

PHARMACOLOGY

Vitamins

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Keywords

Vitamin source, physiological role, deficiency, toxicity, recommended daily allowance, therapeutic use



Introduction

Vitamins are a class of organic compounds categorized as essential nutrients for life and maintenance of normal health. These are required in small quantity in body, thus falling in the category of micronutrients, because body uses them without breaking down, as happens to carbohydrate and other macronutrients.

Vitamins are essential food factors which are required for the proper utilization of the proximate principles of food like carbohydrates, lipid and proteins. These act as cofactor in many enzyme systems and are therefore cardinal for various body functions such as energy production, hemopoiesis, reproduction, neurological functions, hydroxylation and synthesis of fats, amino acids, nucleic acids and nucleoprotein. Any aberrations in these critical mechanisms cause profound changes in the nervous system and integrity of skin, mucous membrane, synthesis and repair of connective tissue and drug metabolism, thus serving the needs of growth, differentiation and maintenance of normal cellular function.

In 1912, Funk described a substance that was present in rice polishing and in foods that cured polyneuritis in birds and beriberi in humans. This substance was referred to as 'vitamin' because it was characterized as an amine and as a vital nutrient. Vital to indicate that these factors are necessary for life and since earlier they are identified as having amino groups, amine was used, but later work showed that most of them did not contain amino groups. Thus finally 'e' was dropped to call vitamin.

Since body is unable to synthesize them (atleast in sufficient amount) they must be provided by food. A well balanced ordinary diet supplies the vitamin needs of a healthy person.

Although vitamins are important nutritionally, their role has been over emphasized in clinical practice. They are useful to correct deficiencies, if any. But taking higher doses of vitamins will not boost up the health. Generally there is increased requirement of vitamins in chronic diarrhea, mal-absorption, and bacterial overgrowth in intestines due to impaired intestinal absorption of vitamins. But there are some evidences available these days, that intake of several vitamins above the minimum daily requirement may prevent heart disease, cancer, osteoporosis and other chronic diseases.

There are vitamins like substitutes that fail to meet all the criteria necessary to be classified as vitamins. They still have some properties of a vitamin and, in some cases, are present in larger amounts than vitamins. There are others that body can synthesize in sufficient amounts to meet its needs if precursors are present; some such substances include bioflavonoids, inositol, choline, PABA(para amino benzoic acid) & carnitine.

Vitamins must have following characteristics in order to be classified as such:

- Required in relatively small quantities.
- Essential because certain biochemical reactions cannot occur without them
- Must be obtained in the diet because the body cannot synthesize them or cannot make adequate amounts.
- Must be eaten regularly because they are stored in limited quantities & are gradually lost.
- A deficiency results in at least one specific disorder.

Deficiency of vitamin can bring about:

- Infections & skin disorders, as well as visual loss.
- Weakened bones.
- Anemia & poor functions of nervous, digestive & immune system, as well as an excess of blood homocysteine.
- Edema & poor wound healing.
- Muscle weakness & nervous system disorders.
- Inflammation of mouth & skin.
- In early stages may cause nausea, loss of appetite & mental and emotional changes.

Vitamins are mainly classified into two broad categories, viz:-

- ❖ Fat soluble vitamins;
 - As Vitamin-A Vitamin-E
 - Vitamin-D Vitamin-K
- ❖ Water soluble vitamins;
 - As Vitamin-B complex
 - Vitamin- C (Ascorbic acid)

Fat soluble vitamins are stored in the body for a while- some stay for few days, some for up to 6 months. They are generally stored in the liver. Whenever to be used, special carriers in body takes them to where they are needed.

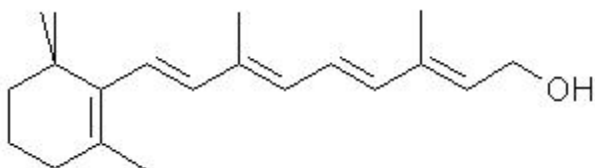
Water soluble vitamins are different. When we take foods having water soluble vitamins, the vitamins do not get stored, as much in the body. Instead they travel through blood stream, and whatever body doesn't use comes out with urine.

Fat Soluble Vitamins

Vitamin A

Vitamin A is a generic term for a large number of related compounds. Vitamin A covers both a pre-formed vitamin, retinol, and a pro-vitamin, β carotene. Oxidized metabolite retinaldehyde & retinoic acid are also pre- formed vitamins identified in animal tissues. Retinol, retinal, retinoic acid and related compounds are known as retinoids. β carotene is a pro-vitamin (precursor for vitamin A) that can be converted to retinol, in the intestinal mucosa.

Retinol and carotenes are fat soluble. In ideal conditions 90% of ingested retinol & 70% of carotenes are absorbed. Cooking, especially frying in oil improves the absorption of carotenes. Absorbed vitamin A is stored in liver as retinyl palmitate. Zinc is required for mobilization of retinyl palmitate to free retinol. Under normal condition a well fed person has sufficient vitamin A reserve in liver to meet his need for 6 to 9 months or more. Free retinol is highly active, but toxic, and is therefore transported in the blood stream in combination with retinol-binding protein (RBP), which is produced by liver. By this complex formation vitamin A is solublized & protected from excretion. In case of vitamin A deficiency RBP production from liver falls.



The Chemical Structure of Retinol
Chemical Formula: $C_{20}H_{30}O$

Source of vitamin A: Vitamin A is widely distributed in animal & plant foods— in animal food as preformed vitamin A (retinol), and in plant foods as provitamins (carotenes).

[A] Animal foods:-

- Liver, eggs, butter, cheese, whole milk, fish & meat.
- Fish liver oils, cod liver oils, shark liver oils are the richest source of retinol.

[B] Plant foods:-

- Green leafy vegetables such as spinach, amaranth, some roots (carrots) & yellow fruits (papaya, mango, pumpkin) are cheaper source of carotenoids.
- Red palm oil is best source for carotene.

[C] Fortified foods:-

- Foods fortified with vitamin A (vanaspati, margarine, milk) can be an important source

Physiological role of vitamin A: Vitamin A is essential for normal maintenance & functioning of body tissues. It participate in many bodily functions.-

- It is essential for normal vision. It contributes to the production of retinal pigments which are needed for vision in dim light.
- It is necessary for maintaining the integrity and the normal functioning of glandular & epithelial tissues, which lines intestinal, respiratory & urinary tracts as well as the skin & eyes.
- It supports growth especially skeletal growth.

