Fat Soluble Vitamins
VITAMIN

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Vitamin A refers to **poly-isoprenoid** compounds.

Polyisoprenoid compounds consists of two distinct structures-

- a cyclohexenyl (\(\beta\)-ionone) ring
- a side chain of isoprene units, which is attached to the cyclohexenyl ring.

\(\beta\)-ionone ring is required for biological activity of vit. A.
FORMS OF VITAMIN A

Vit. A occurs in 2 forms

1-RETINOIDS  2-CAROTENOIDS

- Foods from animal source provide various retinoids

Retinoids occur in 3 different forms:

- Retinol: an alcohol
- Retinal: an aldehyde
- Retinoic acid: an acid and most oxidized form
Retinoid

Retinol

Retinal

Retinoic Acid
Foods from plant source provide **carotenoids**

- Over 500 carotenoids found in nature
- The most common form in food is $\beta$-carotene. Inactive precursor (provitamins) forms of Vit A.
- $\beta$-carotene has two inoene rings and gives 2 molecules of Vit A (retinol)

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Retinol is the immediate precursor to two important active metabolites: retinal and retinoic acid.
**ABSORPTION**

In food the vitamin exists as esters, which are hydrolyzed in the duodenum, a process that is assisted by bile salts.

Absorption of the retinol and carotenes is facilitated by fat in diet being associated with micelles formed during fat digestion.

Dietary protein and zinc help utilization of both retinol and beta-carotene.

Absorption is aided by cellular retinal-binding protein type II situated on the epithelial cells of the small intestine.

Carotene is converted into retinal, which is reduced to retinol as the next step.

Retinol is esterified with long chain saturated fatty acids and the esters are transported in to chylomicrones (molecule which transport fat from liver to peripheral tissues).

They are remained in chylomicrone remnants when triglycerides are removed by lipoprotein lipase (enzyme on endothelial surface to remove triglycerides) and they are taken up by liver and stored there.

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CAROTENOID CLEAVAGE AND STORAGE

- β-carotene is converted to vitamin A in the intestinal mucosa

- 90% is stored in liver, mainly as the ester, retinyl palmitate (~ 6 months storage)
  - Small amounts in adipose and blood

- Transport
  - Retinol binding protein (RBP) acts to transport vitamin A from the liver and in the blood.

- Excretion
  - Small amount in urine
Transport & Storage

- **Retinol**  
  Preformed vitamin A major transport and storage form

- Retinol binding protein (RBP) picks up retinol from liver, carries it in blood

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FUNCTIONS OF VIT A

RETINAL
Involved in VISION

RETINOL
Necessary for the reproductive system

RETINOIC ACID
Involved in growth and cellular differentiation

β Carotene
Plays antioxidant role.
METABOLIC FUNCTIONS OF VITAMIN A

- vital to good vision
- prevents night blindness
- antioxidant (β-carotene)
- necessary for healthy skin, hair growth
- keeps mucous membranes healthy
- promotes bone development
- support immunity (retinoic acid and carotenoids)

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ROLE OF $\beta$-CAROTENE

- **Antioxidant role** of $\beta$-carotene

- Increased consumption of $\beta$-carotene is associated with decreased incidence of heart attacks, skin and lung cancers.

- High doses of carotene for long periods are not toxic.
Retinal’s Role in Vision

Visual phototransduction light is converted into electrical signals in---rod, cone, ganglionic cells of the retina of the eyes.

11-cis retinal, (Vitamin A) acts as a visual pigment in our eyes, by absorbing photons.
Visual Cycle, Rhodopsin Cycle, Wald’s Cycle

- Active form of Vit A: \textit{11cis-retinal}.

- Adaptation to dark is function of photoreceptor cells in retina known as RODS.

- Rods contain photosensitive pigment called RHODOPSIN.
To function, it is connected to the protein “opsin” via a Shiff’s base. Together, the protein-pigment complex is called “rhodopsin.”

The 11-\textit{cis} double bond absorbs light, resulting in a conversion of the 11-\textit{cis} to the 11-\textit{trans} form. The light reaction takes only a few picoseconds and it starts a complex signal transduction pathway that leads to light being perceived in the brain.
Vitamin A as the Visual Pigment

11-cis-Retinal

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Rhodopsin Cycle comprises of 2 events:

- Bleaching of Rhodopsin & Generation of nerve impulse
- Regeneration of Rhodopsin.

