

Vitamins, Trace Elements and Micronutrients

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Objectives for this review:

1. Sources
2. Absorption and metabolism
3. Functions
4. Deficiency and toxicity

Key Words

acrodermatitis	megaloblastic anemia
alpha-tocopherol	niacin
ascorbic acid	pantothenic acid
beriberi	parathyroid hormone
beta carotene	pellagra
biotin	pyridoxine
carcinoid syndrome	retinoic acid
ceruloplasmin	riboflavin
cheilosis	scurvy
chromium	selenium
coagulopathy	serotonin
cobalamin	thiamine
coenzyme A	total parenteral nutrition
copper	tryptophan
follic acid	vitamin A
glossitis	vitamin B1-9
glucose intolerance	vitamin B12
goiter	vitamin C
Hartnup disease	vitamin D
homocysteine	vitamin E
hypothyroidism	vitamin K
intrinsic factor	Wernicke-Korsakoff syndrome
iodide	Wilson's disease
iron	xerophthalmia
Leigh's syndrome	zinc
manganese	

Fat Soluble Vitamins

Vitamin B1 (Thiamine) RDI = 1 mg

Sources of thiamine include pork, rice, legumes, cereals, and yeast. High temperatures and very acidic conditions inactivate this vitamin. Absorption is through the small intestine. The storage capacity of thiamine is limited, and its half-life is ~ 20 days. Thiamine is a catalyst in the oxidative carboxylation reaction that converts pyruvate to acetyl CoA. It also is necessary for the pentose phosphate pathway and for the initiation of nerve impulse propagation.

Three disorders can result from thiamine deficiency: Beriberi, Wernicke-Korsakoff syndrome, and Leigh's syndrome. Descriptions of Beriberi date back thousands of years. When this occurs at a few months of age, the presentation is severe cardiac disease with cardiomegaly, cyanosis, tachycardia, and dyspnea. Gastrointestinal symptoms may occur as well. In adults, a peripheral motor and sensory neuropathy occurs, and cardiac involvement may be prominent with heart failure due to cardiomyopathy.

Wernicke-Korsakoff syndrome is rarely seen outside the setting of alcoholism. Wernicke's disease presents with nystagmus, ophthalmoplegia, ataxia, and confusion. Korsakoff's syndrome presents with confabulation and short term memory disruption, though cognition is otherwise intact. Patients may present with some or all of these findings. Treatment with thiamine, 50 mg IV daily, can prevent sequelae of this disease.

Leigh's syndrome is a very rare mitochondrial disease causing demyelination within the thalamus, brainstem, pons, and peripheral nervous system. The symptoms are ataxia, dysarthria, movement disorders, atrophy, weakness, and areflexia. Excess thiamine is excreted via the kidneys; toxicity is not described.

Vitamin B2 (Riboflavin) RDI = 12-15 mg

Numerous foods contain riboflavin including fish, meat, milk, eggs, green vegetables, yeast and enriched foods. It is absorbed in the small intestine after separation from albumin and other carrier proteins by gastric acid and proteolytic enzymes.

Within the cytoplasm, riboflavin is phosphorylated to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Riboflavin is an essential part of coenzymes involved in respiratory pathways, functions as a catalyst for oxidation and reduction reactions in mitochondria and as an electron transporter. The half-life is < 20 days.

The symptoms of deficiency include a beefy red tongue, and soreness and burning of the lips, tongue, mouth, and oral pharynx. Dermatitis, photophobia, and normocytic, normochromic anemia may also be present. Avoidance of dairy products, starvation, malabsorption disorders, rare genetic disorders of riboflavin metabolism, and use of barbiturates (by impairing riboflavin's function) are all risks for deficiency. Toxicity is unlikely as the ability of the GI tract to absorb excessive amounts is limited.

Vitamin B3 (Niacin) RDI = 13-18 equivalents

Sources of niacin are beef, pork, and chicken. Much of the niacin in cereals is bound and unavailable. Nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), the primary dietary forms of niacin, are converted to nicotinamide and nicotinic acid in the intestinal lumen. These are absorbed and taken up by liver, kidney, and erythrocytes. Here, nicotinamide, nicotinic acid, and tryptophan are converted to NAD and NADP.

