Chapter-15 Fat Soluble Vitamins

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Damodaran Vasudevan
Amrita Institute of Medical Sciences and Research Centre
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Chapter 32

Fat Soluble Vitamins (A, D, E and K)

Chapter at a Glance

The learner will be able to answer questions on the following topics:

- ❒ Vitamin A
- ❒ Wald's visual cycle
- ❒ Deficiency of vitamin A
- ❒ Vitamin D
- ❒ Deficiency of vitamin D
- ❒ Vitamin E
- ❒ Vitamin K

Vitamins may be defined as organic compounds occurring in small quantities in different natural foods and necessary for growth and maintenance of good health in human beings. Vitamins are essential food factors, which are required for the proper utilization of the proximate principles of food like carbohydrates, lipids and proteins. "A vitamin is a substance that makes you ill if you don't eat it" (Albert Szent-Györgyi, Nobel Prize winner, 1937)

Discovery of vitamins started from observation of deficiency manifestations, e.g. scurvy, rickets, beriberi, etc. The vitamin theory was suggested by Hopkins in 1912 (Nobel Prize, 1929). The term "vitamine" was coined from the words vital + amine, since the earlier identified ones had amino groups. Later work showed that most of them did not contain amino groups, so the last letter 'e' was dropped in the modern term of vitamin.

The vitamins are mainly classified into two:

1. The fat soluble vitamins are A, D, E and K
2. Water soluble vitamins are named as B complex and C. The major differences between these two groups of vitamins are given in Table 32.1.

TABLE 32.1: Comparison of two types of vitamins.

	Fat soluble vitamins	*Water soluble vitamins*
Solubility in fat	Soluble	Not soluble
Water solubility	Not soluble	Soluble
Absorption	Along with lipids Requires bile salts	*Absorption simple
Carrier proteins	Present	*No carrier proteins
Storage	Stored in liver	*No storage
Excretion	Not excreted	Excreted
Deficiency	Manifests only when stores are depleted	*Manifests rapidly as there is no storage
Toxicity	Hypervitaminosis may result	Unlikely, since excess is excreted
Treatment of deficiency	Single large doses may prevent deficiency	Regular dietary supply is required
Major vitamins	A, D, E and K	B and C

*Vitamin B_{12} is an exception.

VITAMIN A

McCollum, Simmonds and Kennedy isolated vitamin A in 1913. Richard Kuhn (Nobel Prize, 1938) identified

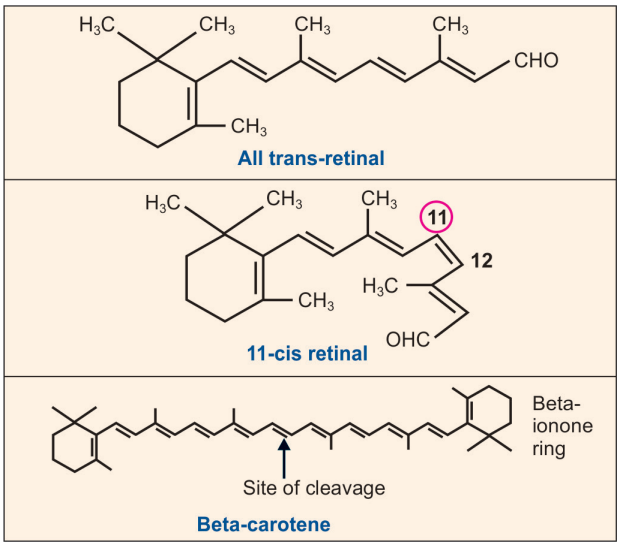


Fig. 32.1: Structure of vitamin A

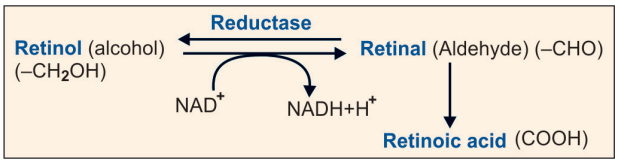


Fig. 32.2: Interconversion of vitamin A molecules

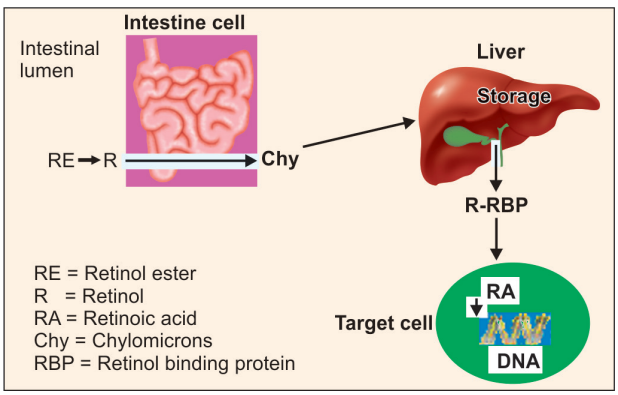


Fig. 32.3: Vitamin A metabolism

carotenes. Paul Karrer in 1931 elucidated the structure of vitamin A_1 (Nobel Prize, 1937).

Chemistry

Vitamin A is fat soluble. The active form is present only in animal tissues. The **provitamin**, beta-carotene is present in plant tissues. **Beta-carotene** has two beta ionone rings (Fig. 32.1). All the compounds with vitamin A activity are referred to as **retinoids**. They have **beta-ionone** (cyclohexenyl) ring system. Three different compounds with vitamin A activity are retinol (vitamin A alcohol), **retinal** (vitamin A aldehyde) and **retinoic acid** (vitamin A acid) (Fig. 32.1). The retinal may be reduced to retinol by retinal reductase. This reaction is readily reversible. Retinal is oxidized to retinoic acid, which cannot be converted back to the other forms (Fig. 32.2). The side chain contains alternate double bonds, and hence many isomers are possible. The **all-trans** variety of retinal, also called **vitamin A_1** is most common (Fig. 32.1). Vitamin A_2 is found in *fish oils* and has an extra double bond in the ring. Biologically important compound is **11-cis-retinal**.

Absorption of Vitamin A

Beta carotene is cleaved by a di-oxygenase, to form retinal. The retinal is reduced to retinol by retinal reductase present in the intestinal mucosa. Intestine is the major site of absorption (Fig. 32.3). The absorption is along with other fats and requires bile salts. Vitamin is incorporated into chylomicrons and transported to liver. In the liver, vitamin is stored as **retinol palmitate**.

Transport from Liver to Tissues

The vitamin A from liver is transported to peripheral tissues as trans-retinol by the **retinol binding protein** or RBP. In the case of vitamin A deficiency, the RBP level in blood falls.

