INE INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Micronutrients: Vitamin B2 (Riboflavin)

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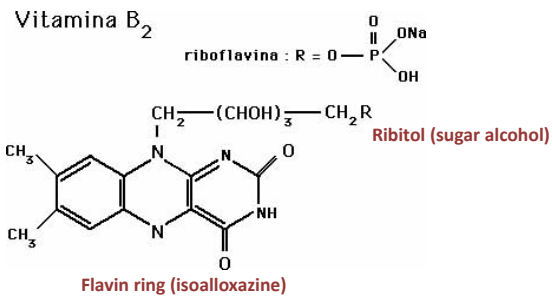
B Vitamins At a Glance

Letter	Names	Notes/Actions
B1	Thiamin, Benfotiamine	Energy, heart, muscle, and nerve function
B2	Riboflavin, R 5'-Phosphate	Energy, red blood cells, vision
B3	Niacin, Nicotinic Acid, Niacinamide	Energy, nerve function, circulation and heart
B4	Choline, Adenine, Carnitine	Loosely considered as B vitamins - cell membranes, memory, neuromuscular
B5	Pantothenic Acid	Coenzyme A, adrenals, skin
B6	Pyridoxine, Pyridoxal 5'-Phosphate	Brain and nerve, hormones, protein synthesis
B7	Biotin	Hair, metabolism
B8	Inositol	Loosely considered a B vitamin
B9	Folate, Methylfolate, Folinic Acid	Red blood cell production, DNA repair, brain
B10	Pteroylmonoglutamic Acid (PABA – Para-aminobenzoic Acid)	Really a form of folate, skin protector
B11	Salicylic Acid	Not technically a vitamin, loosely categorized
B12	Cobalamin	Red blood cells, DNA repair, nervous system

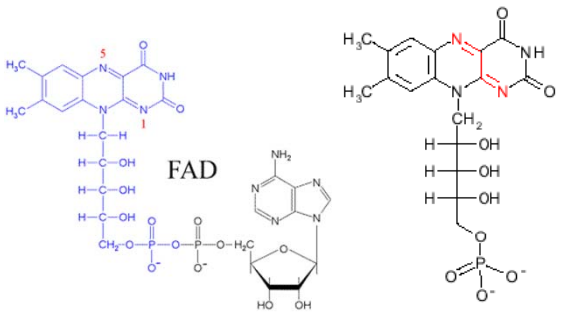
Vitamin B2 General Info

- ✓ Also known as riboflavin
- ✓ Water-soluble B vitamin
- ✓ The word "flavin" comes from the Latin "flavus," meaning yellow
  - ➢ Vitamin B2 gets its name from its color
  - ➢ When consumed in excess of needs, urine becomes bright yellow as the excess riboflavin is excreted
- ✓ Integral component of coenzymes:
  - ➢ FAD: flavin adenine dinucleotide, i.e., in Krebs cycle
  - ➢ FMN: flavin mononucleotide (riboflavin-5'-phosphate)
- ✓ Coenzymes derived from riboflavin are termed flavocoenzymes
- ✓ Enzymes that use a flavocoenzyme are called flavoproteins

Vitamin B2 Chemical Structure



Riboflavin Coenzyme Forms



Riboflavin Absorption

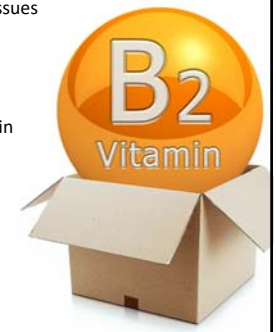
- ✓ Requires strong stomach acid to cleave from protein carrier
  - ➢ Riboflavin, FAD, and FMN need to be freed before absorption
- ✓ Requires intestinal phosphokinases to convert before absorption
  - ➢ FAD Pyrophosphatase: FAD to FMN
  - ➢ FMN Phosphatase: FMN to riboflavin
  - ➢ Nucleotide Diphosphatase and Alkaline Phosphatase: Riboflavin phosphate to riboflavin
- ✓ About 7% of FAD is bound to monoamine oxidase and succinate dehydrogenase and is not absorbed
- ✓ Active transport in proximal small intestine
- ✓ Some passive diffusion occurs in large doses
- ✓ Average absorption of food riboflavin is 95% up to 25 mg
  - ➢ Optimal absorption occurs at 15-20 mg
- ✓ Free form is what traverses intestinal epithelium and into cells

