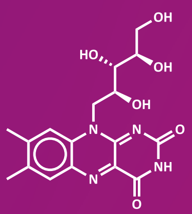
Vitamin B2
(Riboflavin)

Synonyms:

Riboflavine, lactoflavin, ovoflavin.

Chemistry:

7,8-dimethyl-10-(1-D-ribityl)-isoalloxazin – different redox states: flavochinon (Flox), flavosemichinon (Fl-H), flavohydrochinon (FlredH2). Coenzyme Form(s): FMN (flavin mononucleotide, riboflavin mono-phosphate), FAD (flavin adenine dinucleotide, riboflavin adenosine diphosphate).



Molecular formula of riboflavin

Food:

	mg/100g
Brewer's yeast	3.7
Pork liver	3.2
Chicken breast	0.9
Wheat germ	0.7
Camembert/Parmesan	0.6

(Souci, Fachmann, Kraut)

Main functions:

- Reduction-oxidation reactions
- Energy production
- Antioxidant functions
- Conversion of pyridoxine (vitamin B6) and folic acid into their active coenzyme forms
- Growth and reproduction
- Growth of skin, hair, and nails

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Vitamin B2 (Riboflavin)

Vitamin B2, also known as riboflavin, is one of the most widely distributed water-soluble vitamins. A sufficient intake of riboflavin is important, as it helps the body to convert food components into energy, neutralize free radicals that can damage cells and DNA, and also convert vitamin B6 and B9 into their active forms. Ultra violet (UV) light can destroy riboflavin, so milk, eggs, rice and fortified cereals, which are good sources of the vitamin, should be stored out of direct sunlight.

Functions

Flavin coenzymes are essential for energy production via the respiratory chain, as they act as catalysts in the transfer of electrons in numerous reduction-oxidation reactions (redox reactions). Flavin coenzymes participate in many metabolic reactions of carbohydrates, fats and proteins. Riboflavin coenzymes are also essential for the conversion of pyridoxine (vitamin B6) and folic acid into their coenzyme forms and for the transformation of tryptophan to niacin.

Riboflavin also promotes normal growth and assists in the synthesis of steroids, red blood cells, and glycogen. Furthermore, it helps to maintain the integrity of mucous membranes, skin, eyes and the nervous system, and is involved in the production of adrenalin by the adrenal glands. Riboflavin is also important for the antioxidant status within cell systems, both by itself and as part of the glutathione reductase and xanthine oxidase system. This defense system may also help defend against bacterial infections and tumor.

Dietary sources

Most plant- and animal-derived foods contain at least small quantities of riboflavin. However, there are very few natural sources rich in the vitamin.

The most important and common dietary sources are milk and milk products, lean meat, eggs and green leafy vegetables. Cereal grains, although poor sources of riboflavin, are important for those who rely on cereals as their main dietary component. Fortified cereals and bakery products supply large amounts.

Animal sources of riboflavin are more readily absorbed than vegetable sources. In milk from cows, sheep and goats, at least 90% of the riboflavin is in the free form; in most other sources, it occurs bound to proteins.

Absorption and body stores

Most dietary riboflavin is bound to a food protein such as FMN and FAD. These are released in the stomach by acidification and absorbed in the upper part of the small intestine by an active, rapid, saturable transport mechanism. The rate of absorption is proportional to intake and increases when riboflavin is ingested along with other foods. Approximately 15% is absorbed if taken alone versus 60% absorption when taken with food. Passive diffusion plays only a minor role in the physiological doses ingested in the diet. In the mucosal cells of the intestine, riboflavin is again converted to the coenzyme form (FMN). In the portal system, it is bound to plasma albumin or to other proteins, mainly immunoglobulins, and transported to the liver, where it is converted to the other coenzyme form, FAD, and bound to specific proteins as flavoproteins.

Riboflavin, mainly as FAD, is distributed in all tissues, but concentrations are low and very little is stored. The liver and retinal tissues are the main storage places, albeit riboflavin is not stored to any significant extent in the body.

Riboflavin is excreted mainly in the urine where it contributes to the yellow color. Small amounts are also excreted in sweat and bile. During breastfeeding, about 10% of absorbed riboflavin passes into the milk.

Measurement

Body status can be determined by direct and indirect methods. Direct methods include the determination of FAD and FMN in whole blood by HPLC (High Performance Liquid Chromatography). Usually, whole blood concentrations (FAD) of 175 – 475 nmol/L are measured. Another possibility for riboflavin status assessment is the monitoring of urinary excretion. Values <27 µg/g creatinine point to deficiency, 27 – 79 µg/g creatinine are considered marginal, and values >80 µg/g creatinine are considered normal. Urinary excretion rises sharply after tissue saturation is reached. Indirect methods include determining the activity of the FAD-dependent enzyme erythrocyte glutathione reductase (EGR). This biochemical method gives a valid indication of riboflavin status.

