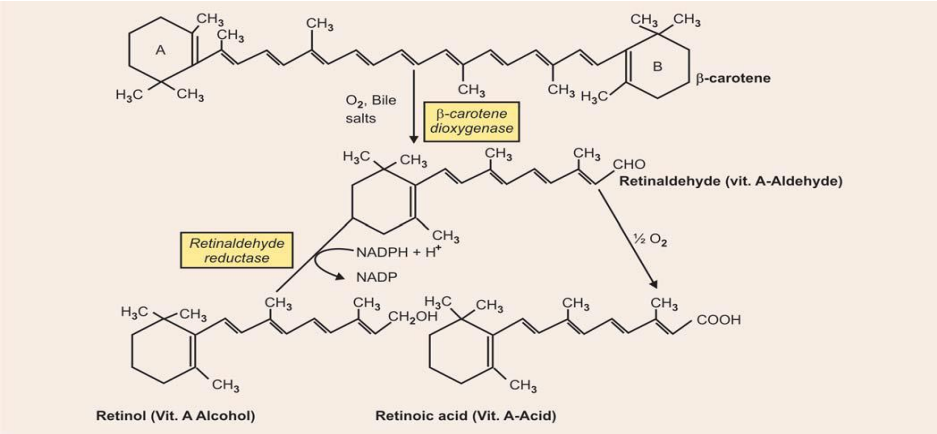


Fig. 9: Interconversion of vitamin A metabolites

Dietary Sources

1. ***Animal sources:*** Liver oil, butter, milk, cheese, egg yolk.
2. ***Plant sources:*** In the form of provitamin carotene, tomatoes, carrots, green-yellow vegetables, spinach, and fruits such as mangoes, papayas, corn, sweet potatoes.

Daily requirement: Adult male and female require about 3000 IU per day. However, a recommended allowance is around 5000 IU per day. ***It is higher in growing children, pregnant women and lactating mothers.*** The requirement is also higher in hepatic disease.

Normal blood level: Normal blood level of vitamin A is found to be 18 to 60 µg/dl and that of carotenoids 100 to 300 µg/dl.

Functions of Vitamin A:

1. Role of vitamin A in Vision

2. Role in Reproduction

3. Role in Epithelialization

4. Role in Bone and Teeth Formation.

5. Growth.

6. Metabolism: It may be involved in protein synthesis and may play a role in metabolism of DNA.

8. β-Carotene as an Antioxidant and Anti-cancer

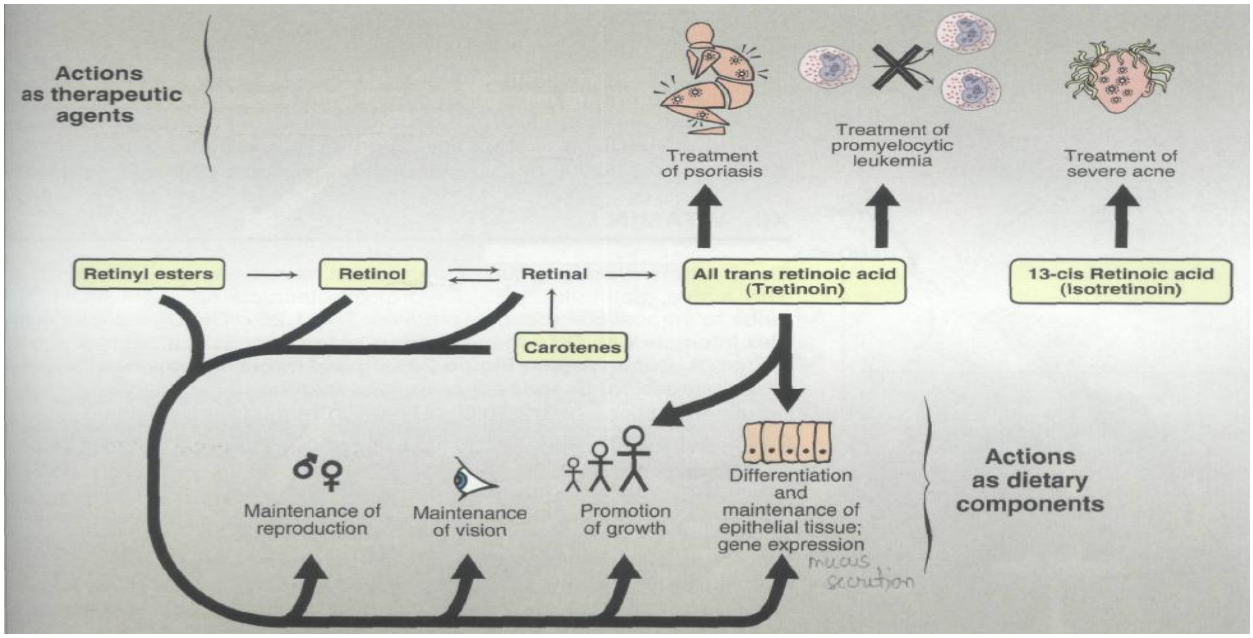


Fig. 10: Summary of retinoid actions.

Effects of excess of vitamin A (hypervitaminosis A):

Excess of vitamin A induces series of toxic effects known under the name of the ***hypervitaminosis A syndrome.*** In man, the main symptoms are:

a. Alterations of the skin and mucous membrane
b. Hepatic dysfunction
c. Headache, drowsiness
d. Peeling of skin about the mouth and elsewhere.

Toxicity of Vitamin A:

Vitamin A is both acutely and chronically toxic. Acutely, large doses of vitamin A (in excess of 300 mg in a single dose to adults) cause nausea, vomiting, and headache, with increased pressure in the cerebrospinal fluid – signs that disappear within a few days. Excess accumulation of vitamin A in the liver can lead to toxicity which manifests as bone pain, hepato-spleenomegaly, nausea and diarrhea.

The chronic toxicity of vitamin A is a more general cause for concern; prolonged and regular intake of more than about 7,500 to 9,000 μg per day by adults (and significantly less for children) causes signs and symptoms of toxicity affecting:

1. **The skin:** excessive dryness, scaling and chapping of the skin, desquamation and alopecia.
2. **The central nervous system:** headache, nausea, ataxia, and anorexia, all associated with increased cerebrospinal fluid pressure.
3. **The liver:** hepatomegaly, hyperlipidemia, and histological changes in the liver, including increased collagen formation.
4. **Bones:** joint pains, thickening of the long bones, hypercalcemia, and calcification of soft tissues, but with reduced bone mineral density. High intakes of vitamin A are associated with an increased rate of loss of bone mineral density with age. At high levels of intake, vitamin A both stimulates bone resorption and inhibits bone formation.

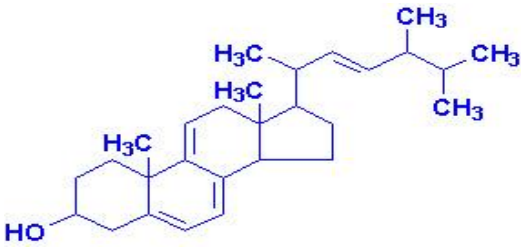
Vitamin D:

Vitamin D3 or cholecalciferol occurs in fish liver and also produced in human skin by ultraviolet light. The inactive natural precursors of the vitamin D are the **'provitamins'.** Only two of these have been found in nature.

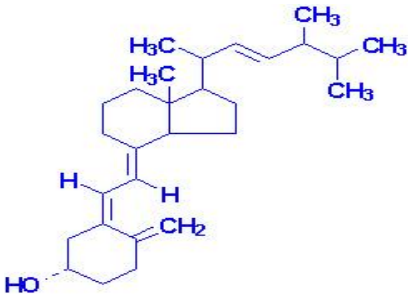
1. **Ergosterol:** ***Provitamin D2 found in plants.***
2. **7-dehydrocholesterol:** ***Provitamin D3 found in the skin.***

Dietary Sources

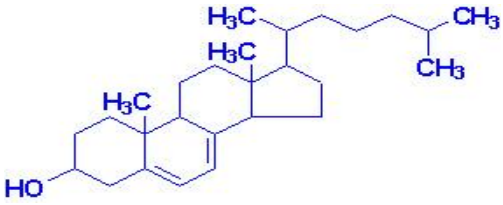
Fish liver oil, egg-yolk are the richest sources of vitamin D. Some quantity is also present in butter, cheese, etc. Ergosterol is widely distributed in plants. It is not absorbed well hence is not of nutritional importance. Calciferol is readily absorbed. 7-dehydrocholesterol is formed from cholesterol in the intestinal mucosa, and principally liver, passed on to the skin where it undergoes activation to vitamin D3 by the action of solar UV-rays