Riboflavin Transport

- ✓ Free form of riboflavin absorbed into intestinal epithelium
- ✓ In mucosal cells it's phosphorylated to FMN
  - ➢ Catalyzed by flavinokinase
  - ➢ Requires ATP
- ✓ It's again dephosphorylated to riboflavin at the blood stream and enters the portal circulation
- ✓ At the liver it's converted back to FMN and FAD by flavokinase
- ✓ FAD is the predominant form in tissue
- ✓ Most flavins in blood are as riboflavin
- ✓ Transported in blood by proteins
  - ➢ Albumin – primary transporter
  - ➢ Globulins (primarily immunoglobulins)
  - ➢ Fibrinogen
- ✓ Free riboflavin transported into most tissues by active transport
- ✓ Brain uptakes as FAD

Riboflavin Storage

- ✓ Found in small quantities in most tissues Highest in:
  - ➢ Kidney
  - ➢ Liver
  - ➢ Heart
- ✓ Mostly converted to FAD and FMN in tissues
- ✓ Synthesis of FAD and FMN is under hormonal control – they increase activity of flavokinase enzyme
  - ➢ ACTH
  - ➢ Thyroid
  - ➢ Aldosterone



Riboflavin Metabolism and Excretion

- ✓ Riboflavin binding proteins specific to pregnancy are essential to normal fetal development
- ✓ Unbound flavins
  - ➢ Relatively labile
  - ➢ Rapidly hydrolyzed to free riboflavin, which diffuses from cells and is excreted
- ✓ Intracellular phosphorylation: metabolic trapping
- ✓ Excess excreted in the urine as
  - ➢ Riboflavin
  - ➢ 7-hydroxymethylriboflavin (7-α-hydroxyriboflavin)
  - ➢ Lumiflavin
- ✓ Some urinary metabolites reflect bacterial activity in the gastrointestinal tract as well

Influences on Riboflavin Absorption and Conversion

Decrease Absorption

- ✓ Divalent minerals chelate FMN and riboflavin
  - ➢ Copper
  - ➢ Zinc
  - ➢ Manganese
  - ➢ Iron
- ✓ Alcohol impairs digestion and absorption
- ✓ Hypothyroidism
- ✓ Adrenal fatigue
- ✓ Homocysteine
- ✓ Medications
  - ➢ Anticholinergic medications
  - ➢ Methotrexate
  - ➢ Probenecid
  - ➢ Thiazide diuretics

Increases Absorption

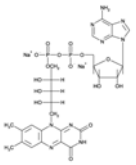
- ✓ Supplement on empty stomach
- ✓ Vitamins
  - ➢ A
  - ➢ B vitamins: B1, B3, B5, B6, B7 (biotin), B9 (folate), and B12,
- ✓ Minerals
  - ➢ Chromium
  - ➢ Copper, folate, magnesium, phosphate, potassium
- ✓ Glutathione
- ✓ Cysteine

Vitamin B2 Roles

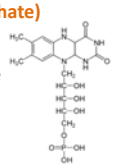
- ✓ Produces energy – important in Krebs Cycle
- ✓ Antioxidant
- ✓ Needed for conversion of vitamin B6 and folate to active forms
- ✓ Growth and repair
- ✓ Methylation
- ✓ Thyroid function
- ✓ Red blood cell production

Active Co-Enzyme Riboflavin Forms and Functions

- ✓ **FAD: flavin adenine dinucleotide**
  - Krebs cycle and electron transport chain
  - Cofactor for methylenetetrahydrofolate reductase (MTHFR)
  - Used by kynurenine 3-monooxygenase to convert tryptophan into vitamin B3 (niacin)
  - Allows recycling of glutathione (cofactor for glutathione reductase)