- It is anti-infective vitamin. That is why it has a role in maintaining integrity of epithelial tissues for resisting invasion of pathogens & for functional immune response.
- Retinol is necessary for spermatogenesis & integrity of testicular and vaginal epithelium.
- β carotene has anti-oxidant property and is scavengers of free radicals. Thus reduces the incidence of lung, breast, oral, esophageal & bladder cancers.

Deficiency of vitamin A (clinical features)

The deficiency of vitamin A manifests only if the hepatic stores are not sufficient to meet the requirements. The manifestations are mainly seen in eye & skin. Some of the most common manifestations are as follows:

[a] Night blindness :- Defective dark adaptation is the most characteristic early clinical feature, resulting in night blindness. Patient cannot read or drive a car in poor light.

[b] Xerophthalmia :- Conjunctiva becomes dry, thick & wrinkled. Conjunctiva gets keratinized & loses its normal transparency and acquires a smoky appearance. When dryness spreads to cornea, it becomes glazy & lusterless due to keratinization of corneal epithelium.

[c] Bitots spot :- These are grayish- white triangular plaques, firmly adherent to the conjunctiva due to increased thickness of conjunctiva in certain areas.

[d] Keratomalacia :- If xerophthalmia persists for a long time, it progresses to keratomalacia that is softening of the cornea. There is degeneration of corneal epithelium, which may get vascularized & corneal opacities develop. Bacterial infection of iris & corneal ulceration may occur. Total blindness may result from perforation of cornea & prolapses of iris.

[e] Deficiency manifestation in skin and mucous membrane :- Follicular hyperkeratosis or phrynoderma results from hyperkeratinization of the epithelium, lining, and the follicles. Skin becomes rough; papules are seen at the site of pilosebaceous follicles.

[f] Other manifestation :- Growth retardation, especially failure of skeletal growth is noticed, which may be due to defective synthesis of chondroitin sulfate. Also may be manifested as decreased protein synthesis, lowered glycoprotein content of cell & reduced immunocompetency.

Factors affecting vitamin A status in body: Major cause for vitamin A deficiency is the decreased intake. Other cause may be.-

- obstructive jaundice causing defective absorption of vitamin A.
- diarrhea, worms & other intestinal disorders impairs vitamin A absorption.
- Respiratory tract infections, measles, and other febrile illness increase the metabolic demand.
- Cirrhosis of liver and also severe malnutrition leads to reduced synthesis of RBP.

- Chronic nephrosis increases the excretion of RBP (retinol binding protein) in urine.

Recommended daily allowances (RDA)

RDA is expressed in terms of retinol or as retinol equivalents (RE):-

1 RE = 1 microgram of retinol

1 RE = 6 microgram of retinal

RDA for:-

Children & infants -- 400-600 µg/day

Men -- 1000 µg/day

Women -- 800 µg/day

Pregnancy -- 1000 µg/day

Prevention of deficiency: Prevention may be done either by:-

- Improvement of people's diet, so as to ensure a regular and adequate intake of food rich in vitamin A.
- Reducing the frequency and severity of contributory factors for example Protein Energy Malnutrition (PEM), respiratory tract infections, diarrhea, and measles.

Treatment

- Deficiency of vitamin A should be treated urgently.
- Generally all early symptoms can be reversed by supplementation by 200,000 IU (International unit) or 110 mg of retinal palmitate in form of capsule or injections.

Therapeutic uses

- Prophylaxis of vitamin A deficiency during infancy, pregnancy, lactation, hepatobiliary disease, steatorrhoea.
- Treatment of established vitamin A deficiency
- Skin diseases like acne, psoriasis, ichthyosis
- Also may be used in treatment of promyelocytic leukemia.

Interactions

- Vitamin E promotes storage & utilization of retinol & decreases its toxicity.
- Regular use of liquid paraffin can result in vitamin A deficiency.
- Long term oral neomycin induces steatorrhoea and interferes with vitamin A absorption.
- Chronic alcohol consumption results in depletion of liver stores of vitamin A.

Hypervitaminosis A or toxicity

- Excessive intake of vitamin A can lead to toxicity symptoms like anorexia, nausea, vomiting, itching, erythema, dermatitis, hair loss, irritability, headache, peeling of skin, loss of appetite, bleeding, drowsiness & chronic liver disease.
- Acute poisoning may be seen after consumption of polar bear liver, which contains excess vitamin A.

Current marketed preparations

Aquasol-A, 50,000 IU cap, 100,00 IU in 2 ml inj.

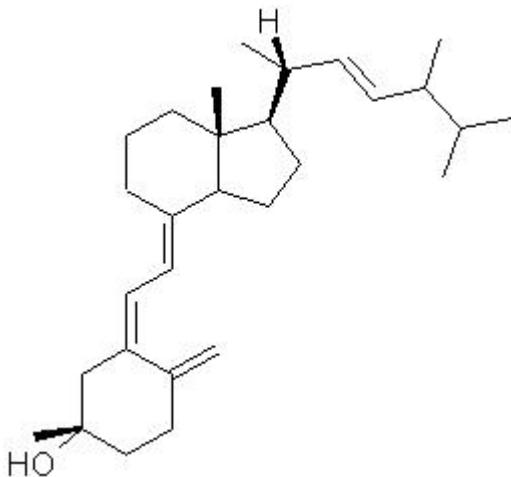
Arovit 50,000 IU tab, 150,000 IU/ml drops, 100,00 IU/2ml inj.

Carofral 50,000 IU tab, 100,00 IU/2ml inj.

Vitamin D

Nutritionally important forms of vitamin D in humans are ergocalceferol (vitamin D₂) & cholecalciferol(vitamin D₃) . Ergocalceferol may be derived by irradiation of the plant sterol, ergosterol. Cholecalciferol is naturally occurring (preformed) vitamin D, found in animal fats & fish liver oils and also derived from exposure to UV(Ultra violet) rays of sunlight.