When light falls on retina 11cis-retinal is isomerised to all trans retinal.

Hence rhodopsin to active rhodopsin called Metarhodopsin11.
Figure 10. Photobleaching process of bovine rhodopsin. After photon absorption and electronic excitation, fast isomerization of the chromophore leads to the formation of a series of intermediate states of rhodopsin. This is called the "bleaching process" because rhodopsin loses its color. The intermediate states were identified by both low-temperature and time-resolved spectroscopy. The peak spectral sensitivity of each state was indicated. BSI, blue-shifted intermediate. Modified from Wolfgang Baehr.
Conformational changes in metarhodopsin results in the activation of Transducin.

Transducin is a G protein.

Activation of transducin results from binding of GTP to $\alpha$ subunit & release of beta and gamma subunit.

Activated Transducin activate enzyme Phosphodiesterase (PDE).

PDE. hydrolyses cyclic GMP to GMP thereby decreasing cGMP levels.
Vitamin A – Retinal’s Role in Vision (Chapter 32)

11-cis-Retinal

Light

All-trans-retinal

Light

Rhodopsin

Transducin αβγ

GTP

GDP

Phosphodiesterase

Na⁺
Ca²⁺
cAMP = gated ion channel

cGMP

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Low levels of cGMP results in closure of Na channels.

Closure of Na channels results in Hyperpolarisation.

Hyperpolarisation generates nerve impulse.

**REGENERATION OF RHODOPSIN**

**PATHWAY 1:** All trans retinal is isomerised to 11 cis-retinal

Retinal by ISOMERASE enzyme in retina to form Rhodopsin.

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PATHWAY 2:

- All trans retinal is reduced to all trans retinol in retina.
- This then reaches liver by blood circulation.
- Now all trans retinol is isomerised to all cis retinol.
- Now 11 cis retinol reaches retina and gets oxidized to 11 cis retinal.
- 11 cis retinal + opsin = rhodopsin.
- CYCLE REPEATS.
Rhodopsin Cycle or Wald’s Visual Cycle

- **Rhodopsin**: combination of a protein part (opsin) and 11-cis retinal (only cis form can bind with opsin).
- When light energy is absorbed by rhodopsin, the rhodopsin decompose: converts 11-cis retinal into all-trans retinal.
- In order to maintain the ability to detect light, the rods must **reconvert the all-trans retinal into 11-cis retinal**.
- This process only **occurs under the dark environment**.
- **Dark adaptation time**

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RECOVERY

- To achieve a rapid response, the signal must be returned to its initial state.

- First step is to block activated Rhodopsin for continuous activating transducin.

- Rhodopsin kinase causes the phosphorylation of the carboxly terminus of activated rhodopsin R*
Then **arrestin** an inhibitory protein binds to phosphorylated R* & prevents additional interaction with transducin.

Secondly the α subunit of transducin must be returned to its inactive state to prevent further signaling.

For this α subunit has built in GTPase activity that hydrolyzes GTP::$\rightarrow$ GDP.
The GDP form of transducin leaves phosphodiesterase & reassociates with $\beta Y$ subunits.

Levels of cGMP must be raised to open the cGMP gated ion channels. The action of Guanylate Cyclase accomplishes this third step by synthesizing cGMP from GTP.

Calcium ions play a essential role in controlling guanylate cyclase. How?

In the dark Na & Ca enter the rod cell through cGMP gated channels.
- Calcium ions are effluxed through an exchanger which uses 4 Na in & 1 K ion out to extrude one Ca ion.

- After illumination the entry of Ca through the cGMP gated channels stops but export through exchanger continues thus resulting in drop of cytoplasmic Ca.

- This drop stimulates guanylate cyclase rapidly restoring the concentration of cGMP to open the channels.

\[
\text{(cGMP)} \downarrow \rightarrow \text{Ion channels} \rightarrow (\text{Ca}^{2+}) \downarrow \rightarrow \text{Guanylate cyclase} \rightarrow \text{cGMP} \uparrow
\]

**Activation** \hspace{2cm} **Recovery**

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Color Vision is possible because of three conopsin binding to three different opsin proteins in three different types of cone cells.

