Vitamin A

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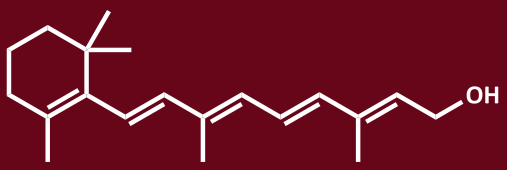
Synonyms:

Retinol, axerophthol.

Chemistry:

Retinol and its related compounds consist of four isoprenoid units joined head to tail and contain five conjugated double bonds. They naturally occur as alcohol (retinol), as aldehyde (retinal) or as acid (retinoic acid).



Molecular formula of vitamin A (retinol)

Food:

	Retinol (µg)	Serving (g)
Liver, tuna fish	200,000	150
Liver, pig	28,000	150
Cod liver oil	24,000	20
Eel	1,050	100
Egg yolk	700	19
Camembert cheese	380	30
Salmon	40	150
Chicken	39	150
Cow's milk, whole	31	200
Beef (muscles)	20	150
Pork (muscles)	6	150
Veal (muscles)	0.1	150

Main functions:

- Vision
- Differentiation of cells
- Fertility
- Embryogenesis, growth and development
- Immunity
- Intact epithelia

Vitamin A

Vitamin A is a generic term for a group of fat-soluble compounds found in animal sources (where it is referred to as 'preformed vitamin A' or 'retinol') and in fruits and vegetables (where it is known as 'provitamin A carotenoid'). Vitamin A has multiple functions in the body but it is considered essential for vision, especially night vision, growth and development, and immune health. Due to its unique role in normal vision, one of the earliest symptoms of its deficiency is night blindness.

Functions

Retinal, the oxidized metabolite of retinol, is essential for normal vision. Retinoic acid, on the other hand, is considered to be responsible for almost all non-visual functions relating to vitamin A. Retinoic acid acts by binding to the retinoic acid receptor (RAR), which is attached to DNA responsible for the expression of more than 500 genes. This influences numerous physiological processes and induces hormone-like activity.

Vision

Receptor cells, also known as rod cells, in the retina of the eye contain a light-sensitive pigment called rhodopsin – a complex of the protein opsin and vitamin A metabolite retinal. The light-induced disintegration of the pigment triggers a cascade of events generating an electrical signal to the optic nerve and promoting vision. Rod cells with this pigment can even detect very small levels of light, making them important for night vision.

Cellular differentiation

The many different types of cells in the body perform highly specialized functions. The process whereby cells and tissues become 'programed' to carry out their special functions is called differentiation. Through the regulation of gene expression, retinoic acid plays a major role in cellular differentiation. In fact, vitamin A is necessary for the normal differentiation of epithelial cells i.e. the cells of all tissues lining the body, including skin, mucous membranes, blood vessel walls and the cornea. If cells are deficient in vitamin A, they lose their ability to differentiate properly.

Growth and development

Retinoic acid plays an important role in reproduction and embryonic development, particularly in the development of the spinal cord and vertebrae, limbs, heart, eyes and ears.

Immune function

Vitamin A is also required for normal immune function. It is essential in maintaining the integrity and performance of skin and mucosal cells, which act as a mechanical barrier to pathogens and defend the body against infection. Vitamin A also plays a central role in the development and differentiation of white blood cells, such as lymphocytes, killer cells and phagocytes, which play a critical role in the defense of the body against disease.

Dietary sources

The richest food source of preformed vitamin A is liver, with considerable amounts also found in egg yolk, dairy products and fish. Provitamin A carotenoids are predominantly found in carrots, yellow and dark green leafy vegetables (e.g. spinach, broccoli), pumpkin, apricots and melon. Until recently, vitamin A activity in foods was expressed as international units (IU). This unit is still the measurement generally used on food and supplement labels; however, nutrition scientists now use retinol activity equivalent (RAE), which accounts for the rate of conversion of carotenoids to retinol.