Vitamin D, by itself, is metabolically inactive. It undergoes endogenous transformation into several active metabolites, first in liver and later in kidney. These metabolites are bound to specific transport proteins and are carried to the target tissues- bone & tissues.



The Chemical Structure of Vitamin D₂ (Ergocalciferol)
Chemical formula: C₂₈H₄₄O

Sources: Derived from both sunlight and foods.

1. foods :-

- It is found only in foods of animal origin.
- Liver, egg yolk, butter, and cheese and some amount of fish contain vitamin D.
- Fish liver oils are the richest source of vitamin D.
- Human milk also contain considerable amount of water- soluble vitamin D sulfate.
- Artificially fortified foods, such as milk, margarine, vanaspati and infant foods are also sources of vitamin D.

2. sunlight :-

- Sun exposure is perhaps the most important source of vitamin D because exposure to sunlight provides most humans with their vitamin D requirement
- vitamin D is synthesized by the body by action of UV rays of sunlight on 7-dehydrocholesterol, which is stored in large abundance in the skin.

Physiological role of vitamin D: The major biologic function of vitamin D is to maintain normal blood levels of calcium and phosphorus. By promoting calcium absorption, vitamin D helps to form and maintain strong bones. Vitamin D also works in concert with a number of other vitamins, minerals, and hormones to promote bone mineralization. Without vitamin D, bones will become thin, brittle, or misshapen.

Research also suggests that vitamin D may help in maintaining a healthy immune system and help in regulating cell growth and differentiation, the process that determines what a cell is to become

RDA (Recommended daily allowance): The daily requirements of vitamin D are:

Adults	-- 2.5 mcg(100 IU)
Infants and children	-- 5.0 mcg(200 IU)
Pregnancy and lactation	-- 10.0 mcg(400 IU)

Deficiency: Nutrient deficiencies are usually the result of dietary inadequacy, impaired absorption and utilization, increased requirement, or increased excretion (loss). A deficiency of vitamin D can occur:

- when usual intake is below recommended levels
- when there is limited exposure to sunlight
- when the kidney cannot convert vitamin D to its active form
- when someone cannot adequately absorb vitamin D from the digestive tract

Vitamin D deficient diets are associated with milk allergy, lactose intolerance, and strict vegetarianism. Infants fed with only breast milk receive insufficient amounts of vitamin D unless they also receive appropriate levels of vitamin D supplementation

The classic vitamin D deficiency diseases are *rickets and osteomalacia*.

1. **Rickets:**

- Observed in young children between ages of 6 months to 2 years.
- There is reduced calcification of growing bones. Disease is characterized by the growth failure, bone deformity, muscular hypotonia, tetany and convulsions due to hypocalcaemia.
- There is an elevated concentration of alkaline phosphate in serum.
- Bony deformities include curved legs, deformed pelvis, pigeon chest etc.

Rickets is the softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D deficiency. Vitamin D is essential in promoting absorption of calcium and phosphorus from the gastrointestinal tract, which children need

to build strong bones. A deficiency of vitamin D makes it difficult to maintain proper calcium and phosphorus levels in your bones. Our body senses an imbalance of calcium and phosphorus in your bloodstream and reacts by taking calcium and phosphorus from your bones to raise blood levels to where they need to be. This softens or weakens the bone structure, resulting most commonly in skeletal deformities such as bowlegs or improper curvature of the spine. Osteomalacia is the adult version of rickets.

If a vitamin D or calcium deficiency causes rickets, adding vitamin D or calcium to the diet generally corrects any resulting bone problems for the child. Rickets due to a genetic condition may require additional medications or specialized treatment. Some skeletal deformities caused by rickets may need corrective surgery.

Signs and symptoms: Vitamin D deficiency begins months before physical signs and symptoms of rickets appear. When rickets symptoms develop, they may include:

- **Skeletal deformities.** These include bowed legs, abnormal curvature of the spine, pelvic deformities and breastbone projection in the chest.
- **Fragile bones.** Children with rickets are more prone to bone fractures.
- **Impaired growth.** Delayed growth in height or limbs may be a result of rickets.
- **Dental problems.** These include defects in tooth structure, increased chance of cavities, poor enamel and delayed formation of teeth.
- **Bone pain.** This includes dull, aching pain or tenderness in the spine, pelvis and legs.
- **Muscle weakness.** Decreased muscle tone may make movement uncomfortable.

Causes: Vitamin D acts as a hormone to regulate calcium and phosphorus levels in your bones. You absorb vitamin D from two sources:

- **Sunlight.** Your skin produces vitamin D when it's exposed to sunlight. This is the most common way for most adolescents and adults to produce the vitamin.
- **Food.** Your intestines absorb vitamin D from the foods you eat or from supplements or multivitamins you may take.

In the past, dietary vitamin D deficiency was the most common cause of rickets in the United States. Now, with the increased use of vitamin supplements and the variety of foods fortified with vitamin D (such as orange juice and breakfast cereals), vitamin D deficiency cases of rickets have fallen. Currently in the United States, conditions that impair vitamin D absorption such as the surgical removal of all or part of the stomach (gastrectomy) and celiac disease, in which the small intestine doesn't absorb certain nutrients from food, cause most cases of rickets.

Other causes of rickets include:

- **Hereditary rickets (X-linked hypophosphatemia),** an inherited form of rickets caused by the inability of the kidneys to retain phosphorus, or a complication of renal tubular acidosis, a condition in which your kidneys are unable to excrete acids into urine
- **Lack of exposure to sunlight,** which stimulates the body to make vitamin D

Risk factors: Children 6 to 24 months old are most at risk of rickets because they're growing rapidly, and vitamin D, calcium and phosphorus play a major role in the growth process. Risk factors for rickets include:

- **Lack of vitamin D.** Breast-fed infants who don't receive supplemental vitamin D are at increased risk of developing rickets. While exposure to sunlight could produce the necessary amounts of vitamin D, sunburn and skin cancer are real dangers for young children. Sunscreens also markedly decrease vitamin D production.
- **Lack of calcium and phosphorus.** Children who don't get enough calcium and phosphorus in their diets are at increased risk of rickets. The availability of milk and other products that contain these minerals make this cause a rarity for rickets in the United States and other developed countries.