Each protein has a slightly different amino acid composition, changing the environment of the 11-cis-retinal pigment.

This change shifts the absorption spectrum of these three proteins to the “blue,” “green,” and ‘red” regions. Signals from each of these three different types of cells are the basis for our color perception.
Retinal and Color Vision

- The genes for the color-shifted opsin proteins lie adjacent to each other on the human X chromosome and share a high degree of similarity.
- Slight changes in the base sequences of these genes result in spectral shifts for light absorption, leading to perceptual differences in the color of light we see.
- Human X chromosomes carry various numbers of color pigment genes. In the general population, the X-chromosome gene content varies significantly:
  - 2% - 1 color pigment gene
  - 20% - 2 color pigment genes
  - 50% - 3 color pigment genes
  - 20% - 4 color pigment genes
  - 5% - 5 color pigment genes
Color Blindness

- Due to the loci of these genes on the X chromosome, most colorblindness is sex-linked, with predominant expression in males.

- ~5% of males lack the green pigment gene. The resulting hybrid gene absorbs light between red and green, making differentiation of these two colors difficult.
VIT. A IN REPRODUCTION

- **ACTIVE FORM**: RETINOL

- **MECHANISM**: Retinol binds to CRBP. Retinol receptor complex binds to DNA & regulates the expression of genes required for reproductive function.

- Mechanism of action is similar to steroid hormone action.
VIT. A IN GROWTH & DIFFERENTIATION

Active form: Retionic acid.

- Mechanism: All trans retionic acid or 9 cis retionic acid binds to specific CRBP.
  
  This complex binds to DNA & regulates the gene reqd. for growth & differentiation.

- Used in cancer treatment: causes differentiation of tumors.

- Induces apoptosis (programmed cell death) of cancer cells.
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VIT. A maintains: Epithelial Integrity & Glycoprotein Synthesis

Active form: **Retinol, Retinyl phosphate**

- Retinol is involved in both the above processes.
- Retinol prevents excess keratin synthesis.
- Retinyl phosphate is formed from retinol & is required for glycoprotein synthesis.
- Glycoproteins are important constituent of the mucous secreted by many epithelial cells.
- Retinyl phosphate forms glycosyl retinyl PO$_4$ & acts as donor of carbohydrates.
Figure 28.21
Summary of actions of retinoids. Compounds in boxes are available as dietary components or as pharmacologic agents.

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VITAMIN A - DEFICIENCY

- More obvious deficiency symptoms than other vitamins
  - Night blindness
    - Leading cause of blindness in third world countries
  - Cell keratinization
    - Dry skin
    - Xerophthalmia (dryness of cornea & conjunctiva)
  - Reproductive failure
  - Abnormal skeletal development/maintenance

Immune dysfunction
Mucous linings harden
increased tendency for infection
vitamin A deficiency increases infection rate

HOW ??

- Vitamin A deficiency reduces the activity of macrophages.

- It is postulated that mucus producing cells are replaced by keratin producing cells in respiratory, gastro-intestinal and genitor-urinary tracts and in the corneal-conjunctival epithelium which results in invasion of organisms causing infections.

- Lysozyme which is an antiviral substance depends on vitamin A for its synthesis.

- Deficiency also reduces T lymphocyte activity to viral infections and levels of immunoglobulins in blood particularly immunoglobulin A.

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Vitamin A–Deficiency Symptom
Night Blindness

In dim light, you can make out the details in this room. You are using your rods for vision.

A flash of bright light momentarily blinds you as the pigment in the rods is bleached.

You quickly recover and can see the details again in a few seconds.

With inadequate vitamin A, you do not recover but remain blinded for many seconds.
Xerophthalmia

↑ curable early stage
after 8 days vitamin A  ➔

incurable late stages ➔

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Daily requirement

- Children
  2000 – 3500 I.U.
- Men
  5000 I.U.
- Women
  4000 I.U.