Ergosterol



Vitamin D_2



7-Dehydrocholesterol

Cholecalciferol, Vitamin D_3

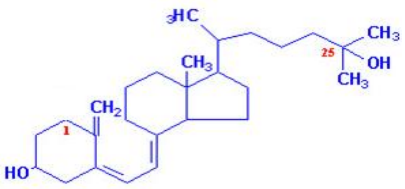
Daily Requirement

About 100 IU or 2.5 µg of vitamin D3 is the daily requirement in adult man. Pregnant and lactating mother as well as infants and children require about 220 IU per day.

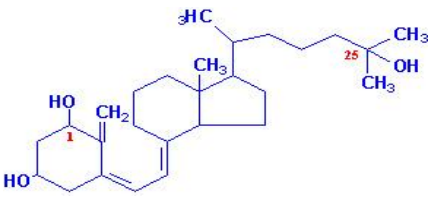
Biologically Active Form of Vitamin D (Calcitriol)

Formation of Calcitriol

The biologically active form of vitamin D is called **calcitriol,** which is synthesized in **liver** and **kidneys, see their structures in Fig. 11.**



25-hydroxyvitamin D_3



1,25- Dihydroxyvitamin D_3

Fig. 11: Provitamin D3 and active form of vitamin D3.

Vitamin D3 as prohormone: Since calcitriol is synthesized in the body and acts like steroid hormone and has a basic sterol nucleus in its structure, ***it is now regarded*** as a hormone and vitamin D as a prohormone. Like hormones, calcitriol has definite "target" organs like small intestine, bones and kidneys to act upon. **Thus, it is produced in one organ and acts upon distant target organs for its activity (property of hormone).** Calcitriol resembles steroid hormone in its mode of action, **i.e. nuclear action (Fig. 10).** Calcitriol maintains calcium homeostasis along with—two other protein hormones parathormone (PTH) and calcitonin. Parathormone (PTH) is considered as a "tropic" hormone for calcitriol, it increases the

calcitriol production by stimulating the enzyme “1α-hydroxylase” in kidney tubules.

Functions of Vitamin D

Vitamin D is found to act on target organs like bones, kidneys, intestinal mucosa to regulate calcium and phosphate metabolisms.

Intestinal absorption of calcium and phosphate:

Mineralization of bones:

Other Functions

Deficiency of Vitamin D

1. **Rickets. Deficiency produces rickets in growing children and osteomalacia in adults.**
2. **Osteomalacia** The deficiency of vitamin D in adults is osteomalacia which is rare. It can occur in:
   a. **Pregnancy and lactation:** Where there is additional requirement of this vitamin and drainage of it in milk.
   b. **Women who observe purdah** or in climates where sunshine is scanty, calcium and phosphorus absorption is decreased. Consequently mineralization of osteoid to form bone is impaired. Such bones become soft. This particularly affects pelvic bones.
3. **Renal Osteodystrophy** When renal parenchyma is lost or diseased quite significantly, it is unable to form calcitriol and calcium absorption is impaired. Hypocalcemia leads to increase in PTH which acts on bone to increase Ca^{++}. Consequently there is excessive bone turnover and structural changes. This condition is known as renal osteodystrophy.

Hypervitaminosis D:

Normally vitamin D is well tolerated if taken in large doses but serious deleterious effects may be produced if taken in extremely large doses, 500 to 1000 times of normal requirement for prolonged periods. Effects are mainly due to induced hypercalcaemia.

1. ***Immediate effects:*** Include anorexia, thirst, lassitude, constipation and polyuria. Followed later on by nausea, vomiting and diarrhoea.
2. ***Delayed effects:*** Persistent hypercalcaemia and hyperphosphataemia may produce:
   a. ***Urinary lithiasis***
   b. ***Metastatic calcification*** which may affect kidneys, bronchi, pulmonary alveoli, muscles, arteries and gastric mucosa. Renal failure may develop and can lead to death. In growing children there may be excessive mineralization of the zone of provisional calcification at the expense of the diaphysis which may undergo demineralization.