Screening and diagnosis: Your doctor or your child's doctor may diagnose rickets by:

- **Physical examination.** Your doctor will check if the pain or tenderness is coming directly from the bones, instead of the joints and muscles surrounding them.
- **Blood tests.** These measure calcium and phosphorus levels to see if they're normal.
- **X-rays.** Your doctor may take images of affected bones to look for softening or weakness.
- **Medical history.** Kidney problems, celiac disease or diagnosis of a sibling with rickets may help lead your doctor to a rickets diagnosis.

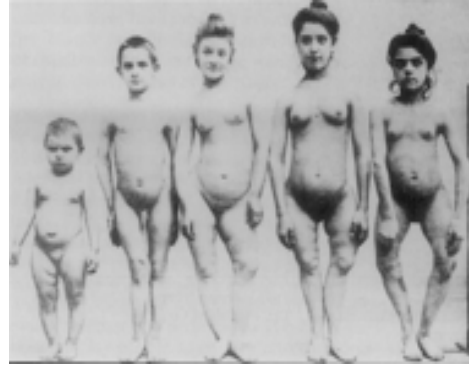
Complications: While easily treated once it's diagnosed, rickets has a severe list of complications if left untreated. Untreated vitamin D deficiency rickets may lead to:

- Delays in your child's motor skills development
- Failure to grow and develop normally
- Increased susceptibility to serious infections
- Skeletal deformities
- Chronic growth problems that can result in short stature (adults measuring less than 5 feet tall)
- Seizures
- Dental defects

Management of rickets: The aim of treatment for rickets is to solve the underlying disorder. If deficiencies in vitamin D, calcium or phosphorus are at fault, replacing vitamin D and those minerals generally eliminates the signs and symptoms of rickets, such as bone tenderness and muscle weakness. Improvement may occur within weeks.

- Administration of 15000 mcg or 600,00 IU of vitamin D3 orally or IM (intra muscular) induces rapid healing.
- Diet should be supplemented with adequate doses of vitamin D.
- Intake of vitamin D-fortified foods, including fortified breakfast cereal, orange juice, fish and processed milk should be increased.
- Little sunlight is also recommended. But moderate exposure is the safest, and infants under 6 months should not be exposed to direct sunlight.

- Getting a sufficient intake of calcium is crucial to maintaining healthy bones. The combination of increased vitamin D intake with calcium may be enough to eliminate the effects of rickets entirely.



2. Osteomalacia:

In adults vitamin D deficiency results in osteomalacia which occurs mainly in women, especially during pregnancy and lactation, when requirement of vitamin D is increased.

Factors which increase demand of Vitamin D: It can be difficult to obtain enough vitamin D from natural food sources. For many people, consuming vitamin D fortified foods and adequate sunlight exposure are essential for maintaining a healthy vitamin D status. In some groups, dietary supplements may be needed to meet the daily need for vitamin D.

1. Infants who are exclusively breastfed
2. Persons with limited sun exposure
3. Persons with greater skin melanin content
4. Persons with fat malabsorption
5. Pancreatic enzyme deficiencies which may be due to:
 - Crohn's Disease.
 - Cystic Fibrosis.
 - Liver disease.
 - Surgical

Prevention of deficiency: Prevention measures includes-

- A) Educating people to expose regularly to sunlight
- B) Periodic dosing (prophylaxis) of young children with vitamin D.

Hypervitaminosis D

- o Excretion of vitamin D is negligible and hence excessive administration can lead to toxicity.
- o Symptoms may include- weakness, polyurea, intense thirst, difficulty in speaking, confusion, weight loss, nausea, vomiting.

- o Patient may lapse into coma, while cardiac arrhythmias and renal failure may occur. These effects are due to hypercalcemia induced by increased intestinal absorption and mobilization of calcium from bone.
- o Hypokalemia and metabolic alkalosis are also associated.

Drug Interactions:

(a)Vitamin D and steroids: steroids may impair vitamin D metabolism, further contributing to the loss of bone and development of osteoporosis associated with long term use of steroidal medications

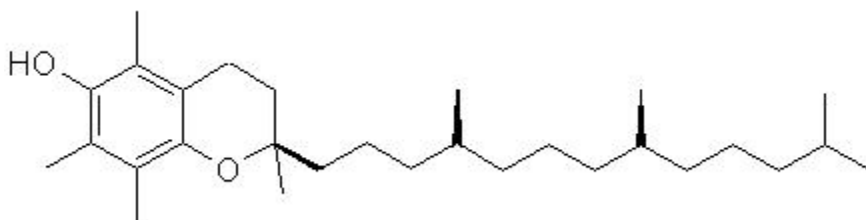
(b)Vitamin D and caffeine: High caffeine intake may accelerate bone loss. Caffeine may inhibit vitamin D receptors, thus limiting absorption of vitamin D and decreasing bone mineral density.

Current marketed preparations:

Arachitol 300,000 IU/ml & 600,000 IU/ml inj.
 Ostelin forte 300,000 IU/ml & 600,000 IU/ml inj.
 Calcirol 60,000 IU in 1 gm granule

Vitamin E

Vitamin E is a fat-soluble vitamin that exists in eight different forms. Each form has its own biological activity, which is the measure of potency or functional use in the body. Alpha-tocopherol (α -tocopherol) is the name of the most active form of vitamin E in humans. It is also a powerful biological antioxidant. Vitamin E in supplements is usually sold as alpha-tocopheryl acetate, a form of alpha-tocopherol that protects its ability to function as an antioxidant. The synthetic form is labeled "D, L" while the natural form is labeled "D". The synthetic form is only half as active as the natural form.



Chemical Structure of α -Tocopherol

Chemical formula: $C_{29}H_{50}O_2$

Sources:

- Vegetable oils, nuts, green leafy vegetables, and fortified cereals are common food sources of vitamin E.
- Richest sources of Vitamin E are vegetable oils, cotton seeds, sunflower seed, egg yolk and butter.
- Foods having polyunsaturated fatty acids are also rich in vitamin E.

Physiological role: Antioxidants such as vitamin E act to protect your cells against the effects of free radicals, which are potentially damaging by-products of energy metabolism. Free radicals can damage cells and may contribute to the development of cardiovascular disease and cancer.