During riboflavin deficiency, EGR is no longer saturated with FAD, so enzyme activity increases when FAD is added in vitro. The difference in activity in erythrocytes with and without added FAD is called the activity coefficient (EGRAC). An EGRAC >1.30 is indicative of biochemical riboflavin deficiency.

Stability

Riboflavin, in its aqueous form, is degradable by light and up to 50 % may be lost if foods are left out in sunlight or any UV light. Because of this light sensitivity, riboflavin will rapidly disappear from milk kept in glass bottles exposed to the sun or bright daylight (85% within 2 hours). Riboflavin is stable when heated and so is not easily destroyed in the ordinary processes of cooking, but it will leach into cooking water. The pasteurization process causes milk to lose about 20% of its riboflavin content. Alkalis such as baking soda also destroy riboflavin. Sterilization of foods by irradiation or treatment with ethylene oxide may also cause destruction of riboflavin.

Physiological interactions

- Thyroxine and triodothyroxine stimulate the FMN and FAD in mammalian systems
- Anticholinergic drugs increase the absorption of riboflavin by allowing it to stay longer at absorption sites

Impact on metabolism, absorption, utilization and storage of riboflavin e.g. by:

- Ouabain (treatment of congestive heart failure)
- Theophylline (muscle relaxant, diuretic, central nervous stimulant)
- Penicillin (displaces riboflavin from its binding protein, thus inhibiting transport to the central nervous system)
- Chlorpromazin (anti-psychotic drug), barbiturates and possibly tricyclic antidepressants prevent the incorporation of riboflavin into FAD
- Riboflavin impairs the antibiotic activity of streptomycin, erythromycin, tyrothricin, carbomycin and tetracyclines
- Caffeine, zinc, copper and iron may chelate with riboflavin and affect its absorption

Deficiency

Overt clinical symptoms of riboflavin deficiency are rarely seen in developed countries.

However, the sub-clinical stage of deficiency, characterized by a change in biochemical indices, is more common. Riboflavin deficiency rarely occurs in isolation, and is usually in combination with deficiencies of other B-complex vitamins, because flavoproteins are also involved in the metabolism of other B-complex vitamins. The absorption of iron, zinc and calcium is impaired by riboflavin deficiency.

Clinically, riboflavin-deficiency affects many organs and tissues. The most prominent effects are on the skin, mucosa and eyes:

- Glossitis (magenta tongue, geographical tongue)
- Cheilosis, angular stomatitis (fissures at the corners of the mouth)
- Sore throat
- Burning of the lips, mouth, and tongue
- Inflamed mucous membranes
- Pruritus (itching)
- Seborrheic dermatitis (moist scaly skin inflammation)
- Corneal vascularization associated with sensitivity to bright light, impaired vision, itching and a feeling of grittiness in the eyes

In severe long-term deficiency, damage to nerve tissue can cause depression and hysteria. Other symptoms are normocytic and normochromic anemia, and peripheral neuropathy of the extremities (tingling, coldness and pain). Low intracellular levels of flavin coenzymes could affect mitochondrial function, oxidative stress and blood vessel dilation, which have been associated with pre-eclampsia during pregnancy.

Groups at risk

- Individuals with inadequate food intake e.g. the elderly, chronic dieters or people with elimination diets
- Pregnant and breastfeeding women (additional demands)
- Infants and school children
- Adolescents, particularly girls
- Chronic alcoholics
- Individuals with chronic disorders (e.g. tuberculosis, diabetes) and intestinal malabsorption (e.g. morbus Crohn's Disease, lactose intolerance) and trauma, including burns and surgery
- Medication users (oral-contraceptives, antibiotics, tranquillizers)
- Athletes
- Newborns after phototherapy for newborn hyperbilirubinemia

Reducing disease risk: therapeutic use

Eye-related diseases

Oxidative damage of lens proteins by light may lead to the development of age-related cataracts. Riboflavin deficiency leads to decreased glutathione reductase activity, which can result in cataracts. Therefore, riboflavin is used in combination with other antioxidants, like vitamin C and carotenoids, in the prevention of age-related cataracts. Riboflavin has been used to treat corneal ulcers, photophobia and noninfective conjunctivitis in patients without any typical signs of deficiency. Most cases of riboflavin deficiency respond to daily oral doses of 5 – 10 mg.