Uptake by Tissues

The retinol-RBP complex binds to specific receptors on the retina, skin, gonads and other tissues. Vitamin binds

Frederick G Hopkins	*Richard Kuhn*	*Paul Karrer*	*Otto P Diels*	*Kurt Alder*
NP 1929	*NP 1938*	*NP 1937*	*NP 1950*	*NP 1950*
1861–1947	*1900–1967*	*1889–1971*	*1876–1954*	*1902–1958*

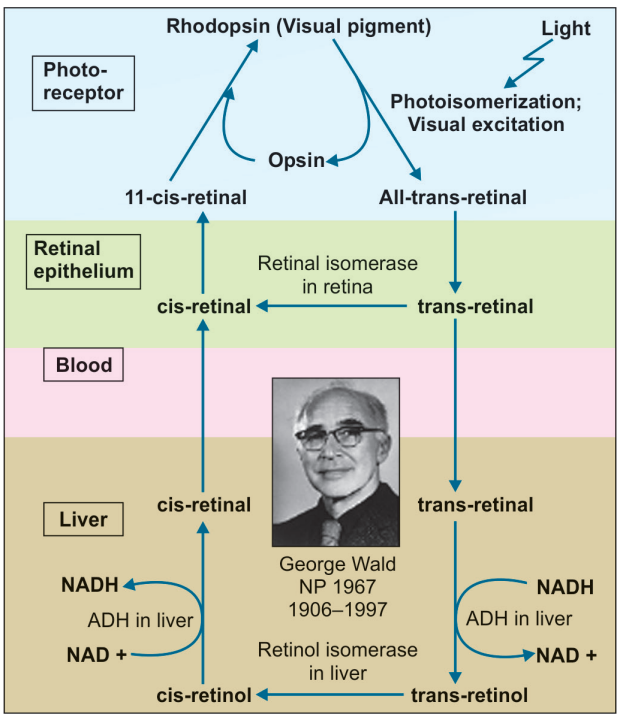


Fig. 32.4: Wald's visual cycle. Blue color represents reactions in photoreceptor matrix. Green background represents reactions in retinal pigment epithelium. Red depicts blood. Brown shows reactions in liver

to cellular retinoic acid binding protein (CRBP) and finally to hormone responsive elements (HRE) of DNA. Thus genes are activated (Fig. 32.3).

Biochemical Role of Vitamin A

Wald's Visual Cycle

Generation of Nerve Impulse: Wald was awarded Nobel Prize in 1967, for identifying the role of vitamin A in vision. **Rhodopsin** is a membrane protein found in the photoreceptor cells of the retina. Rhodopsin is made up of the protein **opsin and 11-cis-retinal**. When light falls on the retina, the 11-cis-retinal isomerizes to **all-trans-retinal** (Fig. 32.4). The photon produces immediate conformational change so as to produce opsin + all-trans-retinal. The all-trans- retinal is then released from the protein.

Visual pigments are G-protein-coupled receptors. The 11-cis retinal locks the receptor protein (opsin) in its inactive form (Fig. 32.5). The isomerization and

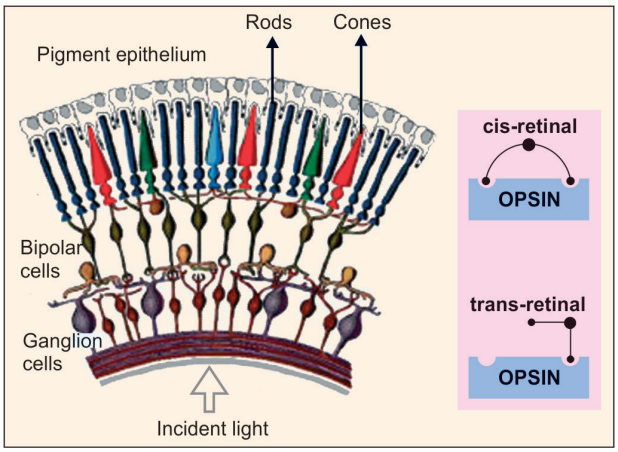


Fig. 32.5: Structure of retina showing rods and cones. The inset on right side shows the structural alteration during photo-isomerization

photo-excitation leads to activation of G-protein and generation of cyclic-GMP. **Transducin** is the G-protein in retina. The Cyclic GMP generates a nerve impulse in the retina which is transmitted to visual centers in the brain.

Regeneration of 11-cis-retinal: After dissociation, opsin remains in retina; but transretinal enters the blood circulation (Fig. 32.4). Later cis-retinal is generated, reaches retina. The all-trans-retinal is isomerized to 11-cis-retinal in the retina itself in the dark by the enzyme **retinal isomerase.** The 11-cis retinal can recombine with opsin to regenerate rhodopsin. Alternatively, all-trans-retinal is transported to liver and then reduced to all-trans-retinol by **alcohol dehydrogenase** (ADH), an NADH dependent enzyme. The all-trans-retinol is isomerized to 11-cis-retinol and then oxidized to 11-cis-retinal in liver. This is then transported to retina. This completes the Wald's visual cycle (Fig. 32.4).

Dark Adaptation Mechanism

For their work on information processing in visual pathways, Torsten Wiesel and David Hubel were awarded Nobel Prize in 1981. Rods and Cons are diagrammatically represented in Figure 32.5.

Bright light depletes stores of rhodopsin in rods. Therefore, when a person shifts suddenly from bright light to a dimly lit area, there is difficulty in seeing, for example, entering a cinema theater. After a few minutes,

rhodopsin is resynthesized and vision is improved. This period is called **dark adaptation time**. It is increased in vitamin A deficiency. Red light bleaches rhodopsin to a lesser extent; so doctors use tinted glasses, during fluoroscopic X-ray examination of the patients.

Rods are for Vision in Dim Light

In the retina, there are two types of photosensitive cells, the rods and the cones. Rods are responsible for perception in dim light. Rhodopsin present in rods is made up of 11-cis-retinal + opsin. Deficiency of cis-retinal will lead to increase in dark adaptation time and night blindness.

Cones are for Color Vision

Cones are responsible for vision in bright light as well as color vision. They contain the photosensitive protein, **conopsin**. There are 3 types of cones, sensitive to blue, green or red colors. In cone proteins also, 11-cis-retinal is the chromophore. Reduction in number of cones or the cone proteins, will lead to **color blindness**.