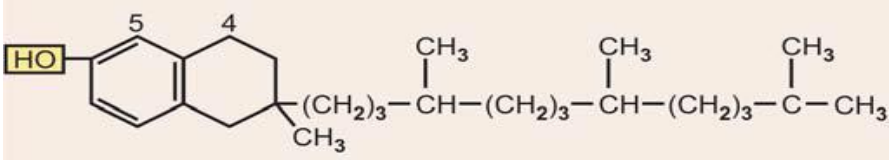
Clinical Aspects:

Recently low vitamin D level has been correlated with certain diseases:

1. **Heart ailments:**
2. **Diabetes:**
3. **Breast cancer:** Recently a link has been suggested between the occurrence of breast cancer in women and vitamin D deficiency.
4. **Peripheral artery disease (PAD):** Vitamin D may protect against an arterial disease in which fatty deposits restrict blood flow to the limbs. It was found that **people with low levels of vitamin D experience an increased risk of peripheral artery disease (PAD),** most often reduces blood flow to the legs causing pains, numbness, impairing the ability to work and in some cases leading to amputation.

Vitamin E (Tocopherols)

The α-tocopherol is the most active in vitamin E activity. The ***presence of the phenolic–OH group on 6th carbon of the chromane ring is the most important group for its antioxidant activity.***



Structure of vitamin E

Fig. 12: Structure of vitamin E

Dietary Sources and Recommended Allowance

Cottonseed oil, corn oil, sunflower oil, wheat germ oil and margarine are the richest sources of vitamin E. It is also found in fair quantities in dry soyabeans, cabbage, yeast, lettuce, apple seeds, peanuts.

Units : 1 mg of d-α-tocopherol = 1.49 IU ; 1 mg of dl-α-tocopherol acetate = 1.0 IU

Normal blood level = 1.2 mg/dl.

Recommended Allowance

1. **For Children:** 10–15 IU/day
2. **For Adults:** 20–25 IU/day

Functions of Vitamin E:

1. Antioxidant Property. This is the most important functional aspect of vitamin E.

a. Removal of free radicals:

b. Vitamin E prevents peroxidation.

2. Other Functions

A. Tocopherol derivative tocopheranolactone may be involved **in synthesis of coenzyme Q or ubiquinone.**

B. Vitamin E may have **some role in nucleic acid synthesis.**

Deficiency of Vitamin E

1. ***Muscular dystrophy:***
2. ***Hemolytic anemia:***
3. **Dietary hepatic necrosis:**

Clinical and therapeutic uses of vitamin E:

Recently, vitamin E has been used in various diseases as shown below:

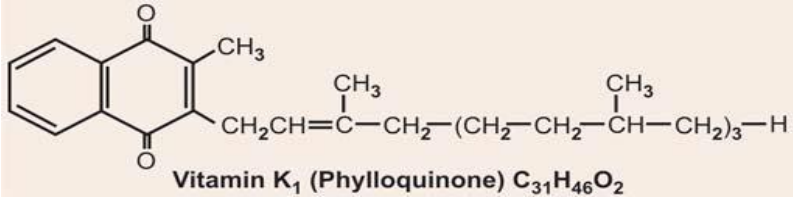
1. **Nocturnal muscle cramp (NMC).** Vitamin E as antioxidant prevents oxidation of certain radicals and ensures better utilization of oxygen in muscle tissue, thereby improving muscle metabolism.
2. **Fibrocystic breast disease (FBD).** It has been suggested that vit. E probably acts by correcting the deranged progesterone/estrogen ratio in women of FBD
3. **Atherosclerosis** Beneficial effects of vit. E in atherosclerosis is due to:
   - **a.** Inhibits the formation of lipid peroxides and restores PG-I2 synthesis
   - **b.** Inhibits platelets aggregation
   - **c.** Elevates HDL-cholesterol level ↑ (increased scavenging action).

Vitamin K

All vitamin K forms are the **naphthoquinone derivatives**. *Vitamins K1 and K2* are the two naturally occurring forms of vitamin K that have been identified. The third form vitamin K3 is the synthetic analogue.