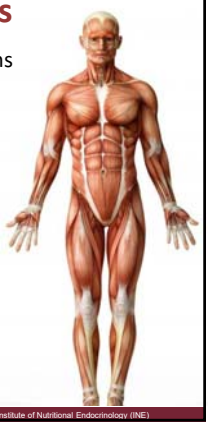


- ✓ **FMN: flavin mononucleotide (riboflavin-5'-phosphate)**
  - Principal form in which riboflavin is found in cells and tissues
  - Requires more energy to produce, but is more soluble than riboflavin
  - Redox reactions
  - Part of glutamate synthase



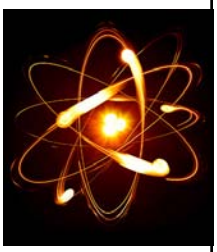
Flavoproteins

- ✓ When FAD and FMN attach to proteins they are called flavoproteins
- ✓ Mainly located where oxygen-based energy production is needed: heart and skeletal muscle
- ✓ There are 90 flavoproteins in the human genome
  - 84% require FAD
  - 16% require FMN
  - 5 require both



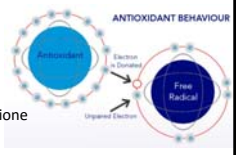
Vitamin B2 and Oxidation-Reduction (Redox) Reactions

- ✓ Processes that involve the transfer of electrons
- ✓ Flavocoenzymes participate in redox reactions in numerous metabolic pathways
- ✓ Critical for the metabolism of carbohydrates, lipids, and proteins
- ✓ FAD is part of the electron transport (respiratory) chain; central to energy production
- ✓ Participate in the metabolism of drugs and toxins In conjunction with cytochrome P-450

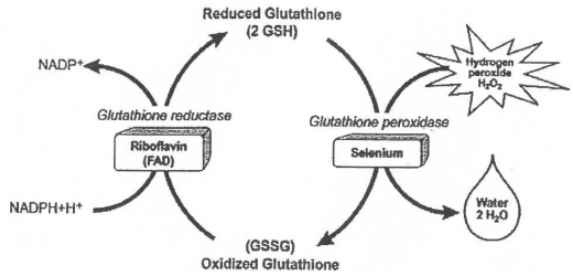


Vitamin B2 and Antioxidant Functions

- ✓ **Glutathione reductase**
  - Redox cycle of glutathione
  - Major role in protecting from reactive oxygen species, such as hydroperoxides
  - Requires FAD to regenerate two molecules of reduced glutathione from oxidized glutathione
- ✓ **Glutathione peroxidases**
  - Selenium-containing enzymes
  - Require two molecules of reduced glutathione to break down hydroperoxides
  - Involved in glutathione oxidation-reduction (redox) cycle
- ✓ **Xanthine oxidase**
  - Catalyzes the oxidation of hypoxanthine and xanthine to uric acid
  - Uric acid is one of the most effective water-soluble antioxidants in the blood
  - Riboflavin deficiency can result in reduced blood uric acid levels



Glutathione Oxidation Reduction Cycle



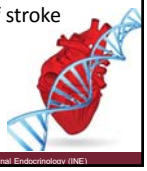
Vitamin B2 and Cataracts

- ✓ Might help prevent cataracts: damage to the lens of the eye, which can lead to cloudy vision
  - Double-blind, placebo-controlled study, niacin and riboflavin supplementation group had fewer cataracts than people who took other vitamins and nutrients
  - Decreased risk of age-related cataract (33% to 51%) in men and women in the highest dietary riboflavin intake (median of 1.6 to 2.2 mg/day)
  - Individuals in the highest quintile of riboflavin status, as measured by red blood cell glutathione reductase activity, had approximately half the occurrence of age-related cataract as those in the lowest quintile of riboflavin status
  - A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of riboflavin intake were 50% less likely to have cataracts than those in the lowest quintile
- ✓ Light-induced oxidative damage of lens proteins may lead to the development of age-related cataracts

http://www.drritamarie.com/go/LPIRiboflavin

Vitamin B2 and Cardiovascular Disease

- ✓ Riboflavin acts as a cofactor for MTHFR
- ✓ Riboflavin is needed to generate 5-methyltetrahydrofolate for remethylation of homocysteine to methionine
- ✓ Genetic studies provide evidence to support a link between suboptimal B-vitamin status and CVD risk
- ✓ MTHFR SNP associated with hypertension: blood pressure 140/90 mm Hg or greater and increased risk of stroke
- ✓ Blood pressure in patients homozygous for MTHFR is highly responsive to low-dose riboflavin