Colors have Profound Influence in Life

About 70% of information inputs to the brain are visual. The optimists view the world through "rose-colored" eyes. When sad, a person is in a "blue" mood. Saffron color has tranquilizing effect, especially in agitated persons. Even a brief display of saffron color produces measurable relaxation in muscles. Blue color, although makes one peaceful and content, increases the muscle tone. Mice living in red light are most active, while in green light, they are least active. The effects of colors on human moods have applications in psychiatry, interior decoration and Yoga.

Other Biochemical Functions of Vitamin A

i. Retinoic acid has a role in the regulation of gene expression and **differentiation** of tissues. Retinoic acid acts like steroid hormones.
ii. Vitamin A is required for normal **reproduction**. In vitamin A deficiency, miscarriages are noticed in female rats.
iii. The anticancer activity has been attributed to the natural antioxidant property of **carotenoids**. Fresh vegetables containing carotenoids were shown to reduce the incidence of cancer.
iv. Vitamin A is necessary for the maintenance of normal epithelium and skin (*see* Fig. 32.6).

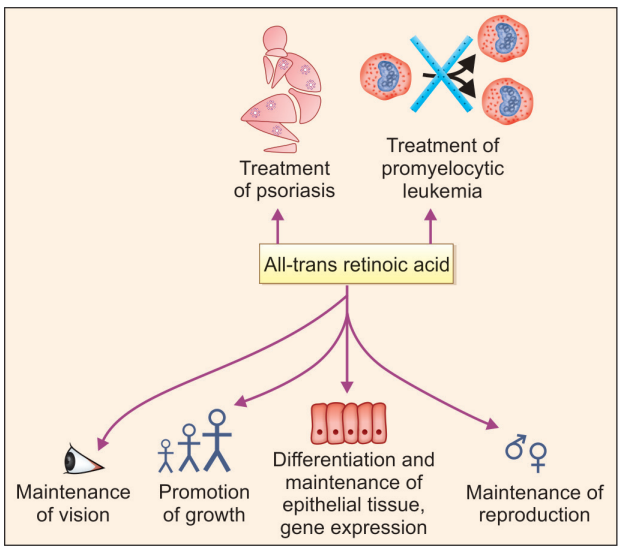


Fig. 32.6: Summary of actions of vitamin A

Deficiency Manifestations of Vitamin A

Night Blindness or Nyctalopia

Visual acuity is diminished in dim light. The patient cannot read or drive a car in poor light. The dark adaptation time is increased.

Xerophthalmia

The conjunctiva becomes dry, thick and wrinkled. The conjunctiva gets keratinized and loses its normal transparency. Dryness spreads to cornea. It becomes glazy and lusterless due to keratinization of corneal epithelium. Infections may supersede.

Bitot's Spots

These are seen as grayish-white triangular plaques firmly adherent to the conjunctiva. This is due to increased thickness of conjunctiva in certain areas. All the ocular changes mentioned so far are completely reversible when vitamin is supplemented.

Fig. 32.7: Keratomalacia

Keratomalacia

When the xerophthalmia persists for a long time, it progresses to keratomalacia (softening of the cornea). There is degeneration of corneal epithelium which may get vascularized. Later, corneal opacities develop (Fig. 32.7). Bacterial infection leads to corneal ulceration, perforation of cornea and total blindness.

Preventable Blindness

The deficiency of vitamin A is the most common cause of blindness in Indian children below the age of 5. One third of the world's blind population is residing in India. About 40% of blindness is preventable. Vitamin A deficiency is a major public health problem. A single dose of vitamin A is given, as a prophylactic measure, to children below 1 year age.

Skin and Mucous Membrane Lesions

i. Follicular **hyperkeratosis** or phrynoderma results from hyperkeratinization of the epithelium lining the follicles. The skin becomes rough. Keratinizing metaplasia of the epithelium of the respiratory, gastro-intestinal and genitourinary tracts have been observed.
ii. The alterations in skin may cause increased occurrence of generalized **infections**. Therefore in old literature, vitamin A is referred to as anti-inflammatory vitamin.
iii. Isoretinone, a synthetic variant of vitamin A is known to reduce the sebaceous secretions, hence it is used to prevent **acne** formation during adolescence.

Fig. 32.8: A parady of the old proverb is "One carrot a day will keep the Ophthalmologist away". Papaya, carrot and mango are good sources of Vitamin A precursors

Causes for Vitamin A Deficiency

i. Decreased intake.
ii. Obstructive jaundice causing defective absorption.
iii. Cirrhosis of liver leading to reduced synthesis of RBP
iv. Severe malnutrition, where amino acids are not available for RBP synthesis.
v. Chronic nephrosis, where RBP is excreted through urine.

Assessment of Deficiency

a. Dark adaptation test— It is the time required to adapt the eye to see objects in dim light. It is increased in vitamin A deficiency.
b. RBP (retinol binding protein) level in serum is decreased. (*see* Table 26.1).
c. Vitamin A in serum is decreased.
d. **Normal blood level** of vitamin A is 25 to 50 mg/dL.

Daily Requirement of Vitamin A

The recommended daily allowance (RDA) for

i. Children = 400–600 mcg/day
ii. Men = 750–1000 mcg/day
iii. Women = 750 mcg/day
iv. Pregnancy = 1000 mcg/day

One international unit = 0.3 mcg of retinol. One retinol equivalent = 1 microgram of retinol or 6 microgram of beta carotene.

Dietary Sources of Vitamin A

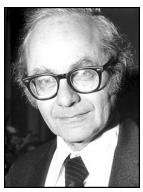
Animal sources include milk, butter, cream, cheese, egg yolk and liver. Fish liver oils (cod liver oil and shark liver oil) are very rich sources of the vitamin. Vegetable sources contain the yellow pigment beta carotene. **Carrot** contains significant quantity of beta carotene (Fig. 32.8). **Papaya**, **mango**, pumpkins, green leafy vegetables

(spinach, amaranth) are other good sources for vitamin A activity. During cooking the activity is not destroyed.

Therapeutic use of Vitamin A

Therapeutic dose is generally 20–50 times higher than the RDA.

Torsten Wiesel
NP 1981
b. 1924



David Hubel
NP 1981
1926 - 2013

Hypervitaminosis A or Toxicity

Excessive intake can lead to toxicity since the vitamin is stored. It has been reported in children where parents have been overzealous in supplementing the vitamins. Eskimos refrain from eating the liver of polar bear due to its high vitamin A content. Symptoms of toxicity include anorexia, irritability, headache, peeling of skin, drowsiness and vomiting.

Hypercarotenemia can result from persistent excessive consumption of foods rich in carotenoids. The skin becomes yellow, but no staining of sclera as in jaundice is observed.