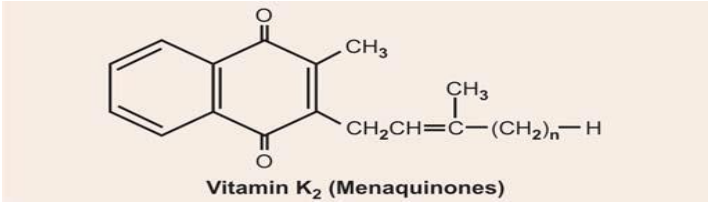
Types of Vitamin K

1. **Vitamin K1.** It is ***phylloquinone*** or phytonadione ***isolated from alfalfa leaves***. Also called ***Mephyton.***



Vitamin K_1 (Phylloquinone) $C_{31}H_{46}O_2$

2. **Vitamin K2.** Also known as ***farnoquinone and it*** is also a yellow oil.



Vitamin K_2 (Menaquinones)

3. **Vitamin K3.** Vitamin K3 is known as ***menadione***), is the ***synthetic analogue*** of vitamin K. It is ***three times more potent*** than natural

varieties. It is **water-soluble** and can be given parenterally. ***Its activity is related to the presence of methyl group at position 2.***

Dietary sources and daily requirement:

Both vitamin K1 and K2 are mainly found in plants and synthesized by bacteria respectively. Vitamin K1 is present chiefly in green leafy vegetables. Vitamin K2 is a product of metabolism of most bacteria ***including the normal intestinal bacteria*** of most higher animal species.

Functions of Vitamin K:

1. Blood Coagulation

The main function of vitamin K is the promotion of blood coagulation by helping in the posttranscriptional modifications of blood factors such as prothrombin, and factors II, VII, IX, X. Vitamin K is first converted to its hydroquinone form in liver microsomes by dehydrogenase using NADPH. It then functions as coenzyme for carboxylase. It uses CO_2 to be incorporated as an additional –COOH group at the γ-C of a specific glutamate of these coagulation proteins. ***This converts the glutamate residues into γ-carboxyglutamate.***

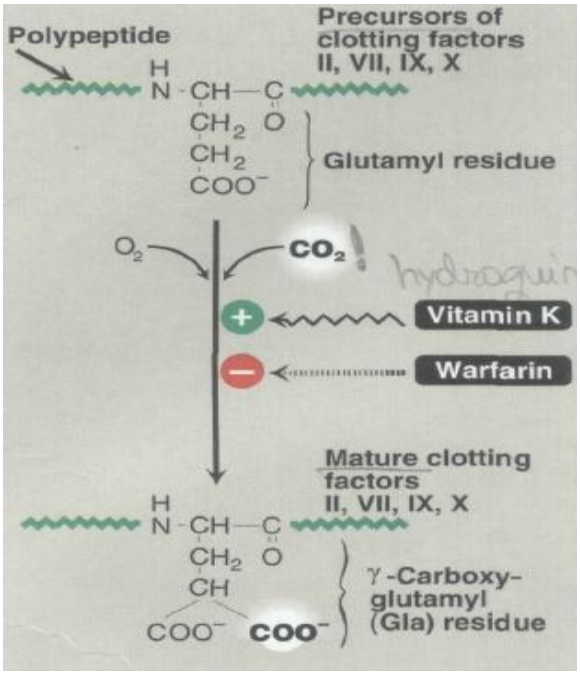


Fig. 13: Carboxylation of glutamate into γ-carboxyglutamate

Interaction of prothrombin with platelets: The Gla residues of prothrombin are good chelators of positively charged calcium ions, because of the two adjacent, negatively charged carboxylate groups. The prothrombin-calcium complex is then able to bind to phospholipid essential for blood clotting on the surface of platelets. Attachment to the platelet increases the rate at which the proteolytic conversion of prothrombin to thrombin can occur.

2. Calcium Binding Proteins

Vitamin K similarly is found to carboxylate specific glutamate residues of ***calcium binding proteins*** of bones, spleen, placenta and kidneys. This enhances the capacity of these proteins to deposit calcium in the tissues concerned.