Vitamin B2 and Cancer

- ✓ MTHFR SNP decreases production of S-adenosylmethionine (SAMe), the methyl donor for the methylation of DNA and histones
- ✓ Aberrant methylation changes alter the structure and function of DNA and histones during cancer development
- ✓ Folate deficiency and elevated homocysteine concentrations may increase cancer risk
- ✓ The substitution of a cytosine by a thymine in position 677 (C677T) in the MTHFR gene affects the binding of FAD
- ✓ MTHFR 677TT genotype may be at increased risk of cancer
- ✓ Riboflavin may improve response to folic acid supplementation in individuals with a reduced MTHFR activity

Vitamin B2 and Migraine Headaches

- ✓ Impaired mitochondrial oxygen metabolism in the brain may play a role in the pathology of migraine headaches
- ✓ Riboflavin is the precursor of FAD and FMN in the mitochondrial electron transport chain
- ✓ Evidence of reduction in frequency and duration of migraines with riboflavin supplementation
- ✓ One double-blind, placebo-controlled study showed that taking 400 mg of riboflavin a day cut the number of migraine attacks in half

Vitamin B2 and Autism

- ✓ Related to fat metabolism, which is often improved by supplemental carnitine (500 mg), riboflavin (50 mg), and copper (1-2 mg)
- ✓ Important to start the riboflavin before CoQ10 and carnitine
- ✓ Supplementation along with vitamin B6 and magnesium, reduces dicarboxylic acids (abnormal organic acids) in the urine of autistic children
- ✓ Related to reducing very-long-chain-fatty-acids (lignoceric, hexacosanoic, and octacosanoic) that are frequently observed in fatty acid blood testing of autistic people
- ✓ Takes part in the conversion of tryptophan and the synthesis of the body's own anti-inflammatory substances

http://www.drritamarie.com/go/PubMed22081621

Substances That Deplete Vitamin B2

- ✓ **Tricyclic antidepressants**
  - ➢ Imipramine (Tofranil)
  - ➢ Desimpramine (Norpramin)
  - ➢ Amitriptyline (Elavil)
  - ➢ Nortriptyline (Pamelor)
- ✓ **Antipsychotic medications**
  - ➢ Chlorpromazine
  - ➢ Thorazine
- ✓ Doxorubicin
- ✓ Phenytoin (Dilantin)
- ✓ Thiazide diuretics
- ✓ Anticholinergic medications
- ✓ Alcohol

Vitamin B2 Interactions

- ✓ **Tetracycline:** Riboflavin interferes with the absorption and effectiveness
- ✓ **Methotrexate:** Interferes with how the body uses riboflavin
- ✓ **Probenecid:** Decrease the absorption of riboflavin from the digestive tract and increases urinary loss; used to treat gout

Risk Factors for Vitamin B2

- ✓ **Alcoholics**
  - ➢ Decreased intake
  - ➢ Decreased absorption
  - ➢ Impaired utilization of riboflavin
- ✓ **Anorexia**
- ✓ **Lactose intolerance**
- ✓ **Hypothyroid and adrenal fatigue**
  - ➢ The conversion of riboflavin into FAD and FMN is impaired
- ✓ **Very physically active people** (athletes, laborers) - slightly increased riboflavin requirement

B-Complex Nutrient Interactions with Vitamin B2

- ✓ Flavoproteins needed for metabolism of vitamin B6, niacin, and folate
- ✓ Severe riboflavin deficiency may affect many enzyme systems
  - ➢ Conversion B6 to its coenzyme form, pyridoxal 5'-phosphate (PLP) - FMN-dependent enzyme, pyridoxine 5'-phosphate oxidase (PPO)
  - ➢ The synthesis of the niacin-containing coenzymes, NAD and NADP, from the amino acid tryptophan - FAD-dependent enzyme, kynurenine mono-oxygenase
  - ➢ Severe riboflavin deficiency can decrease the conversion of tryptophan to NAD and NADP
  - ➢ MTHFR is an FAD-dependent enzyme
- ✓ Higher riboflavin intakes associated with decreased plasma homocysteine