VITAMIN D (CHOLECALCIFEROL)

Experimental rickets induced by dietary deficiency was produced in rats by McCollum in 1919. Angus and coworkers isolated vitamin D in 1931 and named it as calciferol, which was later identified as Vitamin D_3. The structural elucidation was done independently by Otto Diels and Kurt Alder. Both were awarded Nobel Prize in 1950.

Formation of Vitamin D

Vitamin D is derived either from 7-dehydrocholesterol or ergosterol by the action of ultraviolet radiations. **7-dehydrocholesterol**, a derivative of cholesterol, is present in epidermis. In the skin, ultraviolet light breaks the bond between position 9 and 10 of the steroid ring. So, the ring B is opened, to form the provitamin, **secosterol** (Fig. 32.9). The cis double bond between 5th and 6th carbon atoms, is then isomerized to a trans double bond (rotation on the 6th carbon atom) to give rise to vitamin D_3 or **cholecalciferol** (Fig. 32.9). So, vitamin D is called the **"sun-shine vitamin".**

The production of vitamin D in the skin is directly proportional to the exposure to sunlight and inversely proportional to the pigmentation of skin. Vitamin deficiency is seen in winter.

Commercially the vitamin is derived from the fungus, ergot. The ergosterol when treated with ultraviolet light, **ergocalciferol** or vitamin D_2 is produced. Ergocalciferol differs in having an unsaturation in the side chain and an extra methyl group (C28).

Activation of Vitamin D

Vitamin D is a **prohormone**. The cholecalciferol is first transported to liver, where hydroxylation at **25th position** occurs, to form 25-hydroxy cholecalciferol (25-HCC) (Fig. 32.10). 25-HCC is the major storage form. In

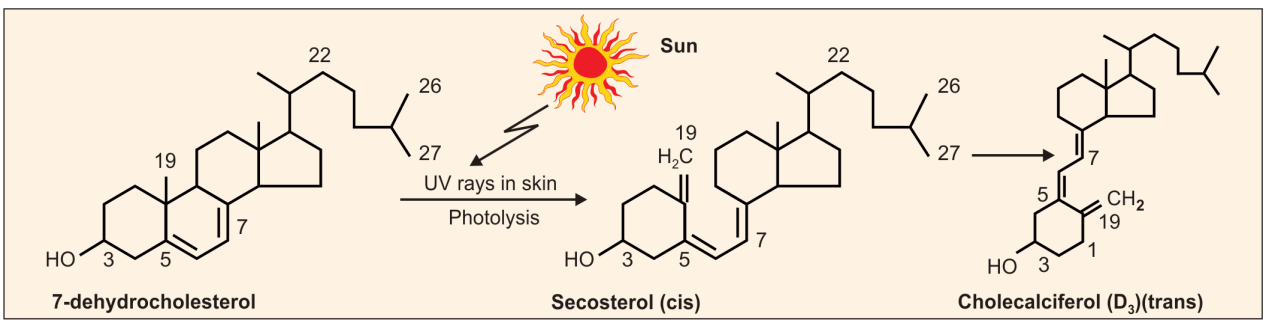


Fig. 32.9: Synthesis of cholecalciferol or vitamin D_3

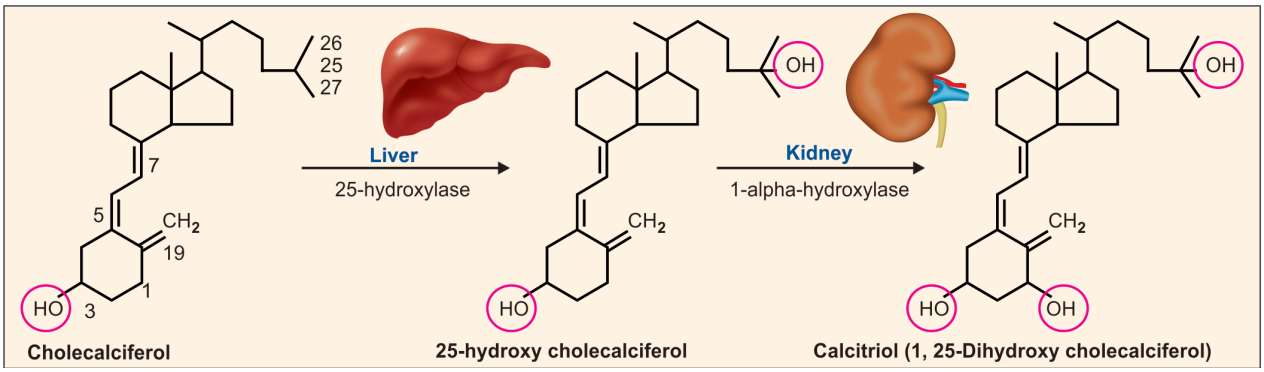


Fig. 32.10: Generation of calcitriol

BOX 32.1: Calcitriol and calcitonin are different

Calcitriol is the physiological active form of vitamin D. It increases the blood calcium level.

Calcitonin is the peptide hormone released from thyroid gland. It decreases the blood calcium.

plasma, 25-HCC is bound to "vitamin D binding protein" (VDBP). In the **kidney**, it is further hydroxylated at the **1st position**. Thus 1, 25-dihydroxy cholecalciferol **(DHCC)** is generated. Since it contains three hydroxyl groups at 1, 3 and 25 positions, it is also called **Calcitriol** (Fig. 32.10). The calcitriol thus formed is the **active form** of vitamin; it is a **hormone** (Box 32.1).

PTH is released in response to low serum calcium and induces the production of calcitriol. The calcitriol binds to its highly specific nuclear receptor VDR, which binds to VDRE (Vitamin D response elements) on DNA and modulates the expression of more than 500 genes. This activation takes place within minutes.

Biochemical Effects of Vitamin D

May be divided into calcemic and extracalcemic effects. Calcemic effects are exerted at—

a. Intestinal villous cells
b. Bone osteoblasts
c. Kidney distal tubular cells.