Vitamin E has also been shown to play a role in immune function, in DNA repair, and other metabolic processes. The usual plasma level of Vitamin E in adults is between 0.8 to 1.4 mg per 100 ml.

Deficiency:

- Vitamin E deficiency is usually characterized by neurological problems associated with nerve degeneration in hands and feet.
- Vitamin E deficiency may result in anemia, reticulocytosis, thrombocytopenia, and erythrocyte metabolism
- Degenerative changes in spinal cord, skeletal muscles and heart may be seen.

Who is at risk for vitamin E deficiency? Vitamin E deficiency is rare in humans. There are three specific situations when a vitamin E deficiency is likely to occur.

1. persons who cannot absorb dietary fat due to an inability to secrete bile or with rare disorders of fat metabolism are at risk of vitamin E deficiency;
2. individuals with rare genetic abnormalities in the alpha-tocopherol transfer protein are at risk of vitamin E deficiency;
3. premature, very low birth weight infants (birth weights less than 1500 grams, or 3 pounds, 4 ounces) are at risk of vitamin E deficiency.

Blood levels of vitamin E may also be decreased with zinc deficiency

Therapeutic uses:

- Supplemental doses in patients at risk (10-30mg/day).
- G-6-PD deficiency – prolonged treatment with 100mg/day increase survival time of erythrocytes.
- Acanthocytosis-100mg/week i.m. normalize fragility of erythrocytes.
- Hypervitaminosis E
- Cytotoxic effect on human lymphocyte.
- Creatinurea and impaired wound healing may be seen.
- Lethargy and loose motion as side effects may be seen.

Vitamin E can interfere with ion therapy.

Current marketed preparations:

Evion 30, 100, 200, 400, 600 mg pearls, 50mg/ml paed. drops.

Tocofer, 100, 200, 400, mg pearls.

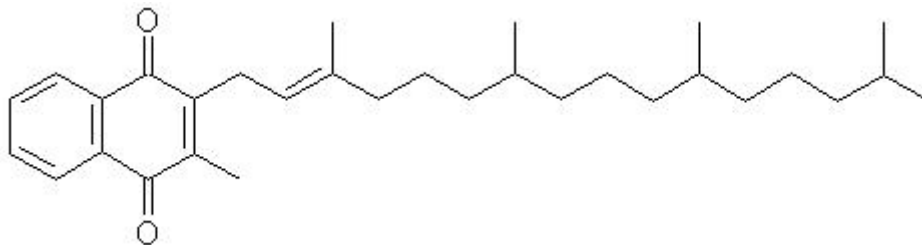
Ephynal 10 mg tab, 100mg/2ml inj

Vitamin K

Vitamin K is a fat-soluble vitamin. The "K" is derived from the German word "koagulation". Coagulation refers to blood clotting, because vitamin K is essential for the functioning of several proteins involved in blood clotting.

Vitamin K occurs in two major forms- Plants synthesize phyloquinone, also known as vitamin K₁. Bacteria synthesize a range of vitamin K forms, using repeating 5-carbon units in the side chain of the molecule. These forms of vitamin K are designated as menaquinone-n (MK-n), where n stands for the number of 5-carbon units. MK-n is collectively referred to as vitamin K₂.

Vitamin K is a necessary participant in synthesis of several proteins that mediate both coagulation and anticoagulation. Vitamin K deficiency is manifested as a tendency to bleed excessively. The daily requirement of vitamin K for an adult man is about 0.03 mg/kg.



Chemical Structure of Vitamin K₁ (Phylloquinone)
Chemical Formula: C₃₁H₄₆O₂

Sources of Vitamin K: Vitamin K₁ is found in a number of foods, including green leafy vegetables, cauliflower and liver. However, the chief source of vitamin K₂ is synthesis by bacteria in the large intestine, and in most cases, absence of dietary vitamin K is not at all deleterious. Vitamin K is a fat-soluble vitamin and both dietary and microbial vitamin K is absorbed into intestinal lymph along with other lipids. The foetus obtains vitamin K from its mother by transplacental transfer.

Physiological Role of Vitamin K: The role of vitamin K is to stimulate the production and/or release of certain coagulation factors. Vitamin K serves as an essential cofactor for a carboxylase that catalyzes carboxylation of glutamic acid residues on vitamin K-dependent proteins. The key vitamin K-dependent proteins include:

- Coagulation proteins: factors II (prothrombin), VII, IX and X
- Anticoagulation proteins: proteins C, S and Z
- Others: bone proteins osteocalcin and matrix-Gla protein, and certain ribosomal proteins

These proteins have in common the requirement to be post-translationally modified by carboxylation of glutamic acid residues (forming gamma-carboxyglutamic acid) in order to become biologically active. Prothrombin, for example, has 10 glutamic acids in the amino-terminal region of the protein which are carboxylated. Without vitamin K, the

carboxylation does not occur and the proteins that are synthesized are biologically inactive.

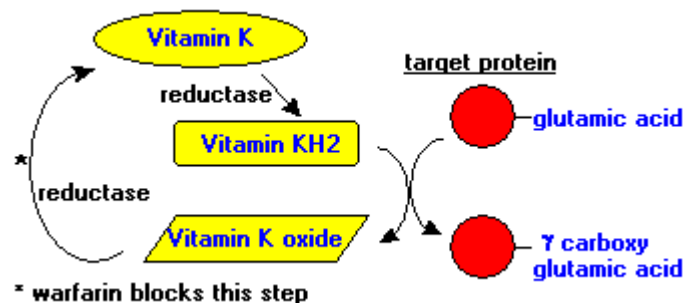
What essential function do gamma-carboxyglutamic acid residues endow upon a protein? There appear to be two major effects:

- First, they enable the protein to bind to membrane surfaces. Much of blood clotting is a result of blood-clotting proteins assembling into a complex on the membranes of platelets and endothelial cells; within these complexes, the factors can efficiently contact one another to become activated and participate in clot formation. Additionally, calcium is necessary for the blood clotting reaction. The proposed mechanism involving carboxylation is that gamma-carboxyglutamic acid residues strongly chelate calcium, and positively-charged calcium forms ion bridges to negatively-charged phosphate head groups of membrane phospholipids.
- Second, gamma-carboxyglutamic acid groups appear to participate in forming the necessary structure of such proteins by forming calcium-mediated intrachain interactions that link two gamma-carboxyglutamic acids to a calcium ion (similar to disulfide bridges, but much shorter).