Iron Interactions with Vitamin B2

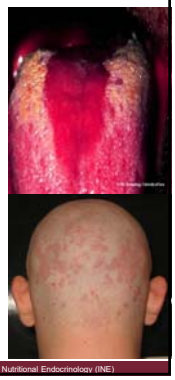
- ✓ Riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin (Hb)
- ✓ Improving riboflavin status found to increase circulating Hb levels
- ✓ Riboflavin improves the response of iron-deficiency anemia to iron therapy when riboflavin is deficient
- ✓ Randomized, double-blind intervention trials conducted in pregnant women with anemia in Southeast Asia showed that a combination of folic acid, iron, vitamin A, and riboflavin improved Hb levels and decreased anemia prevalence compared to the iron-folic acid supplementation alone

Vitamin B2 RDI

- **Infants:**
  - ✓ Birth up to 6 months: 0.3 mg (adequate intake)
  - ✓ 7-12 months: 0.4 mg (adequate intake)
- **Children:**
  - ✓ 1-3 years: 0.5 mg a day
  - ✓ 4-8 years: 0.6 mg a day
  - ✓ 9-13 years: 0.9 mg a day
  - ✓ Males: 14-18 years – 1.3 mg a day
  - ✓ Females: 14-18 years – 1 mg a day
- **Adults:**
  - ✓ Males: 19 years and older – 1.3 mg a day
  - ✓ Females: 19 years and older – 1.1 mg a day
- **Women who are pregnant or breastfeeding:**
  - ✓ Pregnant women: 1.4 mg
  - ✓ Breastfeeding women: 1.6 mg a day

Vitamin B2 Deficiency

- ✓ Common if dietary intake is lacking, as it is continuously excreted in the urine
- ✓ Always accompanied by a deficiency of other vitamins
- ✓ Types of riboflavin deficiency:
  - **Primary riboflavin deficiency:** Diet is poor in vitamin B2
  - **Secondary riboflavin deficiency:** Could be a result of poor absorption, utilization, or increase in the excretion
- ✓ Riboflavin deficiency can result in decreased xanthine oxidase activity, reducing blood uric acid levels
- ✓ Severe riboflavin deficiency can decrease the conversion of tryptophan to NAD and NADP, increasing the risk of niacin deficiency



Signs and Symptoms Vitamin B2 Deficiency

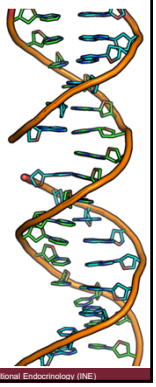
- ✓ Angular cheilitis: cracks at the corners of the mouth
- ✓ Cracked lips
- ✓ Seborrheic dermatitis: Moist, scaly skin inflammation
- ✓ Inflammation of the lining of the mouth and tongue
  - Swollen, magenta-colored tongue
- ✓ Mouth ulcers
- ✓ Red lips
- ✓ Swelling and soreness of the throat
- ✓ Fatigue
- ✓ Slowed growth
- ✓ Digestive problems
- ✓ Iron-deficiency anemia or megaloblastic anemia
- ✓ Eyes may be sensitive to bright light; they may also be fatigued, itchy, watery, and/or bloodshot

Vitamin B2 and Preeclampsia

- ✓ Preeclampsia: Elevated blood pressure, protein in the urine, and edema during pregnancy
- ✓ About 5% of women with preeclampsia progress to eclampsia, a significant cause of maternal and fetal death
- ✓ Eclampsia: seizures, high blood pressure, and increased risk of hemorrhage
- ✓ A study in 154 pregnant women at increased risk of preeclampsia: riboflavin deficient group were 4.7 times more likely to develop preeclampsia than those with adequate riboflavin
- ✓ Causes: Not clear; decreased intracellular flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress, and interfere with nitric oxide release and thus blood vessel dilation
- ✓ Meta-analysis of 51: MTHFR C677T polymorphism associated with preeclampsia in Caucasian and East Asian populations