Vitamin D and Absorption of Calcium

Calcitriol promotes the absorption of calcium and phosphorus from the intestine. On the brush-border surface, calcium is absorbed passively. From the intestinal cell

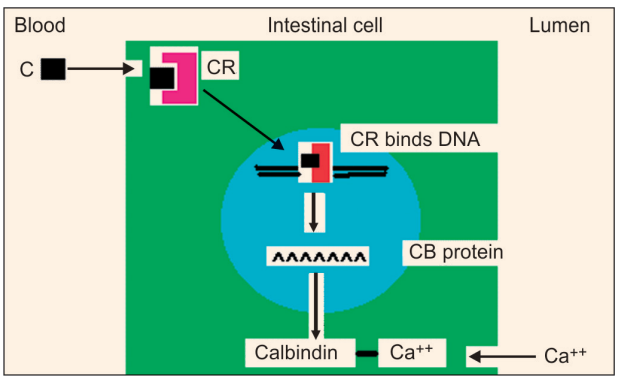


Fig. 32.11: Calcitriol increases calcium absorption
C = Calcitriol; R = Receptor; CR = Calcitriol receptor complex; CB = Calbindin.

to blood, absorption of calcium needs energy. **Calcitriol** acts like a steroid hormone. Transcriptional activation of specific genes that code for calbindin occurs (Fig. 32.11). Due to the increased availability of calcium binding protein, the absorption of calcium is increased.

Effect of Vitamin D on Bone

Mineralization of the bone is increased by increasing the activity of osteoblasts (*see* Chapter 34). Calcitriol coordinates the remodeling of bone and increases bone mineral density.

Intracellular production of calcitriol by osteoblasts promotes their differentiation and mineralization. Osteoclastic bone resorption and alkaline phosphatase activity of osteoblasts provide adequate calcium and phosphorus to promote mineralization.

Effect of Vitamin D on Renal Tubules

Calcitriol increases the reabsorption of calcium and phosphorus by renal tubules, therefore both minerals are conserved. (PTH conserves only calcium) (*see* Chapter 34).

Regulation of Calcitriol Formation by Feedback Control

The hormonal level of calcitriol is maintained by the feedback control. The rate of production is modulated by serum levels of calcium, phosphorus, PTH and calcitriol itself.

Deficiency of Vitamin D

The deficiency diseases are **rickets** in children and **osteomalacia** in adults. Hence vitamin D is known as antirachitic vitamin.

The optimal concentration of 25-hydroxy D_3 is > 30 ng/mL, where as 20–29 ng/mL is considered insufficient and 10–19 ng/mL is deficient. A level below 10 ng/mL indicates severe deficiency. (Concentrations more than 150 ng/mL is toxic).

Various studies have shown that 50–80% of elderly and 20–50% of children have hypovitaminosis D. Even in affluent countries, vitamin D deficiency is very common. Vitamin D deficiency was associated with poor bone health, low calcium concentration, higher systolic blood pressure and lower HDL cholesterol values; all of which are risk factors for heart disease.

Causes for Vitamin D Deficiency

i. Deficiency of vitamin D can occur in people who are not exposed to sunlight properly, e.g. inhabitants of northern latitudes, in winter months, in people who are bedridden for long periods, or those who cover the whole body *(purdah)*.
ii. Nutritional deficiency of calcium or phosphate may also produce similar clinical picture.
iii. Malabsorption of vitamin (obstructive jaundice and steatorrhea). High phytate content in diet may also reduce the absorption of vitamin.
iv. Abnormality of vitamin D activation. Liver and renal diseases may retard the hydroxylation reactions.
v. Deficient renal absorption of phosphates.

Clinical Features of Rickets

Rickets is seen in children. There is insufficient mineralization of bone. Bones become soft and pliable. The bone growth is markedly affected. The classical features of rickets are **bone deformities**. Weight bearing bones are bent. Continued action of muscles also cause bone malformations. The clinical manifestations include bow legs, knock-knee, rickety rosary, bossing of frontal bones, and pigeon chest. An enlargement of the epiphysis at the lower end of ribs and costochondral junction leads to beading of ribs or **rickety rosary. Harrison's sulcus** is a transverse depression passing outwards from the costal cartilage to axilla. This is due to the indentation of lower ribs at the site of the attachment of diaphragm.

Clinical Features of Osteomalacia

The term is derived from Greek "osteon" = bone; and "malakia" = softness. The bones are softened due to insufficient mineralization and increased osteoporosis. Patients are more prone to get fractures. It may be noted that vitamin D deficiency never produces severe hypocalcemia. Tetany will not be manifested. Serum **alkaline phosphatase**, bone isoenzyme, is markedly increased.

Different Types of Rickets

1. The classical vitamin D **deficiency** rickets can be cured by giving vitamin D in the diet.
2. **Vitamin D resistant** rickets is found to be associated with *Fanconi syndrome*, where the renal tubular reabsorption of bicarbonate, phosphate, glucose, and amino acids are also deficient.
3. **Renal rickets**: In kidney diseases, even if vitamin D is available, calcitriol is not synthesized. These cases will respond to administration of calcitriol.

Other Actions of Vitamin D

1,25-DHCC has been found to have a modulatory effect on immune-hematopoietic system. Therapeutic doses given to children with rickets have been found to correct the anemia. It has also been found to reduce the risk of cancer and coronary vascular disease. A negative correlation between IgE and vitamin D concentration; and

a positive relation between vitamin D and lung function were shown in children with asthma. Vitamin D insufficiency is associated with metabolic syndrome, insulin resistance and glucose intolerance.

Requirement of Vitamin D

i. Children = 10 mcg (400 IU)/day
ii. Adults = 5 to 10 mcg (200 IU)/day
iii. Pregnancy, lactation = 10 mcg/day
iv. Above the age of 60 = 600 IU per day.

Sources of Vitamin D

Exposure to **sunlight** produces cholecalciferol. Moreover, fish liver oil, fish and egg yolk are good sources of the vitamin. Milk contains moderate quantity of the vitamin. The current recommendation is to fortify dairy products with vitamin D and adequate exposure to sunlight without sunscreen before 10 am and after 3 pm at least 15 minutes a day (safe sun).

Hypervitaminosis D

Doses above 10,000 units per day for long periods may cause toxicity. Symptoms include weakness, polyuria, intense thirst, hypertension and weight loss. Hypercalcemia leads to calcification of soft tissues, (metastatic **calcification,** otherwise called **calcinosis**), especially in vascular and renal tissues. Although vitamin D is toxic in higher doses, excessive exposure to sunlight does not result in vitamin D toxicity, because excess D_3 is destroyed by sunlight itself.

VITAMIN E

The active vitamin was isolated from wheat germ oil and named tocopherol (*tokos* = child birth; *pheros* = to bear; *ol* = alcohol). Initial studies of induced vitamin E deficiency in laboratory animals resulted in infertility and therefore the vitamin came to be known as anti-infertility vitamin. Now vitamin E is known as the most potent biological antioxidant.