As a cofactor to the carboxylase that generates gamma-carboxyglutamic acid, Vitamin K undergoes a cycle of oxidation and reduction that allows its reuse. The essential details of this cycle are:

- Vitamin K (usually K1) is reduced to vitamin KH₂.
- Oxygenation of vitamin KH₂ provides the energy to drive the carboxylation reaction, leading to formation of gamma-carboxyglutamic acid residues and vitamin K oxide.

Vitamin K oxide is reduced by another reductase back to vitamin K, ready to enter another cycle. Anticoagulants such as Warfarin block the reduction of vitamin K oxide to vitamin K, explaining their antagonistic effects on this cycle.



Deficiency of Vitamin K: Overt vitamin K deficiency results in impaired blood clotting, usually demonstrated by laboratory tests that measure clotting time. Symptoms include easy bruising and bleeding that may be manifested as nosebleeds, bleeding gums, blood in the urine, blood in the stool, tarry black stools, or extremely heavy menstrual bleeding.

In infants, vitamin K deficiency may result in life-threatening bleeding within the skull (intracranial hemorrhage)

Current marketed preparations:

Vitamin K, 10mg/ml inj.

Synkavit, 5 mg tab, 10mg/ml inj.

Kapilin, 10 mg tab.

Acetomenadiones, 5, 10 mg tab

Water Soluble Vitamins

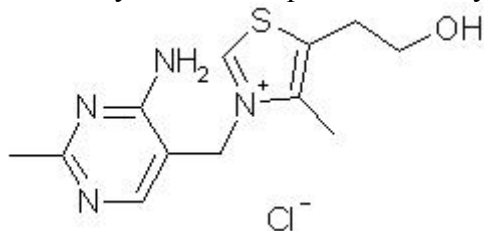
Vitamin B Complex

Vitamin B complex is water soluble vitamins. It includes following compounds:

- Vitamin B1 (Thiamine)
- Vitamin B2 (Riboflavin)
- Vitamin B3 (Niacin)
- Vitamin B6 (Pyridoxine)
- Vitamin B12 (Cyanocobalamine)

Vitamin B₁ (Thiamine)

Thiamine exists in tissues, mostly in the form of thiamine pyrophosphate (TPP), also known as coenzyme B₁. It is required for the synthesis of acetylcholine.



Chemical Structure of Vitamin B1 (thiamine hydrochloride)

Chemical Formula: C₁₂H₁₇N₄OS⁺

Sources of thiamine:

- Occurs in all natural foods, in small amounts.
- Whole grain cereals, wheat, gram, yeast, pulses, oil seeds and nuts, especially groundnuts are rich sources of vitamin B1.
- Meat, fish, eggs, vegetables & fruits contain smaller amounts.
- Cereals (rice and wheat) are main sources for individuals taking normal diet.
- Thiamine is lost from the rice during milling, washing and cooking the rice. It is also lost from the fruits and vegetables after long storage.

Physiological role:

- Thiamine is essential for the utilization of carbohydrates as a co-factor.

- Thiamine pyrophosphate (TPP) or carboxylase plays a role in activating transketolase, enzyme involved in direct oxidative pathway for glucose.
- Thiamine is also required for the synthesis of acetylcholine, which is a main component for nerve conduction.

Deficiency of Thiamine: The two principle deficiency diseases are beri beri and wernick's encephalopathy.

Beri-beri: it may be either- dry or wet.

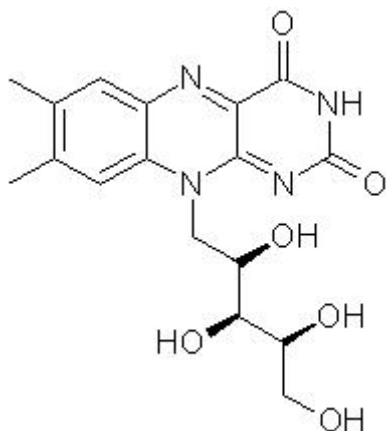
- Dry Beriberi- characterized by neurological symptoms like Polyneuritis with numbness, tingling, hyperesthesia, muscular weakness and atrophy resulting in 'wrist drop', 'foot drop', mental changes, poor memory, loss of appetite and constipation is seen.
- Wet Beriberi- Characterized by cardiovascular symptoms. Palpitations, breathlessness, high output cardiac failure and ECG changes may be seen.

Wernick's encephalopathy: - occasionally seen, often in alcoholics, characterized by ophthalmoplegia, polyneuritis, ataxia and mental deterioration.

Management: Beriberi is treated with 10 mg of thiamine per day orally. In a case of cardiac failure parenteral thiamine is used.

Vitamin B2 (Riboflavin)

Riboflavin was the first B complex component to be isolated in pure state. It is synthesized by all green plants and most microorganisms. It is synthesized in the human body by the intestinal flora and is easily absorbed, although very small quantities are stored, so there is a constant need for this vitamin. It is absorbed from small intestine through portal vein and is passed to all tissue by general circulation.



Chemical Structure of Riboflavin (Vitamin B2)

Chemical Formula: $C_{17}H_{20}N_4O_6$

Sources:

- Richest natural source are milk, eggs, liver, kidney and green leafy vegetables.
- Meat and fish contain small amounts.
- Cereals and pulses also contain smaller amounts, but germination increases the riboflavin contents.

Physiological role: It is required by the body to use oxygen and the metabolism of amino acids, fatty acids, and carbohydrates. Riboflavin is further needed to activate vitamin B6 (pyridoxine), helps to create niacin and assists the adrenal gland. It may be used for red blood cell formation, antibody production, cell respiration, and growth.

It eases watery eye fatigue and may be helpful in the prevention and treatment of cataracts. Vitamin B₂ is required for the integrity of the mucus membranes in the digestive tract and helps with the absorption of iron and vitamin B₆. Although it is needed for periods of rapid growth, it is also needed when protein intake is high, and is most beneficial to the skin, hair and nails.