Bear in mind that too much of a good thing can have side effects and the same applies to vitamin A. Pregnant women should be wary that large doses of vitamin A can cause birth defects.
VITAMIN A TOXICITY

- Acne medication can cause birth defects
- Overdosing:
  - joint pains
  - loss of hair
  - Liver damage: jaundice
  - Blurred vision
  - Loss of appetite
  - Skin coloration death

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Polar Bear Liver

One ounce of polar bear liver contains enough vitamin A (retinol) to kill a person!
Vit. A DEFICIENCY

CAUSES

✓ Inadequate intake
✓ Impaired absorption due to Pancreatic diseases, Obstructive jaundice, small Intestinal diseases
✓ Impaired storage and transport due to LIVER cirrhosis
✓ Increased excretion due to Nephrotic syndrome
✓ Alcoholism
VITAMIN A - SOURCES

- Animal sources
  - Liver
  - Milk
  - Egg yolk

- Plant sources
  - Carrots
  - Green leafy vegetables
  - Orange coloured fruits, e.g. mango and apricots
  - Dark green and yellow vegetables.
Vitamin D
Vitamin D: Sunshine Vitamin

- Body can make it if exposed to enough sunlight
- Made from cholesterol in the skin
Vitamin D - Sources

- Synthesized in body
- Plants (ergosterol)
  - Sun-cured forages
- Fluid milk products are fortified with vitamin D
- Oily fish
- Egg yolk
- Butter
- Liver

- Daily Value
  - 10 micrograms
Vitamin D (calciferol)

- There are 2 major precursor forms:
  - 7-dehydrocholesterol
  - Ergosterol

- **Vitamin D\(_2\) = ergocalciferol**
  - Completely synthetic form produced by the irradiation of the plant sterol ergosterol

- **Vitamin D\(_3\) = cholecalciferol**
  - Produced photochemically by the action of sunlight or ultraviolet light from the precursor sterol 7-dehydrocholesterol
Formation of Vitamin D

- **Skin (UV light)**
  - 7-dehydro cholesterol $\rightarrow$ vitamin D$_3$

- **Liver**
  - OH-group added
    - 25-hydroxy vitamin D$_3$
    - Storage form of vitamin D$_3$ (≈3 months storage in liver)

- **Kidney**
  - OH-group added by 1-hydroxylase
    - 1,25-dihydroxy vitamin D$_3$ (or 1,25-dihydroxy cholecalciferol, 1,25-DHCC)
      - Active form of vitamin D, a “steroid hormone”
  - OH-group added by 24-hydroxylase
    - 24,25-dihydroxy vitamin D$_3$
    - Inactive form of vitamin D, ready for excretion
Conversion to ergocalciferol via reactions analogous to 7-dehydrocholesterol pathway

Ergosterol

Ergocalciferol (vitamin D$_2$)
Calcitriol (1,25-dihydroxy-cholecalciferol, 1,25 DHCC)
<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Abbreviation</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D₂</td>
<td>D₂</td>
<td>Ergocalciferol</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>D₃</td>
<td>Cholecalciferol</td>
</tr>
<tr>
<td>25-hydroxy Vitamin D₃</td>
<td>25(OH)D₃</td>
<td>Calciferol</td>
</tr>
<tr>
<td>1,25-dihydroxy vitamin D₃</td>
<td>1,25-(OH)₂D₃</td>
<td>Calcitriol</td>
</tr>
<tr>
<td>24,25-dihydroxy vitamin D₃</td>
<td>24,25-(OH)₂D₃</td>
<td>Secalciferol</td>
</tr>
</tbody>
</table>
Functions of Vitamin D

- **Calcium and Phosphorus Homeostasis**
  - Calcium and Phosphorus absorption (small intestine)
  - Calcium resorption (bone and kidney)
  - Maintain blood calcium levels

- **Bone formation**
  - Stimulate calcium uptake for deposition as calcium phosphate (Osteoblasts: bone-forming cells)

- **Hormone**
  - Regulation of gene expression
  - Cell growth
Hormone enters target cell by diffusion

Binds to specific hormone binding site of receptor

Conformational change leads to formation of receptor dimmers

Dimer binds to specific DNA base sequences

Alters rate of transcription of specific gene

Induction (or repression) of key proteins

Increased amounts of the protein (enzyme)
HORMONAL ACTION OF VIT. D

- It is important for regulation of differentiation & proliferation of various cells:
  - Immunoregulatory cells
  - Epidermal cells
  - Malignant tumour cells
    - involved in immune modulation
    - depresses Ig production by
    - inhibiting function of helper T cells
    - thereby affecting B cell function

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Actions of Calcitriol

Intestine: absorption of Ca and Phosphate
Kidney
Bone: release of Ca and Phosphate into ECF
Stimulates synthesis of calcium binding proteins calbindins & osteocalcin thereby increasing absorption of Ca & P from intestine.