Chemical Nature

A chromane ring (tocol) system, with an isoprenoid side chain is present in all the eight naturally occurring

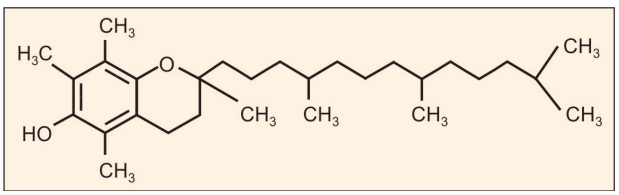


Fig. 32.12: Alpha tocopherol

tocopherols. Of these, **alpha tocopherol** (5, 7, 8-trimethyl tocol) has greatest biological activity (Fig. 32.12). The structure of vitamin E was elucidated by Paul Karrer, who was awarded Nobel Prize in 1937.

Biochemical Role of Vitamin E

i. Vitamin E is the **most powerful natural antioxidant** (*see* Chapter 30). Free radicals are continuously being generated in living systems. Their prompt inactivation is of great importance. Vitamin E is a known biological antioxidant able to quench the lipid peroxidation chain.
ii. The free radicals would attack bio-membranes. Vitamin E protects RBC from **hemolysis**. By preventing the peroxidation, it keeps the structural and functional integrity of all cells.
iii. Gradual deterioration of **aging** process is due to the cumulative effects of free radicals. Vitamin E also boosts immune response.
iv. It reduces the risk of atherosclerosis by reducing oxidation of LDL.

Inter-relationship with Selenium

Selenium is present in **glutathione peroxidase**; an important enzyme that oxidizes and destroys the free radicals (*see* Chapter 30). Selenium has been found to decrease the requirement of vitamin E and vice versa. They act synergistically to minimize lipid peroxidation. Selenium is described in Chapter 34.

Deficiency Manifestations of Vitamin E

In rats, inability to produce healthy ovum and loss of motility of spermatozoa, hemolysis of red cells, acute hepatic necrosis and muscular dystrophy are observed. In a normal adult, the body vitamin E stores can meet the requirement for several months.

No major disease states have been found to be associated with vitamin E deficiency due to adequate levels in the average diet. Vitamin E deficiency is seen in persons (a) who cannot absorb dietary fat, and (b) in premature infants (birthweight less than 1500 grams). Vitamin E deficiency causes neurological problems due to poor nerve conduction. These include neuromuscular problems such as spinocerebellar ataxia, retinopathy, peripheral neuropathy and myopathies. Deficiency can also cause anemia, due to oxidative damage to red blood cells.

Recommended Daily Allowance

Males: 10 mg per day
Females: 8 mg/day
Pregnancy: 10 mg/day
Lactation: 12 mg/day.
15 mg of vitamin E is equivalent to 33 international units. The requirement increases with higher intake of PUFA. Pharmacological dose is 200–400 IU per day.

Henrik Dam
NP 1943
1895–1976

Sources of Vitamin E

Vegetable oils are rich sources of vitamin E; e.g. wheat germ oil, sunflower oil, safflower oil, cotton seed oil, etc. Fish liver oils are devoid of vitamin E.

Edward Doisy
NP 1943
1893–1986

Hypervitaminosis E

At doses above 1000 IU per day, it may cause tendency to hemorrhage, as it is a mild anticoagulant.

VITAMIN K

Chemistry of Vitamin K

The letter "K" is the abbreviation of the German word "koagulation vitamin". They are **naphthoquinone** derivatives, with a long isoprenoid side chain. The length of side chain will differ. Vitamin K_1 has 20C side chain (phylloquinone) (Fig. 32.13). Vitamin K_2 has a 30C side chain. Yet another structurally similar synthetic compound having vitamin K activity is **Menadione.** It is water soluble

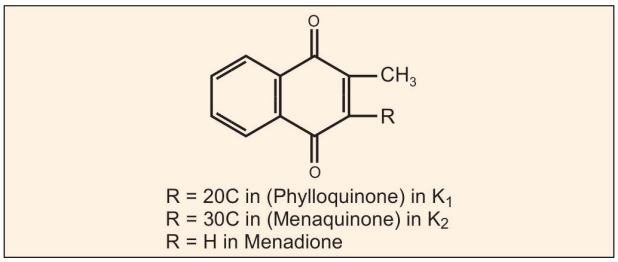


Fig. 32.13: Vitamin K

synthetic vitamin, widely used in clinical practice. Henrik Dam isolated vitamin K1 in 1929, while Edward Doisy isolated vitamin K_2 in 1939. Both of them were awarded Nobel Prize in 1943.

Biochemical Role of Vitamin K

Vitamin K is necessary for coagulation. Factors dependent on vitamin K are Factor II (prothrombin); Factor VII (SPCA); Factor IX (Christmas factor); Factor X (Stuart Prower factor). All these factors are synthesized by the liver as inactive zymogens. They undergo **post-translational** modification; gamma carboxylation of glutamic acid residues. These are the binding sites for calcium ions. The gamma carboxyglutamic acid (GCG) synthesis requires vitamin K as a cofactor (Fig. 32.14).

Vitamin K Dependent Carboxylase

It requires oxygen, CO_2, NADPH and reduced vitamin K. This enzyme is competitively inhibited by **warfarin** and **dicoumarol**.

Causes for Deficiency of Vitamin K

In normal adults dietary deficiency will not occur since the intestinal bacterial synthesis is sufficient to meet the needs of the body. However, deficiency can occur in conditions of **malabsorption** of lipids. This can result from obstructive jaundice, chronic pancreatitis, sprue, etc. Prolonged **antibiotic** therapy and gastrointestinal infections with diarrhea will destroy the bacterial flora and can also lead to vitamin K deficiency.

Clinical Manifestations of Deficiency

Hemorrhagic disease of the newborn is attributed to vitamin K deficiency. The newborns, especially the **premature**

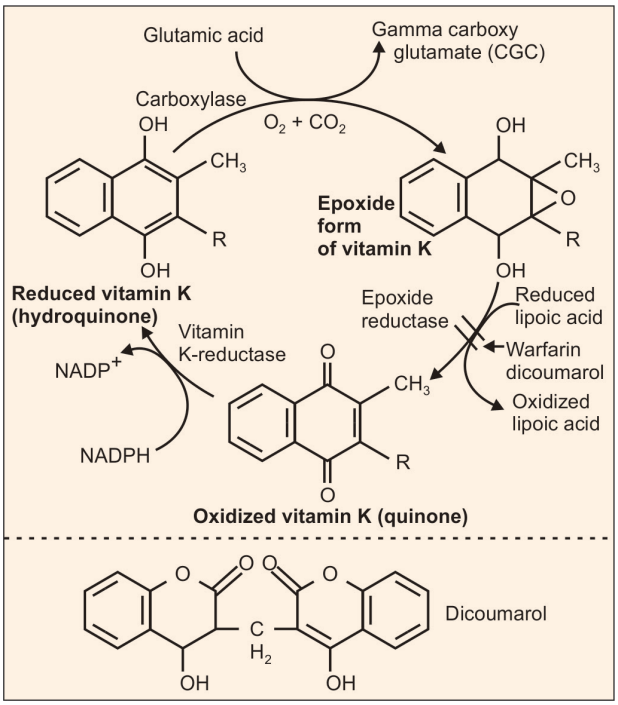


Fig. 32.14: Vitamin K as co-factor in GCG synthesis

infants have relative vitamin K deficiency. This is due to lack of hepatic stores, limited oral intake (breast milk has very low levels-and absence of intestinal bacterial flora. It is often advised that preterm infants be given prophylactic doses of vitamin K (1 mg Menadione).