Migraines

People suffering from migraine headaches have a modified mitochondrial oxygen metabolism. Because riboflavin plays an important role in energy production, supplemental riboflavin has been investigated to alleviate migraines. When migraine sufferers took 400 mg /day of riboflavin for 3 months, they reported significant reductions in both migraine severity and frequency.

Prevention of deficiencies in high-risk patients

Patients suffering from achlorhydria, vomiting, diarrhea, hepatic disease, or other disorders preventing absorption or utilization, should be treated parenterally. Deficiency symptoms begin to improve in 1 – 3 days, but complete resolution may take weeks.

Elevated blood pressure

A placebo controlled double-blind randomized controlled trial in cardiovascular disease (CVD) patients recently reported that riboflavin intervention at the dietary level of 1.6 mg/d resulted in a reduction of systolic blood pressure by 13 mmHg and diastolic blood pressure by almost 8 mmHg, specifically in those individuals with the MTHFR 677 TT genotype. The global distribution of individuals with two copies of MTHFR 677T is thought to range from close to 0% in Sub-Saharan Africa to 32% in Mexico.

Recommended Daily Intake (RDI)

Dietary recommendations for riboflavin exist in many countries, where mean values for adult males vary between 1.3 and 1.6 mg daily. The recommendations of the Food and Nutrition Board of the US National Research Council are based on feeding studies conducted in the 1940s, which showed that riboflavin intake of 0.55 mg or less per day results in clinical signs of deficiency after about 90 days. These data have led to the assumption that an intake of 0.6 mg per 1,000 kcal should supply the needs of healthy people.

Safety

Riboflavin is non-toxic. No cases of toxicity from ingestion of riboflavin have been reported. A harmless yellow coloration of urine occurs at high doses. The limited capacity of the gastrointestinal tract to absorb this vitamin makes any significant risk unlikely, and because riboflavin is water-soluble, excess amounts are simply excreted.

Supplements and food fortification

Riboflavin is available as oral preparations, alone, in multivitamin and vitamin B-complex preparations, and as an injectable solution. Crystalline riboflavin (E101) is poorly soluble in water, so riboflavin-5'- phosphate (E 106), a more expensive but more soluble form of riboflavin, has been developed for use in liquid formulations. Riboflavin is often added to flour, bakery products and beverages to compensate for losses due to processing. It is also used to fortify milk, breakfast cereals and dietetic products. Due to its bright yellow color, riboflavin is sometimes added to other drugs or infusion solutions as a marker.

Production

Riboflavin can be produced by chemical synthesis or by fermentation processes. Chemical processes are usually refinements of the procedures developed by Kuhn and by Karrer in 1934 using xylene, D-ribose and alloxan as starting materials. Various bacteria and fungi are commercially employed to synthesize riboflavin, using cheap natural materials and industrial wastes as a growth medium.

Recommended daily intakes (RDI) *

Group	Life stage	Dose/day**
Infants	<6 months	0.3 mg (AI)
Infants	7 – 12 months	0.4 mg (AI)
Children	1 – 3 years	0.5 mg
Children	4 – 8 years	0.8 mg
Children	9 – 13 years	0.9 mg
Males	>14 years	1.3 mg
Females	14 – 18 years	1.0 mg
Females	>19 years	1.1 mg
Pregnancy	14 – 50 years	1.4 - 5 mg
Breastfeeding	14 – 50 years	1.7 mg

** Institute of Medicine (2001)*
*** Adequate intake (AI)*
If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

History

1879 – Blyth isolates lactochrome – a water-soluble, yellow fluorescent material – from whey.

1932 – Warburg and Christian extract a yellow enzyme from brewer's yeast and suggest that it plays an important part in cell respiration.

1933 – Kuhn and team obtain a crystalline yellow pigment with growth-promoting properties from egg white and whey, which they identify as vitamin B2.

1934 – Kuhn and his team in Heidelberg, and Karrer and colleagues in Zurich, synthesize pure riboflavin.

1937 – The Council on Pharmacy and Chemistry of the American Medical Association names the vitamin 'riboflavin'.

1937 – Theorell determines the structure of flavin mononucleotide, FMN.

1938 – Warburg and Christian isolate and characterize flavin adenine dinucleotide (FAD) and demonstrate its involvement as a coenzyme.

1941 – Sebrell and colleagues demonstrate clinical signs of riboflavin deficiency in human feeding experiments.

1968 – Glatzle and colleagues propose the use of the erythrocyte glutathione reductase test as a measurement of riboflavin status.