Liver, muscle, and other tissues with high energy requirements store and utilize NAD and NADP for numerous enzymatic reactions. NAD and NADP are involved in the synthesis and metabolism of carbohydrates, fatty acids, and proteins.

Niacin deficiency can cause pellagra. This presents with a hyperpigmented rash occurring in sun-exposed areas, red tongue, diarrhea, and neurologic symptoms including insomnia, anxiety, delusions, and dementia. Except for alcoholics, this is now rare in developed countries. Treatment with niacin or tryptophan is effective.

Besides reduced niacin intake, several conditions effecting tryptophan production, absorption, and metabolism result in niacin deficiency and pellagra. Reduced pyridoxal phosphate, which functions to increase tryptophan production, occurs with isoniazid use. Hartnup disease is a rare AR disorder in which there is reduced absorption of tryptophan. In carcinoid syndrome, tryptophan is shunted away from niacin production and toward hydroxytryptophan and serotonin. The most common toxicity of niacin is flushing. Doses > 1000 mg are associated with nausea, vomiting, pruritus, hives, and liver injury.

Vitamin B5 (Pantothenic acid) RDI = 4-7 mg

Pantothenic acid is present in almost all animal and plant food, mainly as a component of coenzyme A (CoA). CoA is a cofactor in acetylation reactions including the tricarboxylic acid cycle (TCA) and fatty acid synthesis and breakdown. Many peptides, such as ACTH, are activated by acetylation. CoA is also essential for synthesizing vitamins A and D, cholesterol, heme, steroids, amino acids, and proteins. After ingestion, CoA is broken down to pantothenic acid and absorbed from the small intestine. Pantothenic acid is taken up by most cells and phosphorylated to CoA.

Deficiency is only seen in the severely malnourished. Manifestations include paresthesias, dysesthesias (burning feet syndrome), gastrointestinal distress, and poor wound healing. Excess pantothenic acid is secreted by the kidney after being hydrolyzed to cysteamine, and there is no described toxicity.

Vitamin B7 (Biotin) RDI = 30-40 micrograms

Biotin is produced by intestinal bacteria and widely present in foods including liver, egg yolk, soybeans, yeast, and a variety of plants. It is mainly absorbed in the small bowel. Biotin is a cofactor for carboxylase reactions. These enzymes include: acetyl CoA carboxylase, pyruvate carboxylase, propionyl CoA carboxylase, and beta-methylcrotonyl CoA carboxylase. Functioning as a CO₂ carrier for these enzymes, biotin is essential in carbohydrate and protein metabolism, protein and DNA synthesis, and cell replication.

Deficiency is rare and was previously seen in patients on long-term total parenteral nutrition (TPN). Raw egg white contains avidin, a substance that binds biotin and makes it unavailable to serve as a cofactor. A genetic deficiency of either biotinidase or holocarboxylase synthetase interferes with biotin metabolism.

Manifestations of biotin deficiency include mental status changes, anorexia, nausea, myalgias, dysesthesias, dermatitis, and alopecia. Defective or absent biotinidase or holocarboxylase synthetase causes multiple carboxylase deficiency. If not discovered and treated early with biotin supplementation, the neurologic complications are irreversible. Screening is done at birth. No toxicity has been described.

Vitamin B6 (Pyridoxine) RDI = 1.6-2 micrograms

Sources include plant foods, especially bananas and navy beans. Pyridoxine is especially important in amino acid metabolism. Pyridoxal phosphate is involved in sphingolipid and neurotransmitter synthesis, and gluconeogenesis.

Deficiency results in irritability, confusion, depression, stomatitis, glossitis, and cheilosis. Genetic abnormalities of enzymes that require pyridoxal phosphate can mimic pyridoxine deficiency. These disorders include homocystinuria, cystathionuria, and xanthurenic aciduria. Recently, attention has focused on the pyridoxal phosphate dependent enzyme cystathionine synthase which acts on serine and homocysteine to produce cystathionine. Pyridoxine deficiency increases level of homocysteine, a risk factor for atherosclerosis.

Toxicity can occur with high doses and includes dizziness, nausea, photosensitivity, peripheral neuropathy, and rash.