- Increases reabsorption of Ca & P from distal convulated tubule of kidney.
- Causes mobilization of Ca & P from bone.
- Vit. D has both anabolic & catabolic role on bone.
- Vit. D is also required for calcification of bone.

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Low blood calcium level → Increased PTH production → Release of calcium and phosphorus from bone → a. Decreased calcium excretion → Normal blood calcium level

Increased calcitonin synthesis → Increased deposit of calcium in bone

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Figure 28.23
Metabolism and actions of vitamin D. [Note: Calcitonin, a thyroid hormone, decreases blood calcium by inhibiting mobilization from bone and reabsorption by the kidney.]
Figure 28.24
Response to low plasma calcium.

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Vitamin D (antirachitic vitamin)-Deficiency

Less common

Young animals
- **Rickets** *(meaning: twist)*
  - Failure of bones to grow properly
  - Results in “bowed” legs or knock-knees, outward bowed chest and knobs on ribs

Older animals
- **Osteomalacia** *(Greek: osteon-bone, malakia-softness)*:
  - Adult form of rickets
- **Osteoporosis** *(porous bones)*:
  - Loss of vitamin D activity with advancing age
  - Associated with fractures ➔ very serious for geriatrics

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Osteoporosis

- progress loss of bone density, thinning of bone tissue and increased vulnerability to fractures in the elderly people of both sexes.

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Vitamin D Toxicity

- Hypervitaminosis D
  - Among the vitamins, vitamin D is the most toxic in overdoses (10-100 times RDA)
  - Calcification of soft tissue
    - Lungs, heart, blood vessels
    - Hardening of arteries, stone formation in kidneys
- Does not occur from sunlight or dietary sources
- Does occur with supplementation
  - In general, vitamin D supplement are not recommended.
  - Upper limit: 50 micrograms a day

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VITAMIN K

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Food sources of vitamin K include cabbage, cauliflower, spinach and other green, leafy vegetables, as well as cereals.
This vit is also called an *anti-hemorrhagic factor*.

Deficiency produces uncontrolled hemorrhages due to defective blood coagulation.
STRUCTURE

- Two naturally occurring forms:
  - Vitamin K1 or phylloquinone derived from plants
  - Vitamin K2 or menaquinones produced by microorganism

- Both have same activity: stable to heat and reducing agent.

- Vitamin K3 or menadione is a synthetic product, alkylated form of vit K2.
K₁ (Phylloquinone)

K₂ (Menatetrenone/MK4)

K₃ (Menadione)
Naturally occurring vit K are absorbed like other lipids in presence of bile salts.

Transported in the form of chylomicrons and stored in the liver.

Menadione a water-soluble medicinal agent (synthetic vit K) is absorbed without bile salt directly into hepatic portal vein.
Functions of Vit. K

- Involved in maintenance of normal levels of blood clotting factors

Clotting factors II, VII, IX, X are synthesized as inactive precursor protein in liver.

Conversion of inactive precursor requires post-transcriptional modification of specific glutamate residue.

This modification is carboxylation of glutamate residues by vitamin K dependent carboxlase enzyme & forms Y-carboxyglutamate (GLA).
Carboxylation of glutamate to form γ-carboxy glutamate

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- **γ-Gla** have high affinity for Ca$^{2+}$ and are effective Ca$^{2+}$ chelators.

- Each GLA contains two negative charges which chelate the positive Ca$^{2+}$ ion.

- The calcium then binds with negatively charged phospholipids on platelet cell membrane.

- This way bridging of phospholipids to the Gla residue of prothrombin occurs via Ca$^{2+}$ ion.