In children and adults, Vitamin K deficiency may be manifested as bruising tendency, echymotic patches, mucous membrane hemorrhage, post-traumatic bleeding and internal **bleeding**. Prolongation of prothrombin time and delayed clotting time are characteristic of vitamin K deficiency.

Measurement of **prothrombin time** (PT) is taken as an index of liver function. When liver function is considerably lowered, prolongation of PT occurs due to deficient synthesis of the coagulation factors. In such cases, administration of vitamin fails to restore PT to normal levels. Hence before undertaking any surgery on jaundiced patients, PT before and after administration of vitamin K should be done.

Warfarin and **dicoumarol** will competitively inhibit the gamma carboxylation system due to structural similarity with vitamin K. Hence they are widely used as anticoagulants for therapeutic purposes.

Daily Requirement of Vitamin K

Recommended daily allowance is 50–100 mg/day. This is usually available in a normal diet.

Sources of Vitamin K

Green leafy vegetables are good dietary sources. Even if the diet does not contain the vitamin, intestinal bacterial synthesis will meet the daily requirements, as long as absorption is normal.

Hypervitaminosis K

Hemolysis, hyperbilirubinemia, kernicterus and brain damage are the manifestations of toxicity.

Clinical Case Study 32.1

A 6-year-old child was brought to the hospital with complaints of slow growth and pain in bones. On examination, he was anemic, had frontal bossing, bowing of legs and swelling of costochondral junction. Laboratory results were: Serum calcium—8.2 mg/dL, serum phosphorus—2.8 mg/dL and serum ALP—720 U/L. What is the likely diagnosis?

Clinical Case Study 32.1 Answer

Interpretation: Rickets.
Tests: Vitamin D, Calcium.
Vitamin D functions as both a vitamin and a prohormone. Low levels of vitamin D are associated with increased mortality; excess as well as deficiency of vitamin D causes premature aging. Low vitamin D levels are associated with osteomalacia, rickets, falls and low bone mineral density. Lower vitamin D levels also seem to be correlated with some cancers, bronchial asthma, heart palpitations, multiple sclerosis, infections and neurodegenerative diseases. Serum 25hydroxy vitamin D levels also have to be maintained for bone and overall health.

LEARNING POINTS CHAPTER 32

1. Vitamin A is a fat-soluble vitamin whose active form is present only in animal tissues, but provitamin A (beta carotene) is present in plant tissues.

2. Retinols are polyisoprenoid compounds with Vitamin A activity, having the b ionone ring system.
3. Active forms of the vitamin A include; Retinol, Retinal, Retinoic acid. The two important isomers are all trans-retinal and 11-cis retinal.
4. Vitamin A is transported with the help of Retinal Binding Protein and this retinal–RBP complex has specific receptors in various tissues.
5. Rhodopsin is a membrane protein made up of opsin plus 11-cis-retinal and it is important in the visual cycle.
6. Rods are for dim light vision and cones for color vision.
7. Decrease in number of cones/cone proteins lead to color blindness.
8. Vitamin D is derived from 7 dehydrocholesterol by the action of UV rays.
9. Vitamin D deficiency results in rickets and osteomalacia. Different types of rickets are; vitamin D resistant, and renal rickets.
10. Vitamin E is tocopherol. It is absorbed along with fats with the help of bile salts. It is transported as chylomicrons and stored in adipose tissue.
11. Vitamin E is the most important antioxidant in tissues.
12. Vitamin K is absorbed in intestine along with chylomicrons. They are also synthesized by intestinal flora.
13. Vitamin K is involved in blood coagulation. Vitamin K is required for post-translational modification of coagulation factors.

PART-1: ESSAY AND SHORT NOTE QUESTIONS

32-1. Describe sources, biochemical functions, requirement and deficiency manifestations of Vitamin A.
32-2. Describe the sources, biochemical functions, normal requirement and deficiency manifestations of Vitamin D.

SHORT NOTE QUESTIONS

32-3. Sources and daily requirement of Vitamin A.
32-4. Functions of Vitamin A.
32-5. Visual cycle.
32-6. Hypervitaminosis A.
32-7. Provitamins.
32-8. Anti-vitamins.
32-9. Functions of Vitamin D.
32-10. Activation of vitamin D.
32-11. Vitamin D deficiency.
32-12. Tocopherol.
32-13. Biological role of Vitamin K.
32-14. Anticoagulants.
32-15. Gamma carboxylation reaction.

PART-2: MULTIPLE CHOICE QUESTIONS

32-1. Daily requirement of vitamin A for a normal adult is:
A. 1 microgram B. 5 microgram
C. 100 microgram D. 750 microgram

32-2. Deficiency of vitamin A leads to:
A. Night blindness B. Rickets
C. Macrocytic anemia D. Microcytic anemia

32-3. Nyctalopia is due to the deficiency of:
A. Vitamin K B. Vitamin E
C. Vitamin B12 D. Vitamin A

32-4. When kidney diseases are present, oral doses of vitamin D may not be effective in curing rickets, because:
A. Hydroxylation reaction is taking place in kidney which activates vitamin
B. Dehydrogenation of vitamin D is taking place in kidney
C. Hydroxylation of vitamin D is taking place in kidney which destroys vitamin
D. Vitamin D is stored in liver

32-5. Daily requirement of vitamin D is:
A. 1 microgram B. 10 microgram
C. 100 microgram D. 750 microgram

32-6. Bleeding tendency is common in deficiency of all the following, *except*:
A. Vitamin K B. Vitamin B12
C. Vitamin C D. Platelets

32-7. Cholecalciferol is synthesized in:
A. Liver B. Skin
C. Kidney D. Intestinal mucosa