1 RAE

= 1 µg retinol

= 12 µg β-Carotene from food sources

= 24 µg α-Carotene from food sources

= 24 µg β-Cryptoxanthin or other provitamin A carotenoids from food

= 2 µg β-Carotene from oil = 3.33 IU

Recommended daily intakes (RDI) *

Group	Life stage	Dose/day**
Infants	>6 months	400 µg (AI)
Infants	7 – 12 months	500 µg (AI)
Children	1 – 3 years	300 µg
Children	4 – 8 years	400 µg
Children	9 – 13 years	600 µg
Males	>14 years	900 µg
Females	>14 years	700 µg
Pregnancy	14 – 18 years	750 µg
Pregnancy	>19 years	770 µg
Breastfeeding	14 – 18 years	1,200 µg
Breastfeeding	>19 years	1,300 µg

* Institute of Medicine (2001)
** As RAEs adequate intake (AI)

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

Absorption and body stores

The absorption of vitamin A takes place primarily in the small intestine. Provitamin A carotenoids can be cleaved into retinol in the intestine and other organs via an enzymatic process. Preformed vitamin A occurs as retinylesters of fatty acids. They are hydrolyzed and retinol is absorbed into intestinal mucosal. After re-esterification, the retinylesters are incorporated into chylomicrons, excreted into lymphatic channels, delivered to the blood and transported to the liver. Vitamin A is stored in the liver as retinylesters, with stores lasting between one to two years for most adults living in developed countries.

Measurement

Vitamin A can be measured in the blood and other body tissues by various techniques. For rapid field tests, a method has been developed using dried blood spots. Typical serum concentrations are 1.1 – 2.3 µmol/L. According to WHO, plasma concentrations of <0,35 µmol/L indicate a vitamin A deficiency.

Stability

Vitamin A is sensitive to oxidation by air. Loss of activity is accelerated by heat and exposure to light. Oxidation of fats and oils (e.g. butter, margarine and cooking oils) can therefore destroy fat-soluble vitamins, including vitamin A. In these cases, the presence of antioxidants such as vitamins C and E contribute to the protection of vitamin A.

Physiological interactions

- The biologically active metabolite, retinoic acid (RA), has a fundamental role in the regulation of vitamin A target genes. RA binds via nuclear hormone receptors (RARs and RXRs) to the promoters of more than 500 genes. The products arising from these genes are necessary for many different pathways
- Chronic liver and kidney diseases can impair storage and transportation of vitamin A
- Protein malnutrition, general malabsorption and infectious diseases decrease the uptake of vitamin A in the intestine. This lowers the vitamin A status of the individual due to impaired binding protein synthesis

Deficiency

Vitamin A deficiency increases the risk of morbidity and mortality, especially in infants, children, pregnant women and breastfeeding mothers. Worldwide, it is estimated that 250 million pre-school children are vitamin A deficient resulting in 250,000 - 500,000 children becoming blind each year. This makes vitamin A deficiency one of the most widespread, yet preventable, causes of blindness in developing countries. The earliest symptom of vitamin A deficiency is impaired dark adaptation, also known as night blindness. Severe deficiency can cause xerophthalmia, a condition characterized by changes in the cells of the cornea that result in corneal ulcers, scarring and blindness. The appearance of skin lesions is also an early indicator of inadequate vitamin A status. Because vitamin A is required for the normal functioning of the immune system, even children who are only mildly deficient in the micronutrient have a higher incidence of respiratory disease and diarrhea, as well as an increased risk of mortality from infection. Some diseases may induce vitamin A deficiency, most notably liver and gastrointestinal diseases, which interfere with the absorption and utilization of vitamin A.

Groups at risk

- Pregnant and breastfeeding women
- Infants, young children and adolescents
- Alcoholics
- Individuals with a chronic illness
- Individuals with protein malnutrition and malabsorption
- Vegetarians and vegans with additional polymorphisms in the BCMO1 gene

Reducing disease risk: therapeutic use

Studies have shown that vitamin A supplementation given to children aged 6 months or older reduces all-cause mortality by 23% to 30% in low income countries. The WHO recommends that supplements are given when children are vaccinated. The currently daily recommended doses of vitamin A are 1,166 IU at age 6 – 11 months and 1,333 IU at age >12 months. Xerophthalmia (vitamin A deficiency) is treated with high doses of the vitamin (50,000 – 200,000 IU daily according to age). In developing countries, where vitamin A deficiency is one of the most serious health problems, children under the age of 6 years and pregnant and breastfeeding women are the most vulnerable groups.