Vitamin B9 (Folic acid) RDI = 200 micrograms

This is present in green leafy vegetables, meat, nuts, fruits, and cereals. Folic acid is absorbed in the jejunum, and there is a large enterohepatic circulation of this vitamin. Folic acid primarily functions as a carbon donor for several reactions. Red cells, short lived cells, and cells with a high proliferation index are dependent on folic acid.

Malabsorption and malnutrition, and the elderly and alcoholic populations are prone to developing this deficiency. Increased folic acid requirements accompany hemolytic anemia, excessive erythropoiesis, and pregnancy. Deficiency of folic acid manifests as GI symptoms (diarrhea, cheilosis, glossitis), megaloblastic anemia, and neural tube defects. Neural tube defects have fallen substantially since foods became fortified with folic acid. Excessive folic acid may cause malaise, somnolence, and gastrointestinal symptoms.

Vitamin B12 (Cobalamin) RDI = 2 micrograms

Vitamin B12 is present in animal products. This vitamin is comprised of a group of compounds called corrinoids, of which cyanocobalamin is the most common. It is comprised of a central cobalt surrounded by 4 side chains. Absorption requires several steps, beginning with freeing B12 from dietary protein by pepsin in the stomach. B12 then binds to R-binders, specific B12 binding proteins in saliva. After the R binder-B12 complex enters the duodenum, it is hydrolyzed by pancreatic trypsin and free B12 then binds to intrinsic factor (IF). Though IF is synthesized and released from parietal cells in the stomach, R binders have a much higher binding affinity for B12 at low pH. The B12-IF complex disassociates after binding to specific receptors in the terminal ileum and B12 is absorbed and transported to the liver.

Dietary B12 deficiency is rare, though strict vegans are at risk. Disorders that interfere with the multi-step absorption pathway may also result in deficiency. Atrophic gastritis or gastric resection may eliminate intrinsic factor, acid, and pepsin. Maldigestion and malabsorption due to bacterial overgrowth, pancreatic insufficiency, or reduced distal ileum (diseased or resected) is the most common cause for deficiency.

The manifestations of B12 deficiency are gastrointestinal, hematologic, and neuropsychiatric. B12 is necessary for folic acid function. The GI symptoms include glossitis, anorexia, and diarrhea. Though a macrocytic anemia is classic, severe B12 deficiency can affect all bone marrow cell lines. Polysegmented neutrophils may be present. Neurologic symptoms include paresthesias from peripheral nerve involvement and long column spinal cord involvement resulting in balance disturbances. Cerebral dysfunction and dementia may also be seen. The diagnosis is made by measuring B12 levels. Serum methylmalonic acid (> 1000nmol/L) is helpful with borderline levels.

Vitamin C (Ascorbic acid) RDI = 60 mg

Vitamin C is found in fruits and vegetables. Vitamin C is absorbed in the distal small intestine. It functions biologically as a reducing agent, and also acts as a cofactor, co-substrate, enzyme complement, or anti-oxidant.

Proper collagen formation relies on vitamin C-dependent hydroxylation of proline and lysine. If this fails to occur, fibroblast and osteoblast function, and wound healing, is impaired. Vitamin C also stabilizes Vitamin E and folic acid, and is necessary for fatty acid transport across mitochondria as it is a cofactor for carnitine synthesis. For synthesis of norepinephrine from dopamine, vitamin C is a necessary cofactor.

Deficiency of vitamin C causes scurvy. Scurvy plagued explorers since ancient times. Today, this disease may be seen in the severely malnourished and in the alcoholic/drug-addicted population. The manifestations primarily relate to improper collagen formation. Findings include impaired wound healing, ecchymoses, loose teeth, gingivitis, petechiae, hair follicle hyperkeratosis, "corkscrew" body hair, arthralgias, joint swelling, weakness, depression and vasomotor instability.

High dose vitamin C may cause diarrhea, bloating, and false negative stool guaiac testing. Fatal cardiac arrhythmias have occurred in those with iron overload ingesting large doses.

Fat Soluble Vitamins

In addition to inadequate ingestion, patients with malabsorption and maldigestion disorders are at risk for fat soluble vitamin deficiency. These include small bowel disease, pancreatic insufficiency, cystic fibrosis, cholestasis, and advanced liver disease.