Deficiency of Riboflavin: A shortage of this vitamin may manifest itself as cracks and sores at the corners of the mouth, eye disorders, inflammation of the mouth and tongue, and skin lesions.

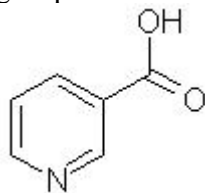
Dermatitis, dizziness, hair loss, insomnia, light sensitivity, poor digestion, retarded growth, and slow mental responses have also been reported. Burning feet can also be indicative of a shortage.

RDA (Recommended daily allowance): Male 1- 6 mg per day and female 1.2 mg per day although 50 mg is mostly recommended for supplementation.

Vitamin B2 Toxicity: The limited capacity to absorb orally administered riboflavin precludes its potential for harm. Riboflavin intake of many times the RDA is without demonstrable toxicity. A normal yellow discoloration of the urine is seen with an increased intake of this vitamin - but it is normal and harmless.

Vitamin B₃ (Niacin)

Niacin also called nicotinic acid, niacinamide or nicotinic acid and referred to as vitamin B₃, which can be manufactured by the body. Niacin is derived from two compounds - nicotinic acid and niacinamide. This vitamin differs from the other vitamins of B complex group in that an essential amino acid, tryptophan serves as its precursor.



Chemical Structure of Nicotinic Acid

Chemical Formula: C₆H₅NO₂

Sources:

- Liver, kidney, meat, poultry, fish, legumes and groundnuts are the rich source of niacin.
- Milk is poor source, but their proteins are rich in tryptophan, which is converted in the body in niacin.
- In cereals it occurs in bound form, so usually unavailable.

Physiological role: Vitamin B₃ is required for cell respiration, helps in the release of energy and metabolism of carbohydrates, fats, and proteins, proper circulation and healthy skin, functioning of the nervous system, and normal secretion of bile and stomach fluids. It is used in the synthesis of sex hormones, treating schizophrenia and other mental illnesses, and a memory-enhancer.

Nicotinic acid (but not nicotinamide) given in drug dosage improves the blood cholesterol profile, and has been used to clear the body of organic poisons, such as certain insecticides. People report more mental alertness when this vitamin is in sufficient supply.

Deficiency of Niacin: A deficiency may cause pellagra, the classic niacin deficiency disease, and is characterized by bilateral dermatitis, diarrhea, and dementia. A shortage of niacin may be indicated with symptoms such as canker sores, depression, diarrhea, dizziness, fatigue, halitosis, headaches, indigestion, insomnia, limb pains, loss of appetite, low blood sugar, muscular weakness, skin eruptions, and inflammation.

RDA (Recommended daily allowance): Male 18 mg per day and female 13 mg per day although 100 mg is mostly used in supplementation.

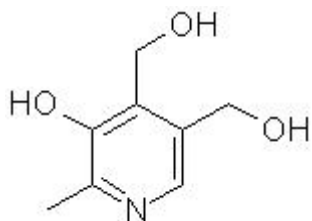
Vitamin B₃ Toxicity:

- Large doses given to lower cholesterol may produce hyperuricemia, and hepatic abnormalities. These effects are reversed if the drug is reduced in amount or discontinued.
- Nicotinic acid, but not nicotinamide in doses larger than 200 mg causes flushing by dilating the blood vessels, which can also cause the blood pressure to drop.
- These flushes are normally harmless. Large dosages can also cause itching, elevated blood glucose, peptic ulcers and liver damage.

Vitamin B₆ (Pyridoxine)

Vitamin B₆, also known as pyridoxine is part of the B group vitamins and is water-soluble and is required for both mental and physical health. It exists in three forms: Pyridoxine, pyridoxal and pyridoxamine.

Sources: It is widely distributed in food. Liver, meat, fish, yeast, cereals and legumes are rich sources of pyridoxime.



Chemical Structure of Pyridoxol (Pyridoxine)

Chemical Formula: $C_8H_{11}NO_3$

Physiological role:

- Pyridoxine is required for the balancing of hormonal changes in women as well as assisting the immune system and the growth of new cells. It is also used in the processing and metabolism of proteins, fats and carbohydrates, while assisting with controlling the mood as well as behavior. Pyridoxine might also be of benefit for children with learning difficulties, as well as assisting in the prevention of dandruff, eczema and psoriasis.
- It assists in the balancing of sodium and potassium as well promotes red blood cell production. It is further involved in the nucleic acids RNA as well as DNA synthesise. It is further linked to cancer immunity and fights the formation of the toxic chemical homocysteine, which is detrimental to the heart muscle.
- Women in particular may suffer from pre-menstrual fluid retention, severe period pains, emotional PMS symptoms, premenstrual acne and nausea in early pregnancy. Mood swings, depression as well as loss of sexual drive is sometimes noted when pyridoxine is in short supply and the person is on hormone replacement therapy or on birth control pills.

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Deficiency of vitamin B₆:

- Irritability, nervousness and insomnia as well as general weakness, skin changes such as dermatitis and acne as well asthma and allergies might develop when pyridoxine is in short supply. Symptoms may include nails that are ridged, an inflamed tongue as well as changes to your bones - which can include osteoporosis and arthritis. Kidney stones may also appear.
- Vitamin B₆ deficiency symptoms will be very much like those of B₂ and B₃. Vitamin B₆ is needed by the body to manufacture its own vitamin B₃.

RDA (Recommended daily allowance): Males 2 mg per day and females 2 mg per day.