Since vitamin A can be stored in the liver, it is possible to build up a reserve in children by administration of high-potency doses. In regular periodic distribution programs for the prevention of vitamin A deficiency, infants <6 months of age receive a dose of 50,000 IU of vitamin A, children between six months and one year receive 100,000 IU every 4 – 6 months and children >12 months of age receive 200,000 IU every 4 – 6 months. A single dose of 200,000 IU given to mothers immediately after delivery of their child has also been found to increase the vitamin A content of breast milk.

However, caution is necessary when considering vitamin A therapy for breastfeeding women as it may pose a risk to a co-existing pregnancy. During pregnancy, a daily dose of 4,333 IU should not be exceeded.

Recommended Daily Intake (RDI)

The recommended daily intake of vitamin A varies according to age, sex, risk group and other criteria applied in individual countries.

Safety

Because vitamin A (as retinylester) is stored in the liver, large amounts taken over a period of time can eventually exceed the liver's storage capacity and produce adverse effects, such as liver damage, bone abnormalities and joint pain, alopecia, headaches, vomiting and skin peeling. On the other hand, hypervitaminosis A can occur acutely following very high doses of the micronutrient taken over a period of several days or as a chronic condition from high doses taken over a long period of time. Thus, there is concern about the safety of high intakes of preformed vitamin A (retinol), especially for infants, small children and women of childbearing age. For example, normal fetal development requires sufficient vitamin A intake, but consumption of excess retinol during pregnancy is known to cause malformations in the newborn. In addition, several studies suggest that long-term intakes of pre-formed vitamin A in excess of 1,500 µg/day are associated with increased risk of osteoporotic fracture and decreased bone mineral density in older men and women. Only excess intakes of preformed vitamin A, not β-Carotene, were associated with adverse effects on bone health. Current levels of vitamin A in fortified foods are based on RDI levels, ensuring that there is no realistic possibility of vitamin A overdosage in the general population. In the majority of cases, signs and symptoms of toxicity are reversible upon cessation of vitamin A intake.

The Food and Nutrition Board of the Institute of Medicine (IOM, 2001) and the E.C. Scientific Committee on Food (2002) have set the tolerable upper intake level (UL) of vitamin A intake for adults at 3000 µg RE/day with appropriately lower levels for children.

Supplements and food fortification

Vitamin A is available in soft gelatin capsules, as chewable or fizzy tablets, or in ampoules (a small sealed glass capsule). It is also included in most multivitamins and supplements as retinyl acetate, retinyl palmitate and retinal. Margarine and milk are also commonly fortified with vitamin A. β-Carotene may also be added to margarine and many other foods, such as fruit drinks, salad dressings, cake mixes, ice cream both for its vitamin A activity and as a natural food colorant.

Production

Nowadays vitamin A is rarely extracted from fish liver oil. The modern method of industrial synthesis of nature-identical vitamin A is a highly complex, multi-step process.

History

1831 Wackenroder isolates the orange-yellow colorant from carrots and names it 'carotene'.

1876 Snell successfully demonstrates that night blindness and xerophthalmia can be cured by giving the patient cod liver oil.

1880 Lunin discovers that, besides needing carbohydrates, fats and proteins, experimental animals can only survive if given small quantities of milk powder.

1887 Arnaud describes the widespread presence of carotenes in plants.

1909 Stepp successfully extracts the vital liposoluble substance from milk.

1915 McCollum differentiates between 'fat-soluble A' and 'water-soluble B.'

1929 Thomas Moore demonstrates that β-Carotene is converted into the colorless form of vitamin A in the intestine. This is the proof that plant derived carotenoids serve as precursor for vitamin A.

1931 Karrer isolates pure retinol from the liver oil of a species of mackerel. Karrer and Kuhn isolate active carotenoids.

1946 Otto Isler was the first to synthesize vitamin A (pure all-trans retinol) at Hoffmann-La Roche. He then developed an efficient and economical industrial synthesis for vitamin A.

1987 Chombon in Strasbourg and Evans in San Diego, and their teams, simultaneously discover the retinoic acid receptors in cell nuclei.

1997 UNICEF, WHO and the governments of countries including Canada, the United States and the United Kingdom, as well as national governments in countries where vitamin deficiency is widespread, launch a global campaign to distribute high-dose vitamin A capsules to malnourished children.