Vitamin A RDI = 1000 retinol equivalents

Vitamin A is comprised of a group of compounds called retinoic acids. These include retinol (animal - liver, kidney, egg yolk, butter), beta carotene (pigmented plants), and carotenoids.

Absorption of vitamin A is in the small intestine, and requires proteolysis in the stomach followed by the action of pancreatic enzymes and bile salts. Retinol is primarily stored in hepatic stellate cells. Vitamin A is important for vision, cellular differentiation, and immune function. Rod cells, which detect motion and regulate night vision, contain a protein partly comprised of retinol - rhodopsin. Cone cells, which absorb light and color in bright light, have the retinol containing protein iodopsin. Different groups of cone cells absorb and are stimulated by light at different frequencies, leading to transmission of stimuli to the brain of the three colors red, green, and blue. Normal fetal development of the eye requires vitamin A. All of the cells of the conjunctiva and retina have retinol binding proteins. Lastly, vitamin A has a role in cellular and humoral immunity.

Though rare in the U.S., this is the third most common vitamin deficiency worldwide and leads to xerophthalmia (abnormal corneal and conjunctival development), night blindness, and complete blindness in 500,000 children each year. Additional ocular manifestations of early childhood include Bitot's spots (squamous cell proliferation and keratinization of the conjunctiva), corneal perforation, keratomalacia, and punctate keratopathy.

High doses of vitamin A are toxic and can be divided into acute, chronic, and teratogenic. Acute toxicity occurs when more than 650,000 units, or 200 mg, are ingested. Symptoms include nausea, vomiting, malaise, vertigo, and blurry vision. Chronic disease may be seen with regular ingestion of $\geq 10X$ the RDI, causing visual problems, ataxia, alopecia, hyperlipidemia, bone and muscle pain, and hepatotoxicity. Hepatic injury presents as venoocclusive disease and cirrhosis. The risk of liver toxicity increases in the presence of underlying liver disease, kidney disease, or alcoholism. Vitamin A doses several times the RDI can cause spontaneous abortions and birth defects including microcephaly and cardiac abnormalities. Up to 10,000 IU/day is safe during pregnancy.

Vitamin D

Minimal daily light exposure ensures adequate vitamin D for most adults. The few foods containing vitamin D include fatty fish, liver, butter, and eggs. Foods fortified with vitamin D include milk, cereals, and infant formula. Exposure to UV light allows dermal synthesis of vitamin D₃ (cholecalciferol) from 7-dehydrocholesterol. Brief exposure is roughly equivalent to ingesting 200 IU.

Vitamin D is absorbed in the small intestine. In the liver, vitamin D₃ is hydroxylated to 25-OH-vitamin D. Further hydroxylation to the active form of vitamin D, 1, 25(OH)₂-vitamin D, occurs within mitochondria of the kidney's proximal tubules. Vitamin D metabolism is regulated by estrogen, growth hormone, and prolactin; however, it is especially dependent on calcium homeostasis. In the setting of hypocalcemia, parathyroid hormone level increases and this subsequently increases both renal tubule absorption of calcium and activity of alpha-1-hydroxylase. This enzyme is responsible for producing 1, 25(OH)₂ vitamin D, which then acts on the small bowel to increase calcium and phosphorus absorption.

Deficiency of vitamin D leads to demineralization of bones in order to maintain calcium homeostasis. Osteoporosis occurs in adults, and rickets in children. Hypophosphatemia and

hypocalcemia eventually occur, the later causing secondary hyperparathyroidism. Chronic glucocorticoid use inhibits vitamin D mediated intestinal calcium absorption.

Excessive vitamin D ($\geq 60,000$ IU/day) can cause hypercalcemia, hypercalcuria, polyuria, polydipsia, anorexia, vomiting, and muscle weakness.

Vitamin E RDI = 8-10 mg

Vitamin E is present in vegetable oils and is made up of a group of compounds known as tocopherols (saturated side chains) or tocotrienols (unsaturated side chains). Alpha-tocopherol is the predominant source in man. Pancreatic esterases are necessary to break down fatty acids, and bile assists with absorption of vitamin E in the small bowel. Vitamin E protects cell membranes from peroxidation through its antioxidant action as a free radical scavenger.