Deficiency of Vitamin K:

Deficiency of vitamin K is very rare, since most common foods contain this vitamin. In addition, intestinal flora of microorganisms also synthesis vitamin K. However, a deficiency may occur as a result of:

1. ***Prolonged use of antibiotics and sulfa drugs:***
2. ***Malabsorption and biliary tract obstruction:***
3. ***Spoilt Sweet-clover hay:***
4. ***Short circuiting of the bowel:***
5. ***In immediate post-natal infants:***

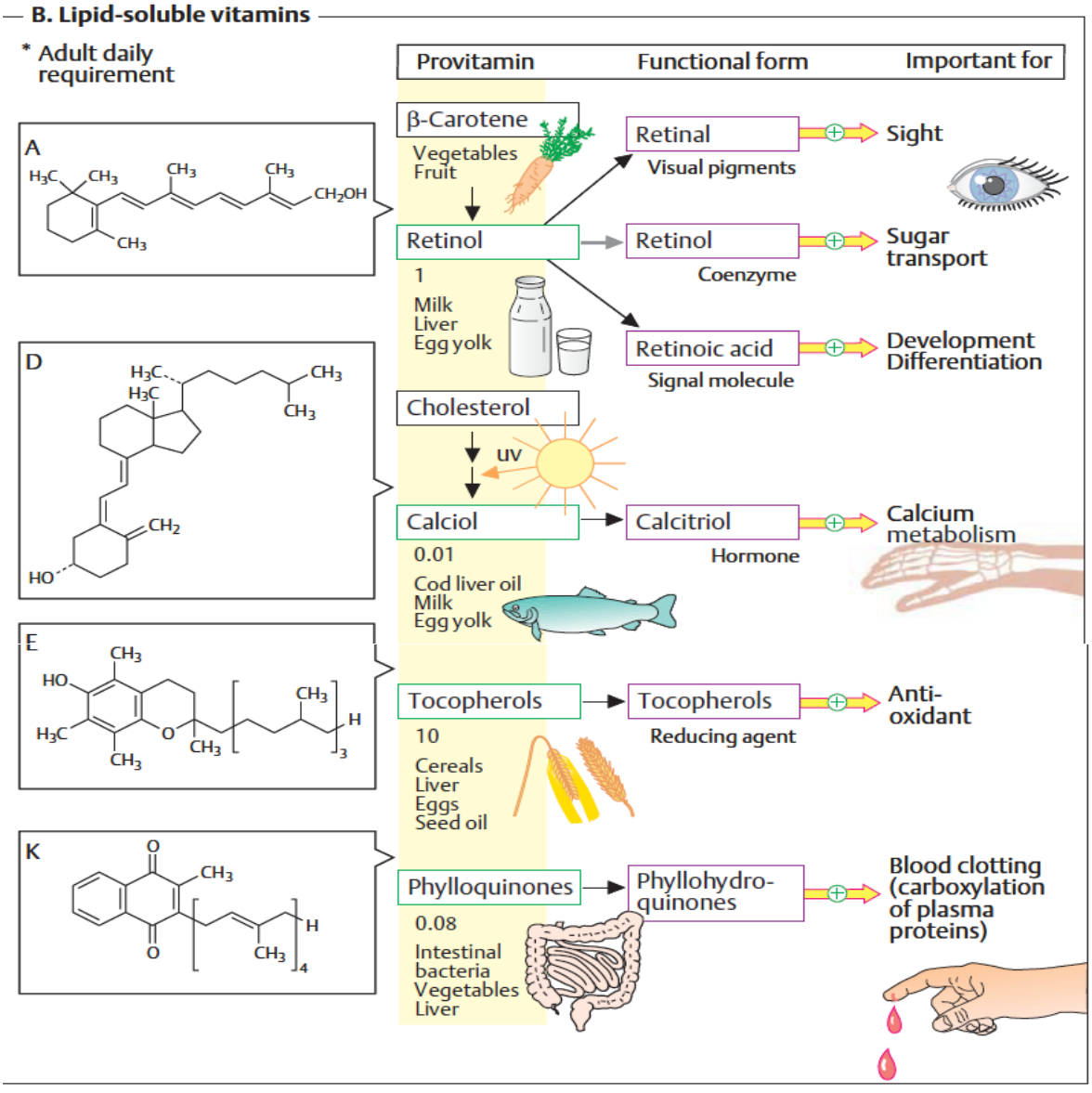


Fig. 14: The overall functions, dietary requirement, structures and deficiencies of fat or lipid-soluble vitamins.