32-8. The most important biological role for vitamin E is:
A. To produce clotting factors

B. Antidote of selenium poisoning
C. Anticoagulant
D. Antioxidant

32-9. Large doses of vitamin K in neonates may cause:
A. Rebound bleeding
B. Porphyria
C. Jaundice
D. Cyanosis

32-10. Deficiency of vitamin K can occur in the following conditions, *except*:
A. Following gastrectomy
B. Prolonged antibiotic therapy
C. Obstructive jaundice
D. Administration of dicoumarol

32-11. Biochemical function of vitamin K is for:
A. Converting proline to hydroxyproline
B. Conversion of prothrombin to thrombin
C. Gamma carboxylation of clotting factors
D. Inhibition of lipid peroxidation in biomembranes

32-12. Vitamin K is inhibited by:
A. Isoniazid (INH) B. Methotrexate
C. Dicoumarol D. Avidin

32-13. Skin and mucous membrane are affected in deficiency of all the vitamins listed below, *except*:
A. Retinol B. Niacin
C. Riboflavin D. Calcitriol

32-14. The active form of vitamin D is known as:
A. Cholecalciferol
B. Cyclopentano phenanthrene
C. Calcitriol
D. Lanosterol

32-15. The structure of vitamin A contains:
A. Chromane ring B. Beta ionone ring
C. Thiazole ring D. Naphthoquinone ring

32-16. The structure of vitamin E contains
A. Chromane ring B. Beta ionone ring
C. Thiazole ring D. Naphthoquinone ring

32-17. All are good sources of vitamin A, *except*:
A. Pumpkin B. Carrot
C. Mangoes D. Oranges

32-18. Rickets may occur in all conditions, *except*:
A. Chronic renal failure
B. Liver diseases
C. Under exposure to sun light
D. Prolonged antibiotic therapy

32-19. Richest source of vitamin D is:
A. Fresh leafy vegetables
B. Fish liver oil
C. Egg yolk
D. Vegetable oils

32-20. Which is the enzyme specially involved in ossification of bone?
A. Alkaline phosphatase
B. Acid phosphatase
C. Hexokinase
D. ATPase

32-21. When kidney diseases are present, oral doses of vitamin D may not be effective in curing rickets, because vitamin D is:
A. Stored in kidneys
B. Dehydrogenated in kidneys
C. Destroyed in kidneys
D. Activated in kidney

32-22. If vitamin K is given to a patient with hemophilia:
A. Bleeding time prolonged, clotting time remains normal
B. Blotting time prolonged, bleeding time remains normal
C. Both bleeding and clotting times prolonged
D. Both bleeding and clotting times decreased

32-23. All water soluble vitamins are excreted through urine and are not stored in the body, *except*:
A. Vitamin B12
B. Vitamin B6 (pyridoxal)
C. Vitamin C
D. Niacin

32-24. All these vitamins are required for normal bone formation, *except*:
A. Vitamin C B. Vitamin D
C. Vitamin A D. Vitamin E

ANSWERS OF MULTIPLE CHOICE QUESTIONS

32-1. D	**32-2.** A	**32-3.** D	**32-4.** A	**32-5.** B	**32-6.** B	**32-7.** B
32-8. D	**32-9.** C	**32-10.** A	**32-11.** C	**32-12.** C	**32-13.** D	**32-14.** C
32-15. B	**32-16.** A	**32-17.** D	**32-18.** D	**32-19.** B	**32-20.** A	**32-21.** D
32-22. D	**32-23.** A	**32-24.** D	**32-25.** B			

PART-3: VIVA VOCE QUESTIONS AND ANSWERS

32-1. What is the major function of vitamin A?
Important in vision, used in the Wald's visual cycle.

32-2. What causes the nerve impulse in retina?
Photoisomerization of 11-cis retinal to all trans retinal.

32-3. How is all-trans retinal regenerated?
Trans retinal is taken to liver, where it Is made to trans-retinol, then isomerised to cis retinol and then to cis retinal.

32-4. What enzymes are required for regeneration?
Alcohol dehydrogenase and retinol isomerase (Fig. 32.4).

32-5. What are the deficiency manifestations of vitamin A?
Night blindness, xerophthalmia, keratomalacia, keratinisation of epithelium.

32-6. What are the sources of vitamin A?
Carrot, mangoes, papaya, green leafy vegetables, fish oil.

32-7. What is the daily requirement of vitamin A?
750 to 1000 microgram.

32-8. How is cholecalciferolsynthesized?
From 7-dehydro cholesterol in the Malpighian layer of epidermis, by the action of ultra violet rays.

32-9. How is vitamin D activated?
Cholecalciferol from skin reaches liver. There it is hydroxylated to form 25-hydroxy cholecalciferol (25-HCC). It then reaches kidney, where further hydroxylation takes place to form 1,25-dihydroxy cholecalciferol (DHCC).

32-10. What is calcitriol?
1,25-dihydroxy cholecalciferol, or active vitamin D, contains three hydroxyl groups at 1, 3 and 25 positions. (Fig. 32.9).

32-11. Which vitamin acts as a pro-hormone?
Vitamin Dis converted to calcitriol.

32-12. What is the function of vitamin D?
It increases absorption of calcium from intestine; it also increases mineralization of bone.

32-13. What are deficiency manifestations of vitamin D?
Rickets in children and osteomalacia in adults.

32-14. In renal disease, oral doses of vitamin D may not be effective, why?
Hydroxylation and activation of vitamin is taking place in kidney.

32-15. What is the daily requirement of vitamin D?
10-15 microgram.

32-16. What is the function of vitamin E?
It is the most powerful anti-oxidant.

32-17. How selenium and vitamin E are related?
They act synergistically as anti-oxidants.

32-18. What is the source of vitamin E?
Vegetable oils e.g. wheat germ oil, sunflower oil, safflower oil, cotton seed oil, palm oil.

32-19. What is the daily requirement of vitamin E?
15 mg or 33 international units.

32-20. What is the function of vitamin K?
Gamma carboxylation of clotting factors such as prothrombin

32-21. Deficiency of vitamin K can occur in which conditions?
Obstructive jaundice; antibiotic therapy; administration of dicoumarol.

32-22. What is the mechanism of action of dicoumarol?
It competitively inhibits vitamin K epoxide reductase.

32-23. Dicoumarol is used for what purpose?
To prevent intravascular thrombosis.

32-24. Excess dose of vitamin K in neonates may lead to which condition?
Hemolysis and jaundice.

32-25. Bleeding tendency is common in deficiency of?
Vitamin K; Vitamin C; Platelets; prothrombin.