Impact of Vitamin B2 Excess

- ✓ There is no known toxicity to riboflavin
- ✓ Excess easily excreted in the urine
- ✓ Possible reactions to very high doses may include:
  - ➢ Itching
  - ➢ Numbness
  - ➢ Burning or prickling sensations
  - ➢ Sensitivity to light
- ✓ Doses above 10 mg per day may cause eye damage from the sun; sunglasses that protect their eyes from ultraviolet light can decrease the risk
- ✓ Excess riboflavin may increase the risk of DNA strand breaks in the presence of chromium (VI), a known carcinogen
  - ➢ This may be of concern to workers exposed to chrome



Assessing Status of Vitamin B2

- ✓ Measurement of glutathione reductase activity in red blood cells: commonly used
  - ➢ Erythrocyte glutathione reductase activation coefficient (EGRac) assay
  - ➢ Measures activity of glutathione reductase before and after reactivation with FAD
  - ➢ EGRac is calculated as the ratio of FAD-stimulated to unstimulated enzyme activity and indicates the degree of tissue saturation with riboflavin
  - ➢ EGRac is a functional measure that has shown to be effective in reflecting biomarker status from severe deficiency to normal status
- ✓ Urinary riboflavin excretion
- ✓ Organic acid test: suberate
  - ➢ Riboflavin helps to metabolize fatty acids

Food Sources of Vitamin B2

The majority of healthy people who eat a well-balanced diet will get enough riboflavin.

Plant-Based

- ✓ Brewer's yeast
- ✓ Almonds
- ✓ Whole grains
- ✓ Wheat germ
- ✓ Wild rice
- ✓ Mushrooms
- ✓ Soybeans
- ✓ Broccoli
- ✓ Brussels sprouts
- ✓ Spinach

Animal-Based

- ✓ Organ meats
- ✓ Milk
- ✓ Yogurt
- ✓ Eggs

Food Preparation That Affects Vitamin B2

- ✓ Destroyed by light
  - ➢ Store away from light to protect its riboflavin content
- ✓ Not destroyed by heat
- ✓ Can be lost in water when foods are boiled or soaked

WH Foods Vitamin B2 Foods Ranking

World's Healthiest Foods ranked as quality sources of vitamin B2

Food	Serving Size	Cals	Amount (mg)	DRI/DV (%)	Nutrient Density	World's Healthiest Foods Rating
Spinach	1 cup	41.4	0.42	32	14.0	excellent
Beet Greens	1 cup	38.9	0.42	32	15.0	excellent
Mushrooms, Crimini	1 cup	15.8	0.35	27	30.6	excellent
Asparagus	1 cup	39.6	0.25	19	8.7	excellent
Sea Vegetables	1 TBS	10.8	0.14	11	17.9	excellent
Eggs	1 each	77.5	0.26	20	4.6	very good
Cow's milk	4 oz	74.4	0.21	16	3.9	very good
Collard Greens	1 cup	62.7	0.20	15	4.4	very good
Broccoli	1 cup	54.6	0.19	15	4.8	very good
Swiss Chard	1 cup	35.0	0.15	12	5.9	very good
Green Beans	1 cup	43.8	0.12	9	3.8	very good
Mushrooms, Shiitake	0.50 cup	40.6	0.12	9	4.1	very good
Bok Choy	1 cup	20.4	0.11	8	7.5	very good
Turnip Greens	1 cup	28.8	0.10	8	4.8	very good
Kale	1 cup	36.4	0.09	7	3.4	very good
Mustard Greens	1 cup	36.4	0.09	7	3.4	very good

http://www.drritamarie.com/go/WHFVitaminB2Foods

Herbs High In Vitamin B2

- ✓Parsley
- ✓Paprika
- ✓Chili powder
- ✓Coriander seed
- ✓Spearmint
- ✓Tarragon
- ✓Basil
- ✓Thyme
- ✓Fenugreek
- ✓Fennel
- ✓Dill weed
- ✓Celery seed
- ✓Mustard seed
- ✓Turmeric
- ✓Rosemary

Vitamin B2 Supplementation

- ✓Generally included in multivitamins and B-complex vitamins
  - ➢Riboflavin
  - ➢Riboflavin 5'-monophosphate
  - ➢Riboflavin 5'-phosphate sodium
- ✓It also comes separately in 25 mg, 50 mg, and 100 mg capsules or tablets
- ✓Also available in liquid form

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