Deficiency due to poor intake is rare, but when it occurs may cause neurologic, muscular, and hematologic disturbances. These include spinocerebellar ataxia, myopathy, retinopathy, and a possible association with Alzheimer's disease. Red cell life span is shortened, and several congenital hemolytic diseases are associated with low vitamin E.

Vitamin E toxicity may cause nausea, vomiting, and diarrhea. There may be an increased risk of bleeding in those with a baseline elevated risk (i.e. taking warfarin), as well as an increased risk for hemorrhagic stroke in those without an increased bleeding risk. High dose supplementation may interfere with absorption of other fat soluble vitamins. Necrotizing enterocolitis in infants has occurred in the setting of high dose vitamin E.

Vitamin K RDI = 80 micrograms

Vitamin K is present in animal and plant foods and synthesized by gut bacteria. Approximately 8% is absorbed, and the $\frac{1}{2}$ life is very short at 2-3 hours. Pancreatic enzymes and bile are needed for proteolysis and absorption in the small bowel. As a coenzyme for carboxylase activity within liver cells, vitamin K acts as an oxidizing agent for the synthesis of clotting factors II, VII, IX, X and the anticoagulant proteins C, Z, S, and M.

Inadequate intake is rare in healthy individuals as a typical daily diet contains 200-500 mg. Vitamin K deficiency presents as a coagulopathy (\uparrow prothrombin time) manifesting as excessive bruising, petechiae, spontaneous bleeding, and bleeding from the GI or urologic tract. In addition to the usual causes of fat soluble vitamin deficiency, antibiotic use is an important etiology. Not only can antibiotics affect the gut flora, but some have a weak warfarin-like effect that inhibits vitamin K synthesis within the hepatocyte by impairing epoxide reductase. Vitamin K deficiency in infants may cause hemorrhagic disease of the skin, GI tract, and CNS. Parenteral vitamin K at birth, and in formula, is recommended. Toxicity is rare.

Trace Elements

Iron (Fe) RDI = 10 mg

Iron is present in meat, vegetables, liver, and eggs. Generally, approximately 10% of oral iron is absorbed. Meat has greater bioavailability than vegetables. Vegans have a further disadvantage in that some foods have phytates and phosphate which can reduce iron absorption by as much as 50%. In children, adolescents, and pregnant women, the physiologic demand for iron is higher. Absorption takes place primarily in the proximal small intestine and is aided by gastric acid. Iron absorption increases in the setting of iron deficiency and erythroid hyperplasia, and is reduced when there is iron overload or excessive intake.

Up to 90% of iron is present in hemoglobin within red blood cells. Total iron stores are between 2 and 4 grams. Myoglobin and non-heme enzymes account for 200-400 mg of iron. Iron deficient

anemia often presents with pallor, fatigue, shortness of breath, and tachycardia. This is a microcytic anemia which is commonly accompanied by thrombocytosis. Physical signs include cheilosis, brittle nails, and smooth tongue. Rarely, dysphagia may occur due to an esophageal web (Plummer-Vinson syndrome). Finally, some individuals develop pica – a craving for certain foods including ice and starch. The diagnosis is made using iron studies; rarely, a bone marrow examination is necessary.

Zinc (Zn) RDI = 10-15 mg

Good sources of zinc include red meat, shellfish, and whole grain cereals. At risk groups include those with a diet low in zinc, alcoholism, TPN, malabsorption, malnutrition, chronic diarrhea, or pregnancy. Absorption is partially dependent on pancreatic enzymes. One quarter of ingested zinc is absorbed, and this primarily occurs in the proximal small intestine. Zinc is a catalyst and cofactor for many enzymes, and is involved in protein and lipid synthesis, and insulin activity. It protects membranes from free radical damage, is a cofactor in transcription, and stabilizes DNA, RNA, and ribosomes.

Deficiency manifests as a characteristic skin rash (acrodermatitis), glucose intolerance, poor wound healing impaired growth, depression, alopecia, immune dysfunction, and impaired taste (dysgeusia), and diarrhea. Acrodermatitis enteropathica is a rare (AR) disorder of impaired zinc uptake. This disorder, requiring lifelong supplementation, may become clinically apparent after breast feeding stops. Zinc toxicity is rare and presents with GI symptoms (N/V, diarrhea, abdominal pain) and possibly copper deficiency. Metalloprotein metallothionein, present in erythrocytes, binds zinc and copper. Pharmacologic doses of zinc interfere with copper binding and are used to treat Wilson's disease.

Selenium (Se) RDI = 55-70 micrograms

Sources include seafood, organ meats, and, depending on the soil selenium concentration, plant food. Its gut absorption is not understood. Glutathione peroxidases are selenium dependent and reduce oxidation of membranes by decreasing hydrogen peroxide. Some geographic regions, particularly in rural China, have low soil SE. Patients on TPN, and who are malnourished, are also at risk.

Selenium deficiency may cause heart and collagen vascular disease (Keshan disease), and increase the risk for malignancy. Keshan syndrome is a cardiomyopathy occurring in regions of China where dietary selenium is insufficient. The risk for malignancy is increased when selenium intake is low. Massive doses of selenium cause nausea, vomiting, delirium, peripheral neuropathy, alopecia, and nail changes.

Iodide (I) RDI = 150 micrograms

Coastal areas are rich in iodide (seafood, water, and ocean mist). It is also present in iodized salt, bread, and dairy products due to feed additives and cleaning solutions used on milking machines and storage tanks. Easily absorbed from the gut, iodide is taken up by the thyroid and combines with tyrosine to form monoiodothyronine (MIT) and diiodothyronine (DIT). These combine to form triiodothyronine (T3) and thyroxine (T4).

Individuals far from the sea where iodized foods are not available, and the malnourished, are at risk for deficiency. This is the most common micronutrient deficiency. Goiter and hypothyroidism (cold intolerance, thin hair, hoarseness, growth failure, constipation, and weakness) can result from deficiency.

Copper (Cu) RDI = 1.5-3 micrograms

Copper is found in organ meats, seeds, nuts, legumes, and seafood. It is absorbed in the small intestine, binds to ceruloplasmin in the liver, and acts on tissues with ceruloplasmin receptors. TPN, prematurity, peritoneal dialysis, and chronic diarrhea can cause deficiency. Copper is excreted in bile, and external biliary drainage requires replacement. Copper is essential for numerous proteins and enzymes including:

1. monoamine oxidase (inactivate catecholamines)
2. lysyl oxidase (collagen)
3. cytochrome C oxidase (mitochondrial electron transport)
4. ferroxidase II (iron oxidation for erythropoiesis)
5. dopamine beta hydroxylase (dopamine → norepinephrine)

Copper is necessary for iron utilization and normal taste. In addition to anemia and impaired taste, copper deficiency may result in neutropenia, bone demineralization, CNS symptoms (ataxia, tremor, rigidity, cognitive, psychiatric), reproductive failure, abnormal pigmentation, and myocardial failure.

Toxicity is seen accidentally (contaminated water, burn creams) or intentionally. Wilson's disease is a genetic disorder in which ceruloplasmin formation and secretion is impaired and there is defective secretion of copper into the biliary system (normally the primary means of excretion). Mild GI symptoms may occur (N/V, abdominal pain) or severe manifestations with liver necrosis and failure, coma, renal failure, and death.

Chromium (Cr) RDI = 50-100 micrograms

Sources are grains, cereals, fruits, vegetables, and processed meats. Bioavailability is low, and there is feedback inhibition regulating absorption from the small intestine. Absorption is decreased with antacids and nonsteroidals, and increased with vitamin C. TPN and malnutrition may lead to deficiency. As a component of metalloenzymes, chromium is a coenzyme for a variety of enzymes involved in protein, lipid, and carbohydrate metabolism. Glucose intolerance is a hallmark of deficiency, and CNS and peripheral neurologic symptoms may occur. Cr³⁺ is the dietary form and no toxicity is described.

Manganese (Mn) RDI = 3-5 micrograms

Manganese is poorly absorbed and is present in whole grains, cereals, fruits, and vegetables. It is a component of the metalloenzymes pyruvate carboxylase and superoxide dismutase. These are important for fatty acid, cholesterol, and mucopolysaccharide synthesis. Deficiency is very rare and manifests as an elevated prothrombin time unresponsive to vitamin K, thinning and lightening of hair, skeletal, CNS, and gonadal abnormalities. Toxicity results in neuropsychiatric symptoms.