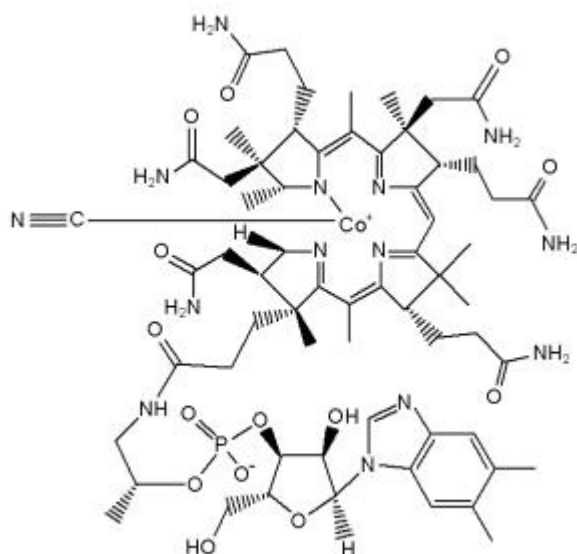
Vitamin B₆ Toxicity:

- Supplementation should be controlled as extreme dosage, such as in excess of 2,000 mg per day, may cause neurological damage.
- People on medication for Parkinson's disease should be careful about taking Vitamin B₆ as it can inactivate levodopa.
- People taking pyridoxine late at night sometimes experience very vivid dreams

Vitamin B₁₂ (Cobalamine)

Vitamin B₁₂, known as cyanocobalamin, cobolamin and also known as the energy vitamin is a very widely researched vitamin, and used in supplementation to a very large degree.

This complex structured compound with its cobalt content forms part of the B group vitamins, and the body needs very small amounts.



Chemical Structure of Vitamin B₁₂

Chemical formula of Vitamin B₁₂ - C₆₃H₈₈CoN₁₄O₁₄P

Sources:

- It is present in only the foods of animal origin. It is not found in the foods of vegetable origin
- Liver, kidney, eggs, fish, milk and cheese are the rich sources of vitamin B₁₂.
- It is also synthesized by bacteria in colon

Physiological role: Cobolamin is needed in the synthesis of red blood cells and the maintenance of red blood cells and it stimulates appetite, promotes growth and release energy. It is often used with older people to give an energy boost, assist in preventing mental deterioration and helps with speeding up thought processes. Some people are also of the opinion that it helps with clearing up infections and provide protection against allergies and cancer. This vitamin is also used in the metabolism of fats, proteins and carbohydrates.

Deficiency of vitamin B₁₂:

- Some symptoms of a deficiency will include a sore tongue, weakness, fatigue, and weight loss, back pain and apathy. It might further result in loss of balance, decreased reflexes, tingling of the fingers, ringing in the ears etc.

- A deficiency may also result in the raising of the level of homocysteine in the blood - which in high doses can be toxic to the brain, which may be involved in Alzheimer disease. Severe deficiency may result in pernicious anemia also called Addisonian pernicious anemia.
- Another problem that appears in deficiency is the eroding of the myelin sheath - the fatty sheath of tissue, which insulates the nerve fibers in your body.

RDA (Recommended daily allowance):

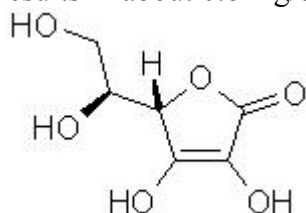
Male and female 3 mcg per day

Vitamin B₁₂ Toxicity: Toxicity not established but people taking vitamin B12 injections may experience skin problems if in large excess, but will normalize once the injections are stopped.

Vitamin C

Vitamin C is a water soluble vitamin. It is most sensitive vitamin, to heat, of all vitamins. Man, monkey and guinea pig are the only species known to require Vitamin C in their diet.

It is generally known as ascorbic acid. It is nearly, completely absorbed from GI (gastrointestinal) tract and widely distributed, extra and intracellularly. Usual 60 mg/day intake results in about 0.8 mg/dl in plasma and 1.5 gm in body as a whole.



Chemical Structure of Ascorbic Acid

Chemical Formula of Ascorbic acid - C₆H₈O₆

Sources:

- Citrus fruits and vegetables including tomatoes, cabbage, leafy greens and germinating pulses are the rich sources of vitamin C
- Large quantities of vitamin C are also found in liver and kidney.
- Traces of vitamin C occur in fresh meat and fish, but scarcely in any cereals.
- Amla and Indian gooseberry is one of the richest sources of vitamin C, both in fresh as well as in dry conditions.
- Guavas are another cheap but rich source of Vitamin C.
- But cooking can destroy the Vitamin C.

Physiological role:

- Vitamin C is required in the synthesis of collagen in connective tissue, neurotransmitters, steroid hormones, carnitine, conversion of cholesterol to bile acids

and enhances iron bioavailability. Ascorbic acid is a great antioxidant and helps protect the body against pollutants.

- Because vitamin C is a biological reducing agent, it is also linked to prevention of degenerative diseases - such as cataracts, certain cancers and cardiovascular diseases.
- Ascorbic acid also promotes healthy cell development, proper calcium absorption, normal tissue growth and repair - such as healing of wounds and burns. It assists in the prevention of blood clotting and bruising, and strengthening the walls of the capillaries.
- Vitamin C is needed for healthy gums, to help protect against infection, and assisting with clearing up infections and is thought to enhance the immune system and help reduce cholesterol levels, high blood pressure and preventing arteriosclerosis.

RDA (Recommended daily allowance):

Infants	-- 30 mg/day
Premature babies	-- 40 mg/day
Adult male	-- 60 mg/day
Pregnant & lactating women	-- 75-90 mg/day

Deficiency of vitamin C: When there is a shortage of vitamin C, various problems can arise, although scurvy is the only disease clinically treated with vitamin C. However, a shortage of vitamin C may result in "pinpoint" hemorrhages under the skin and a tendency to bruise easily, poor wound healing, soft and spongy bleeding gums and loose teeth.

Edema (water retention) also happens with a shortage of vitamin C, and weakness, a lack of energy, poor digestion, painful joints and bronchial infection and colds are also indicative of an under-supply

Deficiency treatment: Ascorbic acid 100-300 mg/day provides quick relief.

Therapeutic uses:

- Treatment of scurvy- 0.5-1.5 g/day.
- Postoperatively – 500 mg/day.
- Anemia: Ascorbic acid enhances iron absorption.

Vitamin C Toxicity: Excess is eliminated mostly through urine. If extremely large amounts are taken gastrointestinal problems may appear, but will normalize when the intake is cut or reduced. To determine a level where a person might experience discomfort is difficult, since some people can easily stomach up to 25,000 mg per day, while others start having a problem at 600 or 1,000 mg.

Some people using mega dose therapy of vitamin C may have side effects such as gastrointestinal complaints including diarrhea, nausea and abdominal cramps. These side effects normally stop as soon as high potency intake is reduced or stopped.