8

Vitamins and Trace Elements

Liam McKeever, MS, PhD(c), RDN

CONTENTS

Thiamin

Functions of Thiamin

Clinical Applications

Riboflavin

Functions of Riboflavin

Clinical Applications

Niacin

Absorption and Metabolism

Functions of Niacin

Clinical Applications

Vitamin B6

Absorption and Metabolism

Functions of Vitamin B6

Routes of Toxicity

Clinical Applications

Vitamin B12

Absorption and Metabolism

Functions of Vitamin B12

Clinical Applications

Folic Acid

Functions of Folate

Clinical Applications

Biotin

Functions of Biotin

Clinical Applications

Pantothenic Acid

Functions of Pantothenic Acid

Clinical Applications

Choline

Functions of Choline

Clinical Applications

Trace Elements

Iron

Absorption and Metabolism

Clinical Applications

Zinc

Functions of Zinc

Clinical Applications

Copper

Functions of Copper

Clinical Applications

Manganese

Functions of Manganese

Clinical Applications

Selenium

Functions of Selenium

Clinical Applications

Iodine

Functions of Iodine

Clinical Applications

Acknowledgments: Susan F. Clark, RDN, PhD, was the author of this chapter for the second edition. The author also thanks Sarah Peterson, RDN, PhD, CNSC, Kelly Roehl MS, RDN, CNSC, and Carol Braunschweig, RD, PhD, for their support and advice in this process, as well as Kelly Hagemes, RN, for his assistance editing the Practice Scenarios.

Objectives

Describe the known metabolism, functions, and requirements for essential vitamins and minerals in human nutrition.

Assess signs and symptoms of vitamin and mineral deficiency and toxicity.

Detect how various disease conditions can influence micronutrient metabolism.

Demonstrate clinical examples of potential vitamin and mineral interactions, deficiencies, and toxicities.

Test Your Knowledge Questions

1. What amount of retinol is equivalent to 24 mcg of beta-carotene from food?

A. 2 mcg
B. 4 mcg
C. 2 mcg
D. 1 mg

2. Which of the following nutrients does not engage in conversion of homocysteine to methionine?

A. Choline
B. Vitamin D
C. Vitamin B12
D. Folate

3. The first B vitamin deficiency to manifest in people with alcoholism is usually:

A. Niacin
B. Pantothenic acid
C. Vitamin B6
D. Thiamin

4. Which of the following trace elements is regulated at the level of absorption but not excretion?

A. Zinc
B. Copper
C. Manganese
D. Iron

Test Your Knowledge Answers

1) The correct answer is A. One mcg retinol has the vitamin A activity of 12 mcg beta-carotene. Therefore, 24 mcg beta-carotene is equivalent to 2 mcg retinol.
2) The correct answer is B. Vitamin B12 and folate are needed to convert the cardiac risk factor homocysteine back into methionine. Alternatively, choline may be used for this conversion.
3) The correct answer is D. Very small amounts of thiamin are stored in the liver. Therefore, this B vitamin tends to be the first to become deficient in malabsorptive or inadequate intake situations.
4) The correct answer is D. The control mechanisms that keep iron levels stable in the body occur at the absorption phase. It is very difficult to eliminate iron except in conditions of blood loss (eg, blood donation or menstruation).

Background

Micronutrients are essential to macronutrient metabolism as well as countless other processes in the body. This chapter examines 14 vitamins and 9 trace elements, and the review of each micronutrient is broadly separated into 2 sections. The first section covers background information regarding absorption, digestion, biochemical functions, and excretion. The second section presents information of direct clinical relevance to nutrition support clinicians, including recommended intakes, at-risk populations, nutrient half-life, diagnostic laboratory tests, clinical signs and symptoms of deficiency/toxicity, nutrient-nutrient interactions, nutrient-medication interactions, and treatment considerations. Ultratrace elements are also briefly discussed.

Assessment of Micronutrient Status

Evaluation of vitamin and trace element status relies on a variety of biochemical measurements. Deficiencies of vitamins and trace elements generally occur in several phases, and alterations in metabolism can occur at biochemical, clinical, morphological, and functional levels. Generally, the biochemical alterations occur before other changes are evident. In fact, by the time clinical, morphological, or functional alterations occur, the concentration of that nutrient in biological fluids will already be greatly reduced. Therefore, early identification of biochemical changes is essential.

A person's age, lifestyle, or disease state can alter both the intake and requirements for specific micronutrients. The ability to identify at-risk populations for specific nutrient deficiencies increases the likelihood of detection.

Understanding of the biological half-lives of the various nutrients gives us a method to at least vaguely assess the impact of the duration of a patient's inadequate intake on the likelihood of deficiency. In this context, half-life is defined as the time it takes for half the amount of an ingested nutrient to be eliminated from the body. Assuming the half-life of a nutrient is the same at all levels of physiological concentration, we expect the nutrient to be approximately 97% eliminated from the system within 5 half-lives. However, the half-lives for most nutrients increase as the concentration of the nutrient decreases due to the activation of nutrient retention mechanisms.

Dietary Reference Intakes

The Dietary Reference Intakes (DRIs) are designed to reflect the latest understanding of nutrient requirements based on optimizing health in individuals and groups. The primary goal of DRI values is to prevent nutrient deficiencies and reduce nutrition-related disease. The following are definitions and descriptions of the 4 DRI categories for micronutrients:

- Estimated Average Requirement (EAR)—the intake that meets the estimated nutrient needs of 50% of the individuals in a group. The EAR must be derived from scientific studies, and it serves as the basis for developing the Recommended Dietary Allowance (RDA). It can also be used for evaluating the adequacy of group intakes and planning recommendations for group intakes.

- Recommended Dietary Allowance (RDA)—the intake that meets the nutrient needs of almost all (97% to 98%) individuals in that group. The RDA may be 2 standard deviations (SD) above the EAR if the variation in requirement for a micronutrient is well defined (RDA = EAR + 2 SD of EAR), or it may be 1.2 times the EAR if the variation is inconsistent or unavailable (RDA = 1.2 × EAR, which assumes a coefficient of variation of 10%).
- Adequate Intake (AI)—the average observed or experimentally derived intake by a defined population or subgroup that seems to sustain a defined nutrition-related state, such as normal circulating nutrient values, growth, or other functional indicators of health. If the EAR cannot be determined for a micronutrient, the RDA cannot be set. In these cases, the AI serves as a goal for intake.
- Tolerable Upper Intake Level (UL)—the maximum intake by an individual that is unlikely to pose risks of adverse health effects in almost all individuals. There is no established benefit of consuming nutrients at levels above the RDA or AI. Therefore, the UL is not intended to be a recommended level of intake. For most nutrients, the UL refers to total intakes from food, fortified food, and nutrient supplements.

The Food and Nutrition Board of the Health and Medicine Division (formerly Institute of Medicine) of the National Academies of Science has published DRI reports for the following nutrient groups:

- Calcium, phosphorus, magnesium, vitamin D, and fluoride
- Folate, vitamin B12, other B vitamins, and choline
- Vitamin C, vitamin E, selenium, and carotenoids
- Vitamin A, vitamin K, and trace elements
- Energy and macronutrients
- Electrolytes and water

The DRIs are periodically updated by the Health and Medicine Division, with the most recent updates being calcium and vitamin D in 2011. As new bioavailability information is gained about micronutrients, DRIs are debated and may be changed in the future.

Vitamins

Vitamins are essential organic substances needed in small amounts in the diet to maintain fundamental functions of the body such as growth, metabolism, and cellular integrity. Vitamins contribute to energy metabolism through their supportive role in macronutrient metabolism. In humans, 13 vitamins plus the dietary component choline are considered essential. These include 8 B vitamins (thiamin, niacin, riboflavin, folate, vitamin B6, vitamin B12, biotin, and pantothenic acid); vitamin C (ascorbic acid); and the fat-soluble vitamins A, D, E, and K. Most vitamins are not related chemically and thus differ in their biochemical and physiological roles.

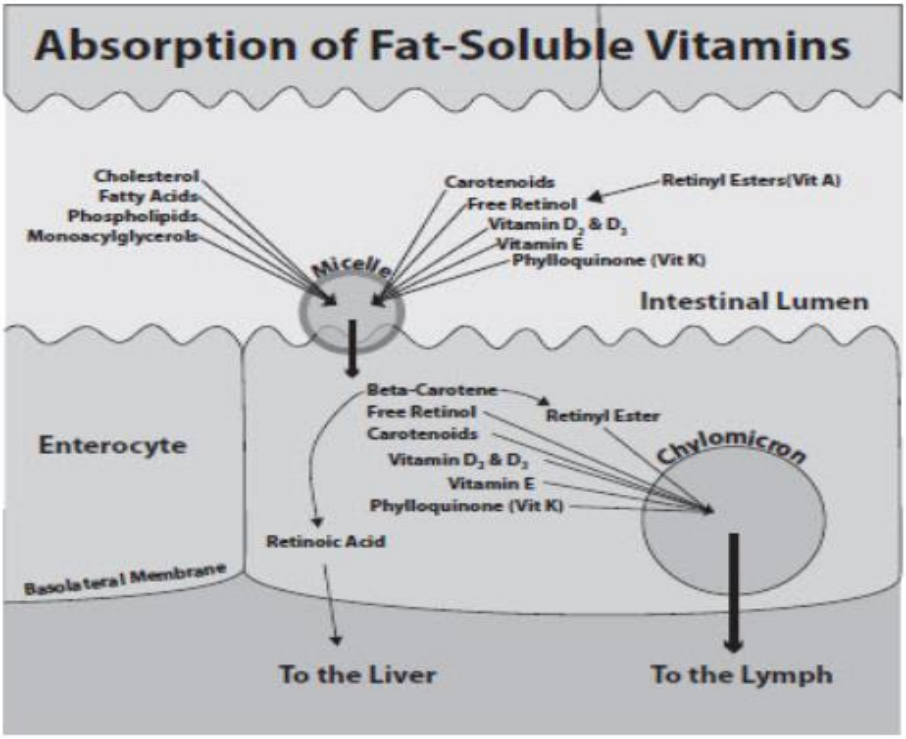
Malabsorption, medications, certain disease states, or excesses of dietary substances such as alcohol can influence nutrient intake as well as the digestion, absorption, and transport of vitamins, which consequently alter vitamin requirements and nutrition status. Clinicians must use a nutrition-focused

physical assessment to identify nutrient deficiencies in tandem with the appropriate biochemical assays to determine the adequacy of a patient's vitamin status. A consultation with multidisciplinary nutrition support teams also improves the nutrition status of patients and the overall safety and efficacy of care.

Fat-Soluble vs Water-Soluble Vitamins

Vitamins are broadly grouped into those that are fat-soluble (vitamins A, D, E, and K) vs those that are water-soluble (vitamin C, the 8 B vitamins, and choline) to account for differences in absorption, transportation, and excretion in the body. In the duodenum, fat-soluble vitamins are incorporated into micelles for absorption into the enterocyte. From there, they are repackaged into chylomicrons for distribution to the extrahepatic tissues. Some are even repackaged into very low-density lipoproteins for redistribution (Figure 8-1). Ultimately, they are stored in adipocytes or excreted through the feces (predominantly) or the urine. In general, fat-soluble vitamins tend to be absorbed better when taken with dietary fat because they are processed similarly to fat. Patients with fat-malabsorptive disorders, either through decreased pancreatic sufficiency, decreased bile acid release or production, or decreased intestinal surface area, are at risk for fat-soluble vitamin deficiencies.

FIGURE 8-1 Absorption of Fat-Soluble Vitamins



Fat-soluble vitamins are absorbed into the enterocyte via the micelle. Here all fat-soluble vitamins except for retinoic acid are repacked into a chylomicron to enter the lymph system.

Vitamin A

Vitamin A represents a subgroup of compounds known as retinoids that have biological activity of retinol. Several plant-derived carotenoids, once metabolized, also possess vitamin A activity. Vitamin A exists in 3 forms: retinol, retinaldehyde (retinal), and retinoic acid. Beta-carotene, the primary provitamin A carotenoid, can be split into 2 molecules of retinal and is a dietary precursor of retinol. Retinol can be oxidized reversibly to retinal, or it can be further oxidized to retinoic acid, each having unique biochemical functions. The intracellular metabolism of retinol involves 4 major processes: it may (1) be esterified and stored, (2) be converted to active metabolites such as retinoic acid or retinal, (3) form covalent bonds with cell proteins, or (4) be catabolized to an excretory form.

Generally, dietary vitamin A exists as retinoids in animal tissues and carotenoids in plants; however, there are carotenes in butterfat, and some plant-based foods such as breakfast cereals and margarines may be fortified with retinyl ester, the most stable form of vitamin A. Typically, vitamin A is ingested as retinyl ester and must be freed by acidic digestion, the emulsifying action of bile salts, and the subsequent integration of retinol into micelles. The micelles are transported to the intestinal cell, where the retinol is then reesterified by intracellular binding proteins and packaged into chylomicrons. The chylomicrons enter the mesenteric lymphatic system and pass into systemic circulation where retinol is removed primarily by the liver. Once in the liver, the vitamin enters the hepatocyte for storage. Although the liver is the primary storage site of vitamin A, extrahepatic locations (eg, adipose tissue, kidneys, bone marrow, lungs, eyes) also contain significant amounts of vitamin A.

Approximately 90% of dietary vitamin A is absorbed. In contrast, dietary carotenoids are absorbed primarily in the upper small intestine at a lower efficiency of approximately 8%. Overall, vitamin A absorption depends on the amount of dietary fat intake as well as disease states that influence fat absorption. Retinol-binding protein (RBP) is a liver-synthesized protein that is required to transport retinol from the liver to the target tissues. Synthesis of this protein is tightly regulated by the availability of retinol and, therefore, is sensitive to the nutrition status of the individual.4 In the plasma, RBP is bound to the protein transthyretin (TTR), also called prealbumin. The protein complex TTR-RBP is responsible for the plasma transport of retinol. Measurement of these binding proteins is used to assess vitamin A status.

Functions of Vitamin A

Vision

Proper vision relies upon impulses sent through the optic nerve to vision centers in the brain. Rods and cones send these impulses. Cones are necessary for vision in bright-light conditions whereas rods are needed for dim-light conditions. The rods of the eye contain a vitamin A–dependent pigment complex called rhodopsin (formerly called visual purple), which is a combination of opsin and cis-retinal. In dim conditions, when light enters the eyes, it converts the cis-retinal to trans-retinal, effectively cleaving rhodopsin, which releases the nerve impulse to the vision centers of the brain. The trans-retinal is regenerated to cis-retinal, rejoins with opsin, and repeats the cycle. When vitamin A is in short supply, the formation of rhodopsin is impeded, leading to night blindness.

Epithelial Cell Regulations

Vitamin A as retinoic acid regulates epithelial cell differentiation. For example, retinoic acid is necessary for the transformation of keratinocytes into mature skin cells. In the absence of vitamin A, keratinocytes grow uncontrolled, causing hyperkeratosis of the skin, and they grow in nondermal areas such as the conjunctiva of the eyes. When keratinocytes replace mucus-secreting cells and cells of the conjunctiva, they cause dryness (xeropthalmia) and rough corneal keratin deposition (Bitot's spots).

Wound Healing

Vitamin A as retinoic acid is also needed for epithelial cell growth. During the inflammatory phase, vitamin A increases the number of macrophages and monocytes in the wound, stimulates epithelialization, and increases collagen deposition by fibroblasts.6 Vitamin A can also reverse the inhibitory effects of corticosteroids on wound healing.

Bone and Cellular Health

Toxic amounts of vitamin A are known to have negative skeletal effects. In a prospective cohort comparing postmenopausal women who consumed 2000 mcg retinol per day vs those who consumed 500 mcg/d, the risk of hip fractures was almost double in the women who consumed 2000 mcg/d, an amount less than the UL for vitamin A of 3000 mcg/d. Thus, chronic intake of retinol may contribute to the development of osteoporotic hip fractures.

Elevated serum levels of vitamin A occur in both chronic and acute renal failure because the binding capacity of RBP is exceeded, which allows more of the vitamin to circulate unbound with the potential to damage cell membranes. It is prudent to supplement vitamin A with caution in renal failure and in accordance with standard practice guidelines.

Clinical Applications

Recommended Intakes for Adults

The RDA for vitamin A is as follows:

- 900 RAE for men
- 700 RAE for women
- 770 RAE for pregnant women
- 1300 RAE for lactating women

RAE refers to retinoic acid equivalent, which equals any of the following: 1 mcg retinol, 3.33 IU retinol, 12 mcg food-based beta-carotene, 24 mcg alpha-carotene, or 24 mcg beta-cryptoxanthin. Note that oil-based oral beta-carotene supplements are highly absorbable, yielding 1 RAE for every 2 mcg beta-carotene.

The UL for retinol is 3000 RAE (3000 mcg). Retinol consumption greater than 3000 mcg/d during the periconceptional period places women at risk for delivering neonates with birth malformations, and this

finding was an influencing factor on determining the UL. However, more than 50 possible signs of vitamin A toxicity have been observed at intakes as low as 1800 mcg/d. Long-term intake of preformed vitamin A in amounts as 3 or 4 times the RDA can lead to toxicity symptoms, but toxicity is more common at intake levels 10 times the RDA.

Sources

Food sources of vitamin A include liver, fortified milk, eggs, and dark-green and yellow-orange vegetables.

Populations at Risk for Deficiency

Patients with fat-malabsorptive disorders and pregnant women with low vitamin A intake may be at risk for vitamin A deficiency.

Half-Life of the Nutrient in the Body

The half-life of retinol is approximately 140 days.

Assessment of Vitamin A Status

Table 8-1 lists clinical signs and symptoms of vitamin A deficiency and toxicity. Serum retinol results from laboratory testing are interpreted as follows:

- ≤0.35 mcmol/L (10 mcg/dL): low/depleted
- ≥1.05 mcmol/L (30 mcg/dL) to 3.5 mcmol/L (100 mcg/dL): adequate
- ≥3.5 mcmol/L (100 mcg/dL): toxic

TABLE 8-1 Selected Clinical Signs and Symptoms of Vitamin A Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Follicular hyperkeratosis	Pruritus
Hair	None	Alopecia
Eyes	Roughened conjunctiva, Bitot's spots, xeropthalmia, night blindness	Vision disorders, conjunctivitis
Mouth	None	Cheilitis
Nervous system	None	Ataxia
Bones	Excessive bone deposition	Bone loss, bone pain, hip fractures
Other	Impaired wound healing	Hyperlipidemia, renal osteodystrophy, membrane dryness, muscle pain, hepatotoxicity, birth defects

Source: Data are from references 11 and 14.

Nutrient-Nutrient Interactions

Because retinol circulates attached to RBP and TTR as a complex, the presence of either protein-energy malnutrition and/or zinc deficiency may compromise circulating serum vitamin A levels. Decreased circulating serum retinol levels may reflect an impaired RBP synthesis and mobilization secondary to inflammatory processes or disease and do not require correction by vitamin A supplementation.

Medication-Nutrient Interactions

Cholestyramine (bile acid sequestrant), lomitapide (lipid-lowering agent), octreotide (antidiarrheal), orlistat (weight control medication), and mineral oil (laxative) decrease absorption of vitamin A through fat malabsorption. In general, corticosteroids (anti-inflammatories) also may cause decreased serum vitamin A.

Treatment Considerations

If patients have a vitamin A deficiency, daily supplementation with 606 to 60,600 RAE (2000 to 200,000 IU) of vitamin A may be warranted.

Vitamin A administration is commonly used to enhance wound healing in patients with comorbidities (diabetes, tumors, and radiation). A wide dosage range of 3000 to 15,000 RAE/d orally for 7 days, or 3000 RAE/d intramuscularly for 7 days, has been recommended to counteract the inhibitory effects that steroids have on collagen synthesis and connective tissue repair, although results have been inconsistent. The application of topical vitamin A can minimize delayed wound healing in patients requiring long-term corticosteroid treatment. Oral administration of 3000 to 4500 RAE/d is recommended to enhance wound healing with concurrent corticosteroid therapy.

Vitamin D

Vitamin D refers to both ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), which are either consumed in the diet or synthesized in the skin from the compound 7-dehydrocholesterol postexposure to solar or artificial ultraviolet (UVB) light (D3). Sun exposure lasting 5 to 15 minutes in the spring, summer, and fall between the hours of 10 AM and 3 PM may be enough to achieve adequate vitamin D levels. About 80% of dietary vitamin D intake is incorporated into a micelle, primarily in the distal small intestine, although uptake is more rapid in the duodenum. Vitamin D absorption occurs in tandem with fat and bile salts via passive diffusion into the intestinal cell where it is packaged as chylomicrons for entrance into the lymphatic system and then into the blood. Approximately 40% of the cholecalciferol is transported via chylomicrons (Figure 8-1), although some is transferred from the chylomicron to a vitamin D–binding protein (DBP) for export to extrahepatic tissues. The chylomicron remnant delivers the remaining vitamin D to the liver. Cholecalciferol synthesized from the skin is transported to the liver bound to DBP; however, some is deposited in muscle and adipose before its liver uptake. These different mechanisms for vitamin D transport influence the distribution in the body.

Once vitamin D is transported to the liver, it undergoes the first of 2 hydroxylation steps at carbon 25 via the enzyme 25-hydroxylase to form 25-hydroxy-D (calcidiol), its major circulating form that has no

biological activity. Although this enzyme is not tightly regulated, its efficiency is dependent on vitamin D status. Enzymatic conversion is more efficient during vitamin D deprivation. When 25-hydroxy-D is transported to the kidneys, it may undergo a second hydroxylation at carbon 1 to form the active form of the vitamin 1,25-dihydroxyvitamin D (calcitriol). Other tissues are also capable of this reaction and thus may make calcitriol for their own (ie, autocrine) uses. (Technically, the terms calcidiol and calcitriol refer only to the D3 versions of these molecules. It has become common convention, however, to conflate the D2 versions of these molecules into these terms and this approach has been taken here.)

Calcitriol made by the kidneys is released into the circulation, where it is necessary for bone mineralization and intestinal calcium uptake, among other actions. The activity of the enzyme is highly controlled via the vitamin D receptor and is affected by several factors that influence calcium homeostasis. Vitamin D can be stored in adipose tissue for later use or converted to calcidiol in the liver. Excretion is primarily via bile, with minimal amounts lost via urine.

Functions of Vitamin D

Calcium Homeostasis

When describing vitamin D functions, it is important to note that calcitriol is the active form. The principal function of vitamin D is to maintain serum calcium and phosphorus levels to support neuromuscular function, bone calcification, and other cellular processes. In its active form, calcitriol functions to maintain circulating serum levels of calcium and phosphorus within normal ranges.

When blood calcium levels are low, the parathyroid glands respond by secreting parathyroid hormone (PTH). PTH increases blood calcium levels as follows:

- PTH in the kidneys stimulates increased renal calcium retention and the conversion of calcidiol (inactive vitamin D) to the active form, calcitriol.
- Both calcitriol and PTH act on the bone, stimulating osteoclast activity for the resorption of calcium into the bloodstream.
- Calcitriol travels to the intestines to increase exogenous calcium absorption. Once serum calcium has normalized, PTH secretion decreases, effectively halting the cycle.

Pleiotropic Effects of Vitamin D

Recent literature suggests that vitamin D may be important in the management of multiple other medical conditions, such as musculoskeletal disorders, falls, immunity, autoimmunity, infections, cancer, diabetes or glucose intolerance, and cardiovascular disease. The potential effects of vitamin D on the cardiometabolic system are thought to be mediated by a variety of mechanisms related to the inflammatory response and have been associated with therapeutic doses greater than the current DRI. Although some experts now recommend up to 800 to 1000 IU vitamin D per day to prevent deficiency in select populations, such as older adults, the most recent RDAs are 600 IU for healthy adults younger than 70 years and 800 IU for those age 70 years or older.

Vitamin D and Nosocomial Infection

Vitamin D receptors are expressed throughout the innate and adaptive immune system and may play a role in fighting infection. Macrophages are activated by calcitriol, increasing their capacity for oxidative bursts of cytokines, acid phosphatases, and hydrogen peroxide in response to pathogens. Furthermore, vitamin D enhances the motility and phagocytic activity of neutrophils.24 These aspects of vitamin D have profound implications for hospital-acquired infections, such as Clostridium difficile. Low calcidiol levels have been associated with increased incidence of C. difficile infection as well as increased severity of infection in those who are positive for C. difficile. Low calcidiol levels decrease the body's ability to make calcitriol within the macrophages, thereby diminishing this aspect of immune function. Prospective randomized controlled trials are needed to determine whether supplementing vitamin D affects rates of C. difficile infection.

Clinical Applications

Recommended Intakes for Adults

The vitamin D RDA for adults younger than 70 years is 600 IU (15 mcg), and the RDA for adults age 70 years or older is 800 IU (20 mcg). The UL for individuals age 9 years and older is 4000 IU (100 mcg). These DRIs assume minimal sun exposure.

Sources

Sources of vitamin D include sunlight as well as fish liver oils, fatty fish, fortified milk, and breakfast cereals.

Populations at Risk for Deficiency

Individuals with inadequate sun exposure are at risk for vitamin D deficiency; populations at risk include older adults, nursing home residents, dark-skinned individuals, people who wear clothing or veils that expose very little skin, people who are indoors much of the time or use sunscreen daily, and exclusively breastfed infants. Patients with extensive skin damage (eg, burns), fat-malabsorptive disorders, or renal disease (insufficient renal calcitriol production), and those on long-term parenteral nutrition (PN) are also at risk. One study suggests that patients on home PN had a high prevalence of vitamin D deficiency despite oral vitamin D supplementation.

Half-Life of the Nutrient in the Body

The half-life of calcitriol is 4 to 6 hours. The half-life for calcidiol can be 2 to 3 weeks but may be as high as 2 to 3 months in patients with high adiposity.

Assessment of Vitamin D Status

Calcitriol is not a good marker of vitamin D status. When calcidiol levels fall, both serum calcium and phosphorus levels decrease, which stimulates PTH secretion to increase renal production of vitamin D's

active form, calcitriol. Consequently, circulating levels of the calcitriol are often normal or elevated in vitamin D deficiency, making it a less-sensitive indicator of vitamin D status.

The measurement of serum calcidiol is a reasonable assay to evaluate vitamin D status. (See Table 8-2.5) However, vitamin D adequacy is more clearly defined using surrogate markers such as PTH and calcium. Normal circulating calcidiol levels vary with the degree of sun exposure and range from 54 to 90 ng/mL.

TABLE 8-2 Interpretation of Serum Calcidiol Levels

Status	Calcidiol Level, ng/mL
Sufficient	>30
Insufficient	>20 to ≤30
Deficient	≤20

Source: Data are from reference 5.

Vitamin D deficiency and toxicity may affect bones, the nervous system, and calcium levels in the blood or urine. See Table 8-3 for clinical signs and symptoms.

TABLE 8-3 Clinical Signs and Symptoms of Vitamin D Deficiency or Toxicity

System	Deficiency	Toxicity
Bones	Osteomalacia	Calcification of soft tissues (cardiovasculature, lungs)
Nervous system	Tetany	Confusion, psychosis, tremor
Other	Hypocalcemia	Hypercalcemia, hypercalciuria

Source: Data are from reference 5.

Nutrient-Nutrient Interactions

Excess vitamin D stimulates hepatic oxidation, and excretion of vitamin K.

Medication-Nutrient Interactions

Cholestyramine (bile acid sequestrant), lomitapide (lipid-lowering agent), orlistat (weight control medication), octreotide (antidiarrheal), and mineral oil (laxative) decrease absorption of vitamin D through fat malabsorption. Phenobarbital (anticonvulsant), phenytoin (antiepileptic), valproic acid (antiepileptic), and rifampin (antibiotic) increase the metabolism of vitamin D and may decrease serum levels. Corticosteroids (anti-inflammatories), carbamazepine (antiepileptic), and isoniazid (antitubercular) also may cause decreased serum vitamin D levels. Vitamin D may increase the drug effects of digoxin (antiarrhythmic).

Treatment Considerations

Serum calcidiol concentrations are expected to increase by 1 ng/mL for every 100 IU vitamin D ingested per day. Vitamin D deficiency is typically treated with 50,000 IU Vitamin D once per week for 8 weeks; the dose is then lowered to approximately 1000 IU/d for several months.5 Maintaining 25-hydroxyvitamin D concentrations between 78 and 100 nmol/L is associated with maximum bone health and the prevention of chronic diseases.21,27,28 Patients receiving long-term PN patients are prone to hypovitaminosis D and must be monitored to ensure optimal levels of calcidiol, calcitriol, PTH, and calcium.

Vitamin E

Vitamin E activity has been found in 8 naturally occurring compounds: 4 tocopherols (α, β, γ, and δ) and 4 tocotrienols (α, β, γ, and δ), each with varying degrees of biological activity.14 Evidence indicates that these 8 forms of vitamin E are functionally unique. The most active and naturally occurring form is the RRR isomer of α-tocopherol, which exhibits antioxidant activity and inhibits cell proliferation, platelet aggregation, and monocyte adhesion.14 γ-Tocopherol represents the predominant form of vitamin E in a typical American diet; it has anti-inflammatory, antineoplastic, and natriuretic properties.30

In 2000, the Food and Nutrition Board of the Institute of Medicine determined that only α-tocopherol should be considered sufficient to meet the vitamin E recommendations because evidence for the activity of other forms of the vitamin were insufficient. α-Tocopherol has 8 different isomers, all of which provide some vitamin E activity. The RRR isomer of α-tocopherol is special in that it is selectively recognized by receptors in the liver and incorporated into very low-density lipoproteins (VLDL) for distribution to the tissues. This capacity for VLDL incorporation greatly increases its half-life compared with other forms of vitamin E and other isomers of α-tocopherol, which are only distributed in the chylomicron phase of lipid circulation.

Since the recommendations of the Food and Nutrition Board were issued, the evidence for the vitamin E activity of the tocotrienols and γ-tocopherol has grown. Tocotrienols have neuroprotective, antioxidant, anticancer, and cholesterol-lowering effects that are different from the properties of tocopherols.30 Some vitamin E molecules, such as γ-tocopherols, δ-tocopherols, and α-tocotrienols, have emerged with roles in health and disease that are distinct from the function of α-tocopherols.5

Vitamin E absorption depends on dietary fat absorption and occurs primarily in the jejunum via nonsaturable, passive diffusion. Absorption varies from about 20% to 50%, decreasing as intake increases.14,30,31 At pharmacological doses (200 mg), absorption drops to less than 10%.14 Tocopherols are found free in foods; however, the tocotrienols are esterified and must be hydrolyzed before they are absorbed via pancreatic and duodenal esterases located in the lumen. Vitamin E is incorporated into micelles within the lumen of the small intestine (Figure 8-1). Once taken up by the enterocytes, vitamin E is transported as part of a lipoprotein complex through the lymph into circulation. Adipose tissue, muscle, and the liver serve as the major storage sites. Excretion occurs primarily via the urine and bile, but significant amounts are found in the feces because of the body's limited absorption of vitamin E.

Functions of Vitamin E

The principal biochemical function of vitamin E is the maintenance of membrane integrity in body cells via its action as an antioxidant. By inhibiting lipid peroxidation, vitamin E protects the integrity of all biological membranes.14 It also acts as an antioxidant by trapping peroxyl free radicals in cell membranes to protect against oxidation. Thus, sufficient vitamin E is critical in the oxidative stress states (chronic inflammation, sepsis, systemic inflammatory response syndrome [SIRS], and organ failure).31

Clinical Applications

Recommended Intakes for Adults

The RDA for vitamin E for all adults is 15 mg. The UL is 1000 mg. Values for vitamin E are often expressed in international units (IU). IU conversions are substance-specific and vary by the type of vitamin E ingested: 1 mg vitamin E can equal anywhere from 1 to 1.5 IU depending on the form. For example, 15 mg of naturally occurring d-α-tocopherol is 22.5 IU. In synthetic supplements, α-tocopherol is often a mixture of D and L forms in which 15 mg vitamin E equals 16.5 IU.

Sources

Food sources of vitamin E include vegetable oils, wheat germ, asparagus, and peanuts.

Populations at Risk for Deficiency

Patients at risk for vitamin E deficiency include those with fat-malabsorptive disorders such as prolonged steatorrhea, Crohn's disease, cystic fibrosis, compromised biliary function, or resection of the ileum or small intestine. Patients receiving long-term PN without vitamin E supplementation are also at risk.

Half-Life of the Nutrient in the Body

The half-life of RRR-α-tocopherol is 44 to 60 hours. The half-lives of other isomers of α-tocopherol are much shorter. For example, the half-life of SRR-α-tocopherol is 15 hours.32

Assessment of Vitamin E Status

Relevant diagnostic laboratory tests for vitamin E levels include plasma or serum Vitamin E (α-tocopherol), which may be interpreted as follows:

- <0.5 mg/dL: deficient
- 0.5 to 2.0 mg/dL: normal
- >2.0 mg/dL: toxicity

In addition, a ratio of plasma α-tocopherol (mcmol/L) to plasma cholesterol (mmol/L) below 2.2 indicates a risk for vitamin E deficiency.33 Table 8-4 lists clinical signs of vitamin E deficiency or toxicity.

TABLE 8-4 Clinical Signs and Symptoms of Vitamin E Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Ceroid pigmentation (age spots)	Bruising from decreased vitamin K absorption
Eyes	Vision changes	None
Bone	None	Inclusion bodies in bone marrow
Nervous system	Ophthalmoplegia, ptosis, vision loss, dysarthria, ataxia, neuronal degeneration	None
Other	Hemolytic anemia, increased platelet aggregation, urinary creatinine wasting	Thrombocytopenia, cerebral hemorrhage, impaired neutrophil function, abrogated granulocytopenic response to antigen, impaired coagulation Prolonged depletion: skeletal muscle lesions with ceroid deposits in smooth muscle

Source: Data are from references 11 and 30–34.

Nutrient-Nutrient Interactions

An intake of more than 1200 mg vitamin E per day interferes with absorption and metabolism of vitamin K and may be problematic for patients receiving warfarin therapy. Daily intake of 800 to 1200 mg vitamin E may decrease platelet adhesion.

Medication-Nutrient Interactions

Cholestyramine (bile acid sequestrant), lomitapide (lipid-lowering agent), orlistat (weight control medication), octreotide (antidiarrheal), and mineral oil (laxative) decrease absorption of vitamin E through fat malabsorption. A form of vitamin E that has been altered to be soluble in water increases the absorption of cyclosporine (immunosuppressant).7

Treatment Considerations

Vitamin E deficiency is rare, but it usually requires treatment with oral vitamin E intakes of 200 to 2000 mg/d.35 Thrombocytopenia and cerebral hemorrhages resulting in death have been reported at pharmacological doses below the UL (50 mg/d and 1000 mg/d).34,36 Consistent intake of excessive amounts of vitamin E is contraindicated in patients with a coagulation defect.30An intake of more than 1200 mg vitamin E per day interferes with vitamin K and may be problematic for patients receiving warfarin therapy (see previous “Nutrient-Nutrient Interactions” discussion).

Vitamin K

Vitamin K is a generic name for a family of compounds that are synthesized by gut microflora in the distal small intestine and colon; these compounds include phylloquinones (K1), which are found in plants, and menaquinones (K2), which are found in fish oils and meats. Menadione (K3) is a common synthetic form that is converted to K2 by intestinal flora. Some of the menaquinones may be synthesized in vivo from vitamin K1. Phylloquinone absorption occurs primarily in the jejunum by a saturable, energy-dependent process. Like the absorption of other fat-soluble nutrients, vitamin K absorption depends on the presence of lipids, which stimulate the bile salt and pancreatic enzyme release necessary for its incorporation into chylomicrons for transport (Figure 8-1). Absorption of

vitamin K normally varies from 40% to 80%. With any impairment in the lipid absorption process, such as in the case of a biliary obstruction or a significant small bowel resection, absorption decreases to 20% to 30%.14,37 The absorption and usefulness of the menaquinone synthesized by bacteria are still unknown. Mineral oil and other nonabsorbable lipids interfere with vitamin K absorption. There is no storage mechanism for vitamin K in the body.14,37

Functions of Vitamin K

Clotting

Vitamin K is involved in a variety of enzymatic reactions within the body that affect blood coagulation. The primary biochemical function of vitamin K is as a cosubstrate in the posttranslational carboxylation of proteins at designated glutamic acid residues. As part of a membrane-bound carboxylase system, vitamin K functions in the posttranslational gamma-carboxylation of clotting factors (II, VII, IX, and X), and normally occurring anticoagulant proteins C and S.14 Clotting is often measured in terms of prothrombin time (PT). Variations in methods for determining PT cause variance in test results. To account for this variance, a standardized measure of PT, the international normalized ratio (INR), is used.

Patients on anticoagulation therapy (warfarin therapy) may find that ingestion of excess vitamin K decreases the ability to achieve a therapeutic INR.38 Warfarin and vitamin K have an antagonistic relationship with each other regarding their effect on INR. Warfarin increases the INR, whereas vitamin K decreases the INR. Achieving a therapeutic INR (typically between 2 and 3) requires a balance between warfarin administration and vitamin K ingestion. One study in healthy patients anticoagulated with a low warfarin dose found that every 100 mcg increase in vitamin K beyond an initial amount of 150 mcg causes a 0.2 decrease in INR. Therefore, assessment of vitamin K intake is an essential part of warfarin therapy.39 The amount of vitamin K from sources of nutrition support can quickly add up. These sources include obvious ones, such as parenteral multivitamin infusions, but also less obvious sources such as lipid emulsions and propofol administration.

Bone Health

Vitamin K may be involved in bone health through its role in converting protein-bound glutamate to gamma-carboxyglutamate (Gla). Osteocalcin is a bone Gla-protein that facilitates calcium binding to the hydroxyapatite matrix of bone.40 Emerging evidence in human intervention studies suggests that vitamin K1 may benefit bone health, particularly when coadministered with vitamin D.37

Several mechanisms have been proposed to explain vitamin K modulation of bone metabolism.35 One relates to the Gla content of osteocalcin, which accounts for up to 80% of the total Gla content of mature bone. Undercarboxylation of osteocalcin secondary to inadequate vitamin K can impair the ability of osteocalcin to bind to the bone mineral matrix and thus regulate bone mineralization. There is also increasing evidence that vitamin K positively affects calcium balance, a key mineral in bone metabolism.37,40 Some researchers contend that the DRI for vitamin K should be increased given its role in bone health.37,40

Clinical Applications

Recommended Intakes for Adults

The AI for vitamin K for men is 120 mcg, and AI for women is 90 mcg. A UL has not been established for vitamin K.

Sources

Food sources of vitamin K include liver, green leafy vegetables, broccoli, peas, and green beans.41 Other sources of vitamin K are propofol and lipid injectable emulsions (ILEs). The amount of vitamin K in ILE varies depending on the composition of the ILE and the manufacturing process.42

Populations at Risk for Deficiency or Adverse Effects

The following conditions and therapies increase a patient's risk for vitamin K deficiency:

- Fat malabsorption
- Inflammatory bowel disease
- Antibiotic therapy
- Long-term PN without lipid emulsion
- Nil per os status

Patients on anticoagulant therapy may require closer monitoring of vitamin K. Some adverse effects have been reported when large doses of this vitamin were given to individuals who had severely compromised liver function.43 In addition, menadione, a water-soluble synthetic vitamin K analog, has produced fatal anemia, hyperbilirubinemia, severe jaundice,5 and anaphylactoid reaction.44

Half-Life of the Nutrient in the Body

The first half-life of phylloquinone is 15 minutes. The half-life then slows down to about 2.5 hours.4

Body pool turnover has been reported to be 1.5 days;45 however, another study found liver pool of phylloquinone to decrease by two-thirds in 3 days.

Assessment of Vitamin K Status

The INR is the most common laboratory procedure used to monitor warfarin therapy and detect potential bleeding problems. A more sensitive indicator of vitamin K status is the measurement of plasma phylloquinone, the major circulating form. Fasting phylloquinone reference values in healthy adults are 0.15 to 1.0 mcg/L and reflect both dietary depletion and repletion.46 Refer to Table 8-5 for clinical signs and symptoms of vitamin K deficiency.14,26,37,47

TABLE 8-5 Clinical Signs and Symptoms of Vitamin K Deficiency

System	Deficiency
Skin	Bruising, prolonged bleeding
Bones	Decreased bone density
Other	Increased prothrombin time

Source: Data are from references 14, 26, 37, and 47.

Nutrient-Nutrient Interactions

Excess vitamin A or vitamin E can diminish absorption of vitamin K. Excess serum/plasma vitamin D levels stimulate hepatic oxidation and excretion of vitamin K.5

Medication-Nutrient Interactions

Cholestyramine (bile acid sequestrant), lomitapide (lipid-lowering agent), orlistat (weight control medication), octreotide (antidiarrheal), and mineral oil (laxative) decrease absorption of vitamin K through fat malabsorption. Vitamin K negates the effects of warfarin and must be carefully titrated to optimize anticoagulation therapy. Vitamin K metabolism is increased by phenobarbital (sedative) and phenytoin (antiepileptic).7

Treatment Considerations

Guidelines for treating vitamin K deficiency do not exist. However, oral or injected supplementation of 2.5 to 10 mg vitamin K twice weekly to daily is common.

The literature continues to support recommendations for increased vitamin K intake to reduce bone loss and fracture risk, especially among older adults.48

As noted, warfarin and vitamin K counter each other in the goal of achieving a therapeutic INR. Therefore, once the goal INR is met, daily vitamin K intake should remain consistent. Increased vitamin K intake without adjustment of warfarin leads to an increased risk of clotting whereas decreased vitamin K intake could increase the risk of bleeding.

Administration of warfarin with continuous enteral nutrition leads to decreased warfarin absorption. Currently, the evidence suggests that warfarin binds irreversibly with plastic tubing. More rapid administration of warfarin through the tubing results in less warfarin binding and more warfarin administered to the patient.49

If a patient on anticoagulation therapy has difficulty achieving a therapeutic INR, consider all sources of vitamin K, including from lipid emulsions and fat-based medicines (propofol).42 See Practice Scenario 8-1.

Practice Scenario 8-1

Question: What considerations should be made when a patient on warfarin therapy is receiving parenteral nutrition (PN)?

Scenario: A 52-year-old man with a diagnosis of stage IV colon cancer status post chemotherapy presents to the emergency department with severe nausea, vomiting, abdominal pain, and distention. The patient reports that his last bowel movement was 5 days ago and he has had nothing but sips of fluid since that time. He also reports "cramping" pain in his left calf and edema is noted in that extremity. A computed tomography scan of the abdomen is positive for ileus. Doppler ultrasound of the left lower extremity reveals deep vein thrombosis (DVT). A nasogastric tube is inserted and connected to low-intermittent suction for abdominal decompression, and intravenous fluids are started for dehydration. A heparin drip is initiated per the hospital's DVT protocol, and the patient is transferred to the intensive care unit for further management. Within 48 hours of admission, patient is still unable to tolerate oral feedings, and PN is initiated. As the patient's condition improves, he is advanced to a liquid diet with supplemental PN and transitioned to warfarin therapy with a target international normalized ratio (INR) of 2 to 3. During the course of the warfarin therapy, his INR remains subtherapeutic despite frequent increases in the warfarin dose until it reaches abnormally high levels.

Intervention: The nutrition support clinician assesses the patient's vitamin K intake from PN sources and its impact on warfarin dosage. PN is adjusted to decrease vitamin K intake to achieve therapeutic INR at a stable warfarin dose. If possible, the patient is switched to a multivitamin product that does not contain vitamin K, such as M.V.I.-12 (Hospira). If the lipid emulsion provides a high dose of vitamin K, it may also be adjusted.

Answer: All sources of vitamin K must be accounted for in the management of a patient on warfarin. PN provides a significant amount of vitamin K. Parenteral multivitamins such as Infuvite contain 150 mcg vitamin K per unit dose (10 mL). Depending upon their fat source, lipid emulsions provide anywhere from 0 to 1000 mcg vitamin K per liter.

Rationale: Vitamin K is necessary for the formation of key clotting factors. Warfarin acts as a vitamin K antagonist and is thus an anticoagulant. Proper dosing of warfarin requires that vitamin K intake be (1) known and (2) consistent. The variable vitamin K content in lipid emulsions along with the periodic nature of their administration adds an extra challenge to the provision of nutrition support to patients receiving warfarin therapy. For example, a 250-mL bag of the 20% lipid emulsion Intralipid has 132.5 mcg vitamin K. If this product is given in addition to a daily multivitamin infusion of 150 mcg vitamin K, the daily intake of vitamin K will be 2 to 3 times the Adequate Intake without a commensurate adjustment in warfarin, making achievement of the target INR difficult. Another considerable source of vitamin K may be the sedative lipid propofol, which is 10% soybean oil. Soybean oil has approximately 1.7 mcg vitamin K per mL. If a patient were receiving both warfarin and propofol, the propofol might need to be discontinued to achieve a therapeutic INR; however, it would be unusual for patients to be receiving both of these medications concomitantly.50

Vitamin C

The total amount of naturally occurring and biologically active vitamin C is available as ascorbic acid (reduced form) and dehydroascorbic acid (oxidized form). Vitamin C absorption occurs predominately in the ileum, with some absorption in the jejunum via the sodium/energy-dependent active transport system. The transport systems for vitamin C are both saturable and dose dependent—that is, absorption efficiency decreases as intake increases. At pharmacological doses (12 g/d), vitamin C absorption falls to about 16%, whereas at low intakes (less than 20 mg/d), absorption can reach 98%. At normal intakes (20 to 120 mg/d), absorption is 80% to 90%.51 Serum ascorbic acid levels rise with dietary intakes of 70 to 140 mg vitamin C per day, and then saturation is reached (at 80 to 90 mcmol/L). Once serum ascorbic acid levels reach 80 mcmol/L, renal clearance sharply increases,14 which explains why few toxic effects are associated with high vitamin C intake.

Functions of Vitamin C

Ascorbic acid serves as an antioxidant, reacting directly with superoxide, hydroxyl radicals, and singlet oxygen.52 Vitamin C also provides reducing equivalents for a variety of reactions and acts as a cofactor for reactions that require a reduced metal. As a result, vitamin C has very complex functional roles, such as the synthesis of collagen, carnitine, and neurotransmitters; the enhancement of intestinal absorption of nonheme iron; cholesterol hydroxylation into bile acids; the reduction of toxic transition (variable positive oxidative states) metals; the reductive protection of folic acid and vitamin E; and the immune-mediated and antibacterial functions of white blood cells.14

Clinical Applications

Recommended Intakes for Adults

The following RDAs have been set for vitamin C:

- Men: 90 mg
- Women: 75 mg
- Pregnant women: 100 mg
- Lactating women: 120 mg

The UL for vitamin C is 2000 mg.

Sources

Food sources of vitamin C include citrus fruits and other fruits and vegetables.

Populations at Risk for Deficiency

Older adults and patients with malabsorptive disorders or poor diets combined with alcoholism are at increased risk of vitamin C deficiency. Type 2 diabetes mellitus and certain types of cancer may increase vitamin C turnover. People who smoke tobacco need more vitamin C because of tobacco use increases free radical production.

Half-Life of the Nutrient in the Body

The half-life of vitamin C varies according to serum status. In replete states, vitamin C half-life is approximately 30 minutes. When plasma levels of vitamin C are less than approximately 70 mcmol/L, the half-life is 8 to 40 days because of renal reabsorption.53 Studies report daily intake of less than 10 mg vitamin C causes frank signs of scurvy within approximately 30 days.5

Assessment of Vitamin C Status

Plasma ascorbic acid analysis is the most feasible procedure for evaluating the status of vitamin C in individuals as well as in population groups. (See Table 8-6.14) Although the concentration of ascorbic acid in leukocytes reflects body stores, this measurement is technically difficult to perform. Table 8-7 presents clinical signs and symptoms of vitamin C deficiency and toxicity.

TABLE 8-6 Interpretation of Plasma/Serum Ascorbic Acid Levels

Status	Plasma/Serum Ascorbic Acid Level, mcmol/L (mg/dL)
Sufficient	>23 (0.4)
Low	12–23 (0.2–0.4)
Deficient	≤11 (0.2)

Source: Data are from reference 14.

TABLE 8-7 Clinical Signs and Symptoms of Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Capillary rupture, delayed wound healing, petechiae, perifollicular hemorrhage, hyperkeratotic papules	None
Hair	Corkscrew hairs	None
Mouth	Bleeding gums (from weakened collagen)	None
Joints	Joint effusions	None
Other	Hypochondriasis, increased susceptibility to infection	Nausea, vomiting, diarrhea, kidney stones

Source: Data are from references 14 and 54.

Nutrient-Nutrient Interactions

Vitamin C assists in the absorption of iron (Fe) by reducing Fe^{3+} to Fe^{2+}. For this reason, patients taking oral iron supplements should consume them with a source of vitamin C. However, this absorptive benefit plateaus at 75 mg vitamin C.5 This same iron-reductive mechanism has been theorized to increase oxidative stress if vitamin C is taken in excess because the resulting Fe^{2+} is capable of reacting with hydrogen peroxide to form the highly deleterious hydroxyl radical.55

Medication-Nutrient Interactions

One study found that vitamin C in amounts of 3g/d or more decreased acetaminophen excretion by 75%. Patients taking allopurinol (xanthine oxidase inhibitor) should refrain from ingesting large amounts of vitamin C because they increase the potential for renal calculi. Tetracycline (antibiotic), aspirin, and corticosteroids increase urinary vitamin C wasting.7

Treatment Considerations

Oral supplementation of 100 mg vitamin C 3 times per day is recommended to treat vitamin C deficiency. An initial intravenous (IV) dose of 60 to 100 mg may also be given.5 Vitamin C intake less than 10 mg/d over a prolonged period can result in classic deficiency signs and symptoms.14,54 Scurvy is rare today because it is preventable with as little as 10 mg vitamin C per day.41

Supplementation of vitamin C (100 to 200 mg/d) is now common in patients who have wounds, including stage I and II pressure ulcers.6,11,14 Surgical and burn patients are frequently reported to have ascorbate deficiency.6 Reports indicate that vitamin C status deteriorates during hospitalization and from medical or surgical stress, which can negatively impact wound healing.15,56 Hyperglycemia is common in acute stress states and prevents vitamin C transport, which is needed for normal leukocyte function.56 Vitamin C supplementation improves leukocyte function, but the extent to which it influences immune response is unclear.

Reports of vitamin C toxicity are uncommon. People given 5 to 15 g/d, which is well above the UL, have reported nausea and vomiting. The hypothesis that rebound scurvy occurs following the cessation of large vitamin C doses is controversial. Individuals with renal failure, kidney stones, or iron overload disease, and patients receiving heparin or warfarin therapy should avoid large vitamin C doses. Vitamin C intake increases both oxalate formation and absorption.57 Furthermore, vitamin C competitively inhibits renal reabsorption of uric acid. Health benefits for vitamin C intakes beyond 500 mg/d are unsubstantiated. Therefore, patients prone to oxalate- or uric acid–based kidney stones should not exceed 500 mg vitamin C intake per day. The relationship between excess vitamin C and oxalate formation is even more pronounced in renal failure. Vitamin C doses greater than 100 mg/d to 500 mg/d can precipitate oxalate crystals in soft tissues of patients with renal failure, increasing the risk of kidney stones and further compromising renal function.10

Thiamin

Thiamin (vitamin B1) consists of a central carbon to which a nitrogen-containing ring and a sulfur-containing ring are attached. Thiamin is readily inactivated by prolonged exposure to heat or alkaline solutions. There are 3 forms of thiamin: thiamin monophosphate (TMP), thiamin triphosphate (TTP), and thiamin pyrophosphate (TPP). TPP is the biologically active coenzyme and is also known as thiamin diphosphate (TDP).

Before absorption, intestinal phosphatases hydrolyze the phosphates, leaving free thiamin. Absorption of thiamin can occur by either active or passive diffusion, depending on the concentration of intestinal

thiamin.14 At low physiological concentrations, thiamin is absorbed via a specific energy-dependent, saturable active transport mechanism. It is mainly absorbed in the proximal small intestine, especially the jejunum, via a carrier-mediated process. Thiamin absorption is passive during high intake. Approximately 30 mg of thiamin is stored in the body as either TPP or TMP, with most found in the skeletal muscle (50%).14 Alcohol abuse is the most common cause of impaired thiamin absorption. In the blood, thiamin is bound to albumin, with most thiamin present in the red blood cells as TPP. Following absorption, most free thiamin is taken up by the liver and is phosphorylated into its coenzyme form, TPP. Whether excess intake is given orally or intravenously, most unused thiamin is rapidly excreted in the urine. A UL has not been set because suitable data are lacking.58

Functions of Thiamin

Key biochemical functions that require thiamin include energy transformation, synthesis of pentoses and reduced nicotinamide adenine dinucleotide phosphate (NADPH), as well as membrane and nerve conduction. TPP plays a major role in carbohydrate metabolism, serving as a magnesium-coordinated coenzyme for the oxidative decarboxylation of α-ketoacids (pyruvate and α-ketoglutarate), and for the activity of transketolase in the pentose phosphate pathway. As a structural component of nerve membranes, TTP may also function in nerve conduction.14

Thiamin deficiency affects the central nervous system. Patients at risk for a deficiency include those with recurrent vomiting or alcoholism, gastric surgery patients, and those who have an increased demand with marginal nutrition status.11

The classic thiamin deficiency neurologic diseases are beriberi and Wernicke encephalopathy, which can develop into Wernicke-Korsakoff syndrome. Beriberi is usually characterized by muscle weakness in the lower extremities coupled with impaired nerve conduction. It is caused primarily by inadequate thiamin intake with adequate carbohydrate intake. Acute post–gastric reduction surgery neuropathy, also called bariatric beriberi, has become more prevalent as the numbers of bariatric surgeries has increased. Although the neuropathy is multifactorial in origin, thiamin deficiencies along with vitamin B12 deficiencies have been implicated in 40% of the cases.59 Wernicke encephalopathy is generally precipitated by ethanol abuse. The classic triad of symptoms encompasses ocular abnormalities, gait ataxia, and mental status changes.11,14 Approximately 80% of patients with Wernicke encephalopathy develop Wernicke-Korsakoff syndrome, resulting in psychosis and memory disturbances. In the absence of thiamin, the resultant inhibition of pyruvate dehydrogenase drives carbohydrate metabolism toward lactic acid fermentation, resulting in a build-up of lactic acid. Untreated thiamin deficiency can result in fatal lactic acidosis.60

Clinical Applications

Recommended Intakes for Adults

The following RDAs for thiamin have been set:

- Men 1.2 mg
- Women: 1.1 mg
- Pregnant women: 1.4 mg
- Lactating women: 1.5 mg

As noted previously, a UL has not been established for thiamin.

Sources

Food sources of thiamin include enriched or fortified whole grain products, pork products, sunflower seeds, and wheat germ.

Populations at Risk for Deficiency

Populations at risk for thiamin deficiency include individuals with chronic alcoholism, patients receiving long-term PN or dialysis, patients with refeeding syndrome or malabsorption, women with hyperemesis gravidarum, patients experiencing protracted vomiting or decreased intake after bariatric surgery, and patients who receive insufficient thiamin supplementation during shortages of injectable multivitamin solutions.11,55

Half-Life of the Nutrient in the Body

The biological half-life of thiamin is 9 to 18 days,14 and thiamin deficit occurs with 14 to 20 days of inadequate intake.61,62 Because of its short biological half-life, thiamin deficiency is often the first nutrient deficiency noted when food intake is limited or when absorption is impaired by alcohol abuse.

Assessment of Thiamin Status

The preferred method for differentiating normal thiamin status from subclinical thiamin deficiency is the measurement of erythrocyte transketolase activity, with and without the in vivo addition of TDP.14 Transketolase is a TPP-dependent enzyme. This enzyme is measured in hemolyzed blood before and after the addition of TPP, and its resulting increased activity is quantified. This test provides a sensitive, specific biochemical functional measurement of thiamin status. A normal value, which indicates an acceptable thiamin status, is 0% to 15% increase in enzyme activity with the addition of TPP. A low value (or marginally deficient status) is an increase of 16% to 24%, whereas a deficient status (or a high risk of deficiency) is an increase greater than 25%. Adequacy of thiamin can also be assessed by the measurement of thiamin in whole blood; values less than 1.7 mcg/dL denote deficiency. Table 8-8 presents clinical signs and symptoms of thiamin deficiency.63,64

TABLE 8-8 Clinical Signs and Symptoms of Thiamin Deficiency

System	Deficiency
Eyes	Nystagmus
Nervous system	Dry beriberi: paresthesia, weakness in lower extremities Wernicke-Korsakoff syndrome and Wernicke encephalopathy: mental status changes, global confusion, nystagmus, polyneuritis, gait ataxia, and stupor
Other	Wet beriberi: high-output cardiac failure, dyspnea, hepatomegaly, tachycardia, oliguria, sodium and water retention, elevated lactic acid

Source: Data are from references 63 and 64.

Thiamin is remarkably nontoxic. Toxic effects of thiamin have been reported with an excess of 3 g/d (ie, 50 mg per kg body weight); otherwise, it is generally recognized as safe.

Nutrient-Nutrient Interactions

Magnesium is necessary for the conversion of thiamin to its active form, thiamin diphosphate. Thus, a magnesium deficiency effectively renders thiamin unusable.61

Medication-Nutrient Interactions

Furosemide (diuretic) therapy has been shown to cause thiamin deficiency secondary to the drug's diuretic effect, which results in increased urinary thiamin excretion. Theophylline (bronchodilator) decreases serum thiamin.62

Treatment Considerations

Some experts recommend prophylactic thiamin dosing when a deficiency is probable, especially in patients with a history of alcohol abuse who are receiving PN.62,65 The standard recommendation is 5 to 20 mg parenteral thiamin per day; however, wider ranges between 50 to 300 mg/d (IV, intramuscular, or oral) have been suggested.11,62,65 In cases of Wernicke encephalopathy or Wernicke-Korsakoff syndrome, recommendations vary greatly. For patients with suspected Wernicke encephalopathy or Wernicke-Korsakoff syndrome, a recent compilation of the evidence suggests 100 to 200 mg IV or intramuscular thiamin 3 times daily before high-carbohydrate meals for 3 to 5 days followed by 100 mg oral thiamin supplementation 3 times daily for 1 to 2 weeks and then once daily thereafter.66 For confirmed Wernicke encephalopathy or Wernicke-Korsakoff syndrome, increasing the initial dosing period to 200 to 500 mg thiamin 3 times daily and sustaining this regimen for 5 to 7 days before switching to the oral regimen is recommended.66

The clinician should be aware that hypersensitivity and anaphylactic reactions are possible, especially if thiamin is given repeatedly via the parenteral route.11,14 It is also important to note that thiamin supplementation is only effective if magnesium is replete. For this reason, it may be advisable to give

patients an initial dose of 1000 mg magnesium sulfate (approximately 200 mg elemental magnesium) unless repletion status is known.61 See Practice Scenario 8-2.

Practice Scenario 8-2

Question: How does thiamin deficiency affect nutrient metabolism?

Scenario: A patient presents to the emergency department with shortness of breath, restlessness, and mild confusion. Severe edema in the lower extremities and abdominal ascites secondary to alcoholic liver cirrhosis are noted. The patient's spouse states that the patient's oral food intake has been inadequate for the past month because of "binge drinking." The physician orders furosemide 40 mg. By Day 2, the patient's restlessness progresses to combative behavior, increased confusion, nystagmus, and leg tremor. Arterial blood gas is indicative of metabolic lactic acidosis, which is unresponsive to treatment. Wernicke encephalopathy secondary to inadequate thiamin deficiency is suspected. The patient's serum magnesium is 1.5 mg/dL, which is slightly below normal.

Intervention: Furosemide is discontinued and replaced with oral spironolactone. A multivitamin is administered along with thiamin (200 mg 3 times daily) for 5 days. The initial dose is given with 1 g magnesium sulfate. The confusion and agitation, as well as the metabolic lactic acidosis, resolve within 6 hours of initial treatment. The patient is sent home on an oral thiamin supplement of 100 mg 3 times daily. Two weeks later, this dose is decreased to 100 mg/d.

Answer: Thiamin is necessary for the conversion of pyruvate to acetyl coenzyme A (acetyl-CoA), a major step in the transformation of glucose to adenosine triphosphate. In the absence of thiamin, energy metabolism is impaired. As pyruvate builds up, it is driven toward lactic acid fermentation, which causes the spike in lactate and contributes to metabolic acidosis. Furthermore, thiamin is necessary for the Krebs cycle enzyme α-ketoglutarate dehydrogenase. Together, these conditions decrease the acetyl-CoA entering the Krebs cycle from carbohydrate metabolism and limit the energy substrates produced in the Krebs cycle from fatty acid–derived acetyl-CoA.

Rationale: Wernicke's encephalopathy is a thiamin deficiency–induced neurologic disorder. Its main symptoms include ataxia, ophthalmoplegia, and mental confusion. Severe alcoholism frequently causes thiamin deficiency through the following mechanisms:

- People with alcoholism often replace nutrient-dense energy sources with energy from alcohol intake, which can lead to malnutrition.
- Ethanol inhibits intestinal thiamin absorption.
- The active form of thiamin, thiamin pyrophosphate, is synthesized in the liver, making liver cirrhosis a possible contributing factor in thiamin deficiency.

The placement of this patient on furosemide may have compounded thiamin deficiency. Furosemide is a diuretic that promotes urinary thiamin wasting. Once furosemide is discontinued, the patient's diuretic is switched to spironolactone. The treatment protocol includes supplementation of both thiamin and magnesium sulfate. Magnesium is a necessary cofactor in the conversion of thiamin to its active form in

the liver. If magnesium is depleted, administered thiamin cannot be utilized. Therefore, unless magnesium adequacy is a certainty, supplementation with magnesium is advisable. This patient is given 1 g magnesium sulfate (approximately 200 mg elemental magnesium by weight). These doses are followed by a high-carbohydrate meal, which is thought to enhance thiamin absorption.

Riboflavin

Riboflavin (vitamin B2) chemically contains 3 linked 6-membered rings, with a sugar alcohol attached to the middle ring. It is a precursor to 2 major coenzyme derivatives, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are involved in a wide variety of enzymatic reactions in intermediary metabolism. Dietary sources of riboflavin are primarily in the coenzyme forms, whereas the free form is found in milk and enriched grain products. All these forms can be used to meet the requirement for riboflavin.

Before absorption, riboflavin dissociates from the coenzyme derivatives in the stomach via the action of hydrochloric acid (HCl). The extent of absorption is proportionate to the dose and occurs predominately in the proximal portion of the small intestine via a saturable, sodium-dependent carrier mechanism. Riboflavin deficiency results in an increased intestinal uptake, whereas high riboflavin intake results in decreased absorption efficiency. The upper limit of absorption is estimated to be approximately 66.4 mcmol/d (25 mg/d).14 Several factors can enhance or impair riboflavin absorption. Evidence indicates that the presence of food increases riboflavin absorption, most likely by delaying the intestinal transit time.14 Bile salts also increase the absorption of riboflavin. In contrast, several metals and drugs can impede riboflavin. For example, many of the divalent metals, such as copper, zinc, iron, and manganese, form chelates with riboflavin and prevent its absorption.14 The clinical significance of this binding may become relevant when deciding the amount of supplementation of these trace elements. Alcohol ingestion can also impair both the digestion and absorption of riboflavin. Once absorbed into the mucosal cells, riboflavin then enters the portal circulation destined for the liver, where it undergoes phosphorylation into FMN and FAD. The synthesis of these coenzymes is under hormonal control; adrenocorticotropic hormone, aldosterone, and the thyroid hormones stimulate synthesis.14 Riboflavin undergoes little metabolism before it is excreted in the urine. Intake that exceeds plasma saturation levels is lost via the urine primarily as free riboflavin.

Functions of Riboflavin

The major biochemical function of riboflavin is to serve as a component of FMN and FAD as an electron transport intermediary for oxidation-reduction reactions. As a component of FMN and FAD, riboflavin participates in pyridine- and non-pyridine-dependent dehydrogenases, oxygen and monooxygen reductases, disulfide reductases, and one-electron transfers. FAD is a key player in macronutrient metabolism because of its ability to receive electrons from the breakdown of fatty acid oxidation and Krebs cycle intermediates and donate them to the electron transport chain for the production of adenosine triphosphate (ATP). Although seldom recognized, riboflavin also has antioxidant activity because the coenzyme FAD is required for the enzyme glutathione reductase, a pivotal enzyme protecting against lipid peroxides. Riboflavin deficiency has been associated with increased lipid

peroxidation, especially in association with excessive ethanol intake.14 Other micronutrient pathways that require riboflavin include the conversion of vitamin B6 to its active form, the synthesis of the active form of folate, and the catabolism of choline. Riboflavin deficiency rarely occurs alone and is most often accompanied by multiple nutrient abnormalities, such as deficits of the other B-complex vitamins.

Clinical Applications

Recommended Intakes for Adults

The RDA for riboflavin is 1.3 mg for men and 1.1 mg for women. A UL for riboflavin has not been established because suitable data are lacking.58 Riboflavin toxicity from food or supplements is rare.

Sources

Food sources of riboflavin include organ meats, milk, bread products, and fortified cereals.58

Populations at Risk for Deficiency

Individuals with alcoholism are at risk for riboflavin deficiency because intake and absorption are limited. Patients with thyroid disorders may have riboflavin deficiencies as a result of altered riboflavin metabolism. Patients with type 2 diabetes, trauma, or extreme stress may excrete more riboflavin than normal. Patients with chronic malabsorptive disorders are also at risk for riboflavin deficiency.

Half-Life of the Nutrient in the Body

The half-life of riboflavin is 66 to 84 minutes.

Assessment of Riboflavin Status

The erythrocyte glutathione reductase activity coefficient (EGR-AC) assay is a sensitive, functional indicator of riboflavin status and the method of choice for its analysis.69 An EGRAC value less than 1.2 (ie, less than 20% stimulation of activity upon addition of FAD) indicates an acceptable riboflavin status. A value between 1.2 and 1.4 indicates marginal status, and a value greater than 1.4 indicates a riboflavin deficiency. This assay is invalid in individuals with a glucose 6-phosphate dehydrogenase deficiency.

Although riboflavin is not associated with a specific deficiency disease, characteristic symptoms of overt deficiency are known (see Table 8-9).

TABLE 8-9 Clinical Signs and Symptoms of Riboflavin Deficiency

System	Deficiency
Skin	Seborrheic dermatitis of face and scrotum
Eyes	Visual impairment, corneal vascularization, photophobia
Mouth	Cheilosis, angular stomatitis, glossitis, edema, and hyperemia of oral and pharyngeal mucosa, sore throat
Nervous system	Peripheral nerve dysfunction
Other	Normochromic normocytic anemia

Source: Data are from reference 14.

Nutrient-Nutrient Interactions

Alcohol as well as divalent metals such as copper, zinc, iron, and manganese form chelates with riboflavin and prevent riboflavin absorption.14

Medication-Nutrient Interactions

Tricyclic antidepressant medications and tetracycline (antibiotic) inhibit riboflavin absorption.7

Treatment Considerations

Riboflavin deficiency is rare in the general US population. However, suboptimal riboflavin status can be found in critically ill patients.70 If a patient has riboflavin deficiency, supplement 10 to 20 mg riboflavin daily until the deficiency is resolved.5

Niacin

The term niacin (vitamin B3) is a generic descriptor for the vitamin's water-soluble active forms, nicotinic acid and nicotinamide. Nicotinamide serves as a component of 2 coenzymes: nicotinamide adenine dinucleotide (NAD) and NADP. In dietary sources of animal origin, niacin occurs mainly in these 2 forms. In addition to dietary sources, NAD can be synthesized from the essential amino acid tryptophan: 60 mg tryptophan produces 1 mg niacin.

Absorption and Metabolism

Both nicotinic acid and nicotinamide are absorbed rapidly and efficiently from the stomach and intestine by active transport (at low concentrations) or passive diffusion (at high concentrations).14 Both NAD and NADP are enzymatically hydrolyzed in the intestinal mucosa to release nicotinamide, the major form in the blood. The amount of niacin excreted in the urine is related to the form of niacin ingested and niacin status of the individual. Very little nicotinamide and nicotinic acid is excreted because they both are actively reabsorbed from the glomerular filtrate. Excess niacin is methylated in the liver to form methylnicotinamide, one of the primary urinary metabolites.

Functions of Niacin

The nicotinamide portion of NAD and NADP serves as a hydrogen donor or an electron acceptor for more than 200 enzymes involved in intermediary metabolism.14 In this role, niacin functions in the metabolism of amino acids, fatty acids, and carbohydrates, accepting electrons from key macronutrient intermediates to form reduced nicotinamide adenine dinucleotide (NADH) and later donating those electrons to the electron transport chain for the production of ATP. Following hydrolysis, hepatic NAD releases adenosine diphosphate ribose, which, in turn, may be transferred to acceptor proteins and functions in the repair of DNA, as well as calcium mobilization.14,58 Niacin, as NADPH, is also involved with reducing the antioxidants dehydroascorbate (oxidized vitamin C) and glutathione, thus serving as a

general regenerator of the body's antioxidant systems. In addition, NADPH is required for activation of folate.

Pellagra

The classic niacin deficiency disease is pellagra, which is rare in developed nations. It can affect the gastrointestinal (GI) tract, the skin, and the nervous system, and presents as "three Ds": dermatitis, diarrhea, and dementia. In the United States, dietary deficiency of niacin is rare because many food products are fortified with niacin.14

Niacin as Treatment for Hyperlipidemia

Pharmacological doses of nicotinic acid are used to treat hyperlipidemia but may cause vasodilatation as a result of prostaglandin release. Most individuals taking 3 g/d will experience this phenomenon and other effects.14,58 Low-dose aspirin, ibuprofen, or naproxen therapy taken 30 minutes before nicotinic acid helps mitigate these adverse effects. Pharmacological doses of niacin have been shown in some studies to inhibit adipocyte lipolysis as well as very low-density and low-density lipoprotein synthesis,71 while raising high-density lipoprotein cholesterol. However, these changes have not translated into decreased cardiovascular risk.

Clinical Applications

Recommended Intakes for Adults

The RDAs for niacin are as follows:

- Men: 16 mg
- Women: 14 mg
- Pregnant women: 18 mg
- Lactating women: 17 mg

The UL for niacin is 35 mg.

Sources

Food sources of niacin include meat, fish, poultry, enriched and fortified breads, and fortified cereals.

Populations at Risk for Deficiency

Patients with malabsorptive disorders, individuals with alcoholism, older adults, and patients on the antitubercular medication isoniazid or mercaptopurine are at risk for niacin deficiency.5

Half-Life of the Nutrient in the Body

The biological half-life of niacin is 20 to 45 minutes. One study found that approximately 70% of administered niacin was excreted in urine within 96 hours.73

Assessment of Niacin Status

Tests to measure the urinary excretion of 2 major niacin-methylated metabolites, N-methylnicotinamide (NMN) and 2-pyridone, are the most common methods to determine niacin status. A niacin deficiency is defined as urinary levels of NMN less than 5.8 mcmol/d and urinary excretion of 2-pyridone less than 2 mg/g of creatinine.14,58 The measurement of plasma levels of 2-pyridone or NMN may also be used to assess niacin status.58 A decreased concentration of NAD in red blood cells, coupled with a low plasma tryptophan concentration, may also suggest niacin deficiency.14 Clinical signs and symptoms of niacin deficiency and toxicity are listed in Table 8-10.5,14,58

TABLE 8-10 Clinical Signs and Symptoms of Niacin Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Dermatitis, sun sensitivity causing symmetrical pigmented rash	Flushing, heat, vasodilation, itching
Mouth	Glossitis	None
Nervous system	Dementia, apathy, fatigue, memory loss, peripheral neuritis, and extremity paralysis	None
Other	Diarrhea, vomiting	Gastrointestinal irritation, severe hepatitis, glucose intolerance, myopathy

Source: Data are from references 5, 14, and 58.

Nutrient-Nutrient Interactions

Nutrient interactions with niacin have not been identified.

Medication-Nutrient Interactions

Isoniazid (tuberculosis treatment) may decrease niacin levels by inhibiting niacin production from tryptophan. Mercaptopurine (cancer/autoimmune treatment) may cause niacin deficiency by interfering with the conversion of niacin to NAD.

Treatment Considerations

Advanced stages of pellagra are treated via intramuscular injections of nicotinic acid (50 to 100 mg) 3 times daily for 3 to 4 days, followed by oral therapy of nicotinic acid.11

Vitamin B6

There are 3 forms of vitamin B6: pyridoxine, pyridoxal, and pyridoxamine. These 3 forms are metabolically, chemically, and functionally related and can be converted to the active coenzymes pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP). Plant foods contain the more stable

pyridoxine, whereas animal products have more pyridoxal and PLP. Ingested phosphorylated forms must undergo hydrolysis to remove the phosphate group via intestinal phosphatases prior to absorption.14

Absorption and Metabolism

Uptake of pyridoxine, pyridoxal, and pyridoxamine by intestinal epithelial cells occurs via a carrier-mediated, pH-dependent mechanism before entry into the portal vein. Absorption rates range from 71% to 82%.11,14 After uptake by the liver, the hepatocyte converts the dephosphorylated pyridoxine, pyridoxal, and pyridoxamine into the metabolically active PLP form. Both PLP and pyridoxal are released for transport to the extrahepatic tissues, with muscle containing most of the PLP (75% to 80%).14 Approximately 60% to 90% of the vitamin B6 in the plasma is in the form of PLP, and most of this is bound to albumin for transport. The major excretory metabolite is urinary 4-pyridoxic acid, the oxidation product of pyridoxal.

Functions of Vitamin B6

The coenzyme forms of vitamin B6 participate in more than 100 enzymatic reactions. These reactions include, but are not limited to, protein, amino acid, and lipid metabolism; gluconeogenesis; steroid receptor binding; central nervous system development; neurotransmitter synthesis; heme biosynthesis; and normal immune function.14 Vitamin B6 as PLP and PMP plays a key coenzyme role in the interconversion of amino acids by facilitating transamination and deamination reactions. Vitamin B6 also provides a pathway for decreasing levels of homocysteine, facilitating its conversion to cysteine.5

Routes of Toxicity

Adverse effects due to high food intakes of vitamin B6 have been reported,11,14 and large oral supplemental doses (greater than 500 mg/d) have resulted in a variety of adverse effects. Doses as low as 100 mg/d have been associated with Lhermitte's sign, which suggests an effect on the spinal cord.11,14 Adverse effects have also been related to prolonged intakes of 300 mg/d. Patients undergoing intestinal transplantation given 50 mg/d more than the UL of 100 mg had an accumulation of PLP within the red cells 30 times the upper limit of normal.74 Patients with intakes greater than 2000 mg/d have impaired motor control and paresthesia. Animal research suggests this nervous system impairment is caused by degeneration of the gasserian and dorsal root ganglia.75 Clinicians should adopt a cautious approach to vitamin B6 supplementation.

Clinical Applications

Recommended Intakes for Adults

RDAs for vitamin B6 are as follows:

- Men and women ages 50 years or younger: 1.3 mg
- Men older than 50 years: 1.7 mg
- Women older than 50 years: 1.9 mg
- Pregnant women: 1.9 mg

- Lactating women: 2.0 mg

The UL for vitamin B6 is 100 mg.

Sources

Food sources of vitamin B6 include fortified cereals, organ meats, and whole grains.11,58

Populations at Risk for Deficiency

Individuals with alcoholism, renal patients maintained on dialysis, older adults, and people receiving medication therapies that inhibit vitamin activity (ie, isoniazid, penicillamine, corticosteroids, and/or anticonvulsants) are at risk for vitamin B6 deficiency.

Half-Life of the Nutrient in the Body

The half-life of vitamin B6 is approximately 25 days. 58

Assessment of Vitamin B6 Status

A combination of the following 3 tests is recommended to assess vitamin B6 status because each individual test has limitations:

- Direct plasma PLP levels, which respond to intake, reflect liver stores, and plateau in 6 to 10 days.
- 24-hour urinary excretion of 4-pyridoxic acid, a hepatic B6 metabolite. Excretion of greater than 3 mcmol/d suggests adequate status.
- The activation of erythrocyte aspartate aminotransferase (EAST) and erythrocyte alanine aminotransferase (EALT) by PLP, which is used to evaluate long-term vitamin B6 status. An EAST index value less than 1.6 and an EALT index value less than 1.25 reflect adequate B6 status.

In critically ill intestinal transplant patients, intracellular (red cell) PLP concentrations are a more reliable measure of status than are plasma measurements.74

Table 8-11 presents clinical signs and symptoms of vitamin B6 deficiency and toxicity.

System	Deficiency	Toxicity
Skin	Seborrheic dermatitis	Dermatologic lesions
Mouth	Angular stomatitis, cheilosis, glossitis	–
Nervous System	Epileptiform convulsions, confusion, depression	Sensory neuropathy, ataxia, areflexia, impaired cutaneous and deep sensations
Other	Microcytic anemia	–

Source: Data are from references 5, 11, 14, and 76.

Nutrient-Nutrient Interactions

Because vitamin B6 is needed for the interconversion of one amino acid to another, B6 deficiency may lead to alterations in the amino acid pool.

Medication-Nutrient Interactions

Isoniazid (tuberculosis medication), oral contraceptives, corticosteroids (anti-inflammatories), and penicillamine (chelating agent) all have potential to diminish vitamin B6 levels or activity.5,7

Treatment Considerations

Vitamin B6 deficiency may be treated with 100 mg vitamin B6 per day.5 Patients receiving isoniazid may be given 25 to 50 mg/d as prophylactic against deficiency.7

Recently, patients with a neuromyopathic disorder associated with progressive muscle weakness and gait disturbances 2-years post–intestinal transplantation were found to have PLP deficiency. Patients who undergo intestinal transplantation should have their preoperative PLP status assessed, and serial long-term monitoring is warranted postoperatively in intestinal transplantation patients receiving PN. In these patients, preemptive replacement of vitamin B6 should be done when indicated.76

Vitamin B12

Naturally occurring vitamin B12 is found exclusively in foods of animal origin. These foods provide vitamin B12 in the coenzyme forms methylcobalamin, hydroxylcobalamin, and deoxyadenosylcobalamin. The complex structure of cobalamin contains a corrin ring with cobalt incorporated into the center. The only reliable sources of vitamin B12 come from animal products or synthetic non-animal-based B12 supplementation. Cyanocobalamin is the form primarily used in supplements and fortified foods. Oral vitamin B12 is relatively nontoxic in its naturally occurring forms. A rare allergic reaction to crystalline cyanocobalamin, which is the form used in many oral formulations, has been reported.14 Because suitable data are unavailable, a UL for vitamin B12 could not be set.58 All forms are readily converted into the biologically active forms, methylcobalamin and deoxyadenosylcobalamin.

Absorption and Metabolism

The digestion and absorption process for vitamin B12 is complex and dependent on normal GI function. Vitamin B12 is released from ingested proteins via the action of HCl and pepsin in the gastric secretions. The free B12 binds to the glycoprotein haptocorrin (also called R-protein or transcobalamin I), which is secreted by the salivary glands and swallowed with food. This complex travels into the small intestine, where pancreatic proteases hydrolyze haptocorrin and free B12 is released.14 In the duodenum, free B12 encounters another glycoprotein, intrinsic factor (IF), which is produced by the gastric parietal cells. The IF-B12 complex moves into the ileum, where it attaches to a specific IF receptor, cubilin, on the GI epithelial cells for absorption into the enterocyte.77 Three to four hours after intestinal absorption, the vitamin is transferred to a specific transport protein, transcobalamin II. This carrier protein enters the

portal circulation. It is first taken up by the liver and then by bone marrow and erythrocytes. Unlike other water-soluble vitamins, vitamin B12 can be stored in the liver.14,78

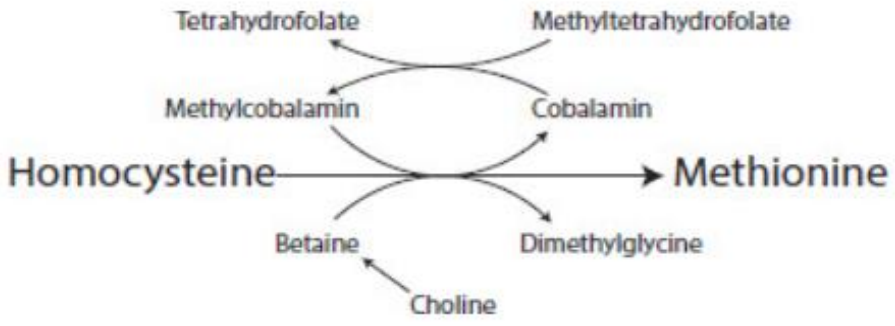
Adults with normal gastric function absorb approximately 50% of dietary vitamin B12. Because vitamin B12 is secreted into the bile, most of the vitamin is reabsorbed via enterohepatic circulation. Failure of any of these processes can decrease absorption of the vitamin. For example, pancreatic insufficiency could interfere with the release of free B12 from IF and reduce the amount absorbed. Individuals with impaired HCl production, such as older adults, patients with Helicobacter pylori infections, and those taking histamine-2 (H2) antagonists or proton pump inhibitors have reduced absorption.14,77 Patients who have had a portion or all of the ileum or stomach removed and patients with chronic malabsorption syndromes also have reduced absorption.

Functions of Vitamin B12

The Methyl-Folate Trap

Vitamin B12 is needed for the conversion of homocysteine to the benign amino acid methionine. Elevated homocysteine levels have been associated with increased risk for cardiovascular disease, stroke, dementia, Alzheimer's disease, and osteoporosis.79–81 Vitamin B12 must be converted to 1 of its 2 coenzyme forms, methylcobalamin or 5'-deoxyadenosylcobalamin, to be metabolically active. Methylcobalamin is a cofactor for methionine synthetase, the enzyme that converts homocysteine to methionine. Simultaneously, this conversion of homocysteine to methionine involves the demethylation of 5-methyltetrahydrofolate into its active form, tetrahydrofolate (THF) (Figure 8-2).5 When vitamin B12 is lacking, folate becomes "trapped" in its methyl, or inactive, form. For this reason, vitamin B12 deficiency often presents as folate deficiency and is, therefore, commonly misdiagnosed. A second major known reaction requiring B12 (as deoxyadenosylcobalamin) is the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA and for the degradation of certain amino acids and odd chain fatty acids. Between these 2 reactions, B12 prevents a host of deficiency symptoms.

FIGURE 8-2 Conversion of Homocysteine to Methionine



Source: Data are from reference 5.

Stages of Vitamin B12 Deficiency

There are 4 stages of vitamin B12 status: stage I, low serum B12; stage II, low cell stores of B12; stage III, a biochemical deficiency; and stage IV, a clinically apparent deficiency.82 The first manifestations of marginal or inadequate vitamin B12 status are usually neurologic and are possibly followed by hematologic and GI abnormalities. Other common age-related problems associated with vitamin B12 deficiency include cognitive decline, cardiovascular disease, and bone fractures.14,81–83 Clinical vitamin B12 deficiency has been associated with malabsorption syndromes that may occur in patients after gastrectomy, gastric bypass, or ileal resection, or those with Crohn's disease.84 Vitamin B12 deficiency has also been reported in some vegetarian/vegan populations.85

Clinical Applications

Recommended Intakes for Adults

RDAs for vitamin B12 are as follows:

- Men and women: 2.4 mcg
- Pregnant women: 2.6 mcg
- Lactating women: 2.8 mcg

As noted previously, a UL for vitamin B12 has not been established.

Sources

Food sources of vitamin B12 include fortified cereals, meat, fish, poultry, and eggs.58

Populations at Risk for Deficiency

Patients with malabsorption syndromes, vegetarian and vegan populations, and patients with low HCl secretion are at risk for vitamin B12 deficiency.

Half-Life of the Nutrient in the Body

The serum half-life of vitamin B12 is approximately 6 days. The half-life of B12 in the liver is approximately 12 months.

Assessment of Vitamin B12 Status

The earliest indicator compromised vitamin B12 status is a low serum level of holotranscobalamin II, the primary delivery protein for vitamin B12. However, this laboratory test is not routinely available in hospital settings. The decrease in serum vitamin B12 levels occurs later than the decrease in holotranscobalamin II and suggests a decline in cellular stores. In fact, serum vitamin B12 levels may even be maintained at the expense of its stores.58 The serum levels of methylmalonic acid (MMA) and homocysteine are elevated in more than 90% of individuals with a vitamin B12 deficiency.82 Homocysteine serum concentrations may also be elevated in folic acid deficiency and, therefore, are not

a specific indicator of B12 deficiency. Measuring the serum concentration of vitamin B12 is the procedure of choice for determining B12 status. According to the World Health Organization, serum values of B12 less than 150 pg/mL (110 pmol/L) denote a deficiency for all ages.87 Other sources suggest that levels less than either 300 or 350 pg/mL should be considered B12 deficient.4

Because of the close interrelationships between vitamin B12 and folic acid, especially in the presence of megaloblastic anemia, the status of both vitamins should be determined simultaneously. Megaloblastic anemia is recognizable as a mean corpuscular volume (MCV) >100 fL/cell. However, the absence of megaloblastic anemia should not be taken as lack of B12 deficiency because folate can mask B12 deficiency. Serum homocysteine and MMA are increased in B12 deficiency; measurements of both are useful when diagnosing vitamin B12 deficiency.71,72 Normal serum MMA levels are 0.08 to 0.56 mcmol/L. Homocysteine levels between 5 and 15 mcmol/L are considered normal. Homocysteine and MMA values greater than normal ranges do support vitamin B12 deficiency.

Patients with vitamin B12 deficiency may exhibit a variety of clinical signs and symptoms. See Table 8-12 for details.

TABLE 8-12 Clinical Signs and Symptoms of Vitamin B12 Deficiency

System	Deficiency
Bone	Bone marrow changes, bone fractures
Mouth	Glossitis
Nervous system	Diminution of vibration and/or position sense, hand/feet paresthesia, unsteadiness, cognitive decline, confusion, depression, mental slowness, poor memory, delusions, or overt psychosis
Other	Megaloblastic anemia, leukopenia, thrombocytopenia, cardiovascular disease, neutrophil nuclei hypersegmentation

Source: Data are from references 81 through 83.

Nutrient-Nutrient Interactions

An excess intake of vitamin C (500 mg) in a single dose may temporarily impair the vitamin B12 bioavailability from foods and destroy the vitamin.14

Medication-Nutrient Interactions

Metformin (insulin sensitizer), proton pump inhibitors (PPIs) (gastroesophageal reflux disease medications), and colchicine (anti-gout agent) decrease vitamin B12 absorption. Tetracycline (antibiotic), oral contraceptives, and octreotide (antidiarrheal) decrease serum B12. Methyldopa (antihypertensive) increases the need for B12 supplementation, and rifampin (antitubercular) confounds B12 assay measurements.7

Treatment Considerations

Vitamin B12 supplementation may be done by intramuscular injection or via a sublingual, nasal spray, oral, or gel B12 preparation. The common doses for treating B12 deficiency are intramuscular injections

of either 100 mcg or 1000 mcg at 1-month intervals until corrected. If patients have symptomatic B12 deficiency, injections may initially be done injections more frequently than monthly.

Adult vegans and strict vegetarians with normal vitamin B12 absorption may safely take a standard multivitamin supplement to avoid a B12 deficiency.

Folic Acid

Folic acid (folate, folacin) is also called pteroylglutamate or pteroylmonoglutamate. The metabolically active forms of folate have reduced (tetrahydro-) pteridine rings with up to 11 glutamic acids (polyglutamates) attached. Pteroylpolyglutamate is the form of folate in foods and often contains up to 9 glutamate residues. Prior to absorption, polyglutamates are converted to the monoglutamate form by hydrolytic zinc-dependent enzymes (conjugases) located in the jejunal brush border.14 The monoglutamates produced are actively transported via a pH-dependent, carrier-mediated mechanism.14 Within the intestinal cell and before entry into the portal circulation, the monoglutamate form of folate undergoes a reduction to THF, which is then converted to either N5-methyltetrahydrofolate (N5-MTHF) or N10-formyltetrahydrofolate. These 2 forms are secreted into the bile and recirculate via enterohepatic circulation. They may account for as much as 50% of the folate that reaches the peripheral tissues.14 The predominant form found in the plasma is N5-MTHF, which is loosely bound to albumin and folate-binding proteins (also called folate carriers or folate receptors). Folate transport across membranes into cells of various tissues occurs via a carrier-mediated process. Folate-binding proteins are found within the intestinal brush border and facilitate cellular folate uptake. Intracellularly, N5-MTHF is demethylated via a vitamin B12–dependent enzyme and converted back into a polyglutamate form to become the active coenzyme capable of transferring 1-carbon units. Excretion of folate metabolites is minimal, due to reabsorption via enterohepatic bile circulation.

Both zinc deficiency and chronic alcohol consumption can impair the conjugase activity and, thus, the absorption of folate. Any change in luminal jejunal pH secondary to drug therapy or disease can also limit folate absorption. Conditions or diseases that impair bile secretion may also limit folate recirculation.

Functions of Folate

The primary biochemical role of folic acid is as a coenzyme in the transfer of single carbon fragments from one compound to another for amino acid metabolism and nucleic acid synthesis.14,58 Folate (THF) functions as a coenzyme to accept 1-carbon groups generated from amino acid metabolism. These THF derivatives serve as donors of 1-carbon units for the synthesis of amino acids, purines, and pyrimidines. THF donates a methyl group to cobalamin (B12) for the regeneration of methionine from homocysteine (Figure 8-2).

Dietary folate equivalents (DFEs) are used to express folate requirements and to reflect differences in absorption of food vs synthetic folate (1 DFE = 1 mcg food folate, 0.6 mcg fortified/supplemental folic acid taken with food, or 0.5 mcg supplemental folic acid taken without food).

Pregnant women are at greater risk of developing a folate deficiency secondary to the increased demand for DNA synthesis for embryonic development. Folate deficiency causes the DNA misincorporation of uracil in place of thymine, leading to DNA fragility and strand breakage that cause neural tube defects (NTDs) during fetal development.5 Since the US Food and Drug Administration (FDA) mandated folate fortification of cereal and grain products in January 1998, the number of reported cases of NTDs has declined.88 Low serum folate levels during pregnancy have also been associated with poor pregnancy outcomes.89

Clinical Applications

Recommended Intakes for Adults

The RDAs for folate are as follows:

- Men and women: 400 DFE
- Pregnant women: 600 DFE
- Lactating women: 500 DFE

The UL for folic acid is 1000 mcg.

Women of childbearing age should take a synthetic daily supplement with 400 mcg folic acid to prevent NTDs in offspring. Women who have a history of delivering neonates with NTDs should take 4000 mcg synthetic folic acid per day beginning 1 month prior to attempting conception through the first 3 months of pregnancy.90

Sources

Food sources of folate include enriched grain foods, dark-green leafy vegetables, and fortified cereals.58

Populations at Risk for Deficiency

People with alcoholism are at risk for folate deficiency because of decreased folate intake and absorption. As noted earlier, folate deficiency is a risk for pregnant women because of the increased demand for the nutrient for DNA synthesis in embryonic development. Other populations at risk for folate deficiency include periconceptual and premenopausal women and patients taking phenytoin, cholestyramine, or sulfasalazine.

Half-Life of the Nutrient in the Body

The half-life of folate is approximately 90 days.91 With deficient intake, plasma folate levels decrease within 1 month. If this deficiency is not corrected, red blood cells can become folate deficient within 3 to 4 months and megaloblastic anemia can occur within 4 to 5 months.5

Assessment of Folate Status

There are 4 stages of folate deficiency:

- Stage 1 is early negative balance with serum folate levels less than 3 ng/mL (6.8 nmol/mL).
- Stage 2 is tissue depletion when red blood cell folate levels are less than 160 ng/mL (362.67 nmol/mL).
- Stage 3 is folate-deficient erythropoiesis, indicated by neutrophil hypersegmentation and an abnormal deoxyuridine suppression test (correctable by folate in vitro).
- Stage 4 is a clinical folate deficiency, manifested by megaloblastic or macrocytic anemia.

The goal is early detection and correction of deficiency. As has been discussed, vitamin B12 status and homocysteine concentrations should be determined in tandem with folate status. New methodologies to accurately assess folate status via folate derivatives are under development and hold promise for the future.

Patients with folate deficiency may exhibit a variety of clinical signs and symptoms. See Table 8-13 for details.

TABLE 8-13 Clinical Signs and Symptoms of Folate Deficiency

System	Deficiency
Mouth	Cheilosis
Nervous system	Nervous instability, dementia
Other	Megaloblastic or macrocytic anemia, neutrophil hypersegmentation (early indicator of deficiency), diarrhea, weight loss, depression of cell-mediated immunity, cardiovascular disease

Source: Data are from references 14 and 58.

Nutrient-Nutrient Interactions

Zinc deficiency can impair the absorption rate of folate.

Medication-Nutrient Interactions

Carbamazepine (antiepileptic), estrogen therapy, oral contraceptives, phenobarbital (sedative), phenytoin (antiepileptic), and triamterene (diuretic) cause decreased folate in the serum. Cholestyramine (bile acid sequestrant), metformin (insulin sensitizer), sulfasalazine (anti-inflammatory), and pancrelipase (pancreatic enzyme) decrease folate absorption. Trimethoprim (antibiotic) interferes with folate metabolism. Rifampin (antitubercular agent) confounds folate assay measurements.7

Treatment Considerations

Treatment for folate deficiency is 1 to 5 mg folate daily.5 Excessive amounts of folic acid (100 times the RDA) may result in seizures in individuals on phenytoin therapy. Some evidence supports folate treatment of 10 mg/d to improve hyperhomocysteinemia as well as endothelial dysfunction via improvements in coagulation and free radical scavenger activity.92 No signs of toxicity were observed when women were given 10 mg folic acid daily for 4 months.14 Allergic reactions to oral and parenteral folic acid products have been observed.14,58 As mentioned earlier in this chapter, the metabolism and

functions of folate and vitamin B12 are interrelated. Consumption of large folate amounts can mask a B12 deficiency.

Biotin

Biotin (vitamin B7) is ubiquitous in the diet and exists in the free biotin and the protein-bound coenzyme form biocytin, which is biotin bound to the amino acid lysine. Free biotin is absorbed via facilitated diffusion. Biocytin requires the enzyme biotinidase in the small intestine to cleave the protein portion from biocytin, releasing the free vitamin for jejunal absorption.14 Evidence suggests that biotinidase may also function as a biotin carrier protein.93

Functions of Biotin

Biotin is necessary for the genetic expression of more than 2000 enzymes. Additionally, biotin functions as a cofactor for 4 carboxylase enzymes in mammalian systems, which transport carbon dioxide (carboxyl units) to various substrates. These biotin-dependent carboxylases catalyze vital reactions in important metabolic pathways: acetyl-coA carboxylase for fatty acid synthesis, pyruvate carboxylase for gluconeogenesis, propionyl-CoA carboxylase for propionate metabolism, and 3-methylcrotonyl-CoA carboxylase for branched-chain amino acid catabolism.

Overall, biotin deficiency is rare because biotin is synthesized by colonic microflora.5 However, approximate 1 person in 60,000 has biotinidase deficiency, an inherited autosomal recessive trait.93 These individuals improve clinically when they are given pharmacological doses of biotin