- Protrombin is then proteolyzed to thrombin through the action of activated factor X.
Role of vit K in blood coagulation
VIT. K CYCLE

- Vit.K cycle exists in E.R. of liver.

- Here vit.K dependent carboxylase adds carboxy grp. of CO$_2$ to $\gamma$ carbon of glutamate.

- Vit K acts as e$^{-}$ donor & is converted to vit K epoxide.

- Epoxide form is converted to quinone form of vit K by epoxide reductase & finally to hydroquinone by enzyme reductase & NADPH regenerating active form of vit. K
1. Vitamin K γ-glutamyl carboxylase
2. Vitamin K epoxide reductase
3. Vitamin K quinone reductase
Vit K antagonists

- VIT K antagonists **dicoumarin or warfarin.**
- They:—
  
  are competitive inhibitor of gamma carboxylation system
  
  structurally similar to vit.K
  
  inhibit enz. Epoxide reductase.
  
  used in treatment of thrombosis
Warfarin Interrupts Vitamin K Cycle
Vit. K is also required for carboxylation of glutamic acid of osteocalcin (synthesized by osteoblast) creating Ca binding sites, which helps to retain calcium.

Other proteins such as C-reactive protein and structural proteins of kidney, lungs & spleen also require vit K for carboxlation.
DEFICIENCY MANIFESTATION

- Widely distributed intestinal production by microflora ensures no deficiency.

- Deficiency occurs:
  - Patients with liver diseases & biliary obstruction
  - In infants*
  - Following antibiotic therapy
  - In fat malabsorption
Vitamin K deficiency is associated with hemorrhagic diseases.

Clotting time is increased.

Even minor cuts cause prolonged bleeding.

Imp. deficiency sign is *increase in prothrombin time* & is used for evaluation of vit.K status.
THERAPEUTIC USE

- It is used as an antidote to poisoning by dicumarol type drug.

TOXICITY

- Produces haemolytic anaemia in rats.
- Krenicterus in infants with low birth weight.
- Due to increased breakdown of RBC & undeveloped capacity for its conjugation.
VITAMIN E

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Vitamin E (tocopherol)

- A naturally occurring antioxidant.
- Essential for normal reproduction in many animals. Tocopherol (Greek: tokos-child birth; pheros-bear; ol-alcohol), Anti-sterility vitamin.

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Vitamin E - Sources

- **Plant sources**
  - Cereal grains
    - Especially in germ
  - Vegetable and seed oils

- **Animal sources**
  - Meat, milk, butter, eggs

- **RDA**: 10 mg for men, and 8 mg for women
Vitamin E (tocopherol)

- The term vitamin E refers to a family of 8 related compounds, the tocopherols and the tocotrienols.
- The four major forms of vitamin E are designated $\alpha$, $\beta$, $\delta$, $\gamma$, of which $\alpha$-tocopherol is the most active.
Absorption, Transport and Excretion of Vitamin E

Absorption and Transportation

- Micelles into chylomicrons
- Transported via lipoproteins
- Stored in adipose tissue

Excretion

- Bile, urine and skin
Major function in the body

- **Antioxidant**

Vitamin E is very unstable, easily oxidized

- protect cells against oxidative damage by free radicals, for example oxidation of the lipids in the cell membranes

- plays a role in aging, sexual performance, or prevention of cancer and/or heart disease
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I. Cell membrane
- PuFA-H (Polyunsaturated FA)

II. Chain terminator
- PuFA-OO°
- Toc.OH (α-tocopherol)
- Vit C (OX) or GS-SG
- Toc-O° (free radical of α-tocopherol)

III. Free radical (initiator of chain reaction)
- PuFA-OO° → PuFA-OOH

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Vitamin E - Deficiency

- Rare
  - Erythrocyte hemolysis and hemolytic anemia

  disruption of red blood cell membranes, perhaps due to polyunsaturated fatty acids (PUFAs) oxidation

- Sterility: reproductive failure
Vitamin E Toxicity

- **Toxicity rare:** wide range of safe intake compared to other fat soluble vitamins

- **Vitamin E is one of the most popular nutrient supplements.** There are many health claims for supplementation – slowing of the aging process or an improvement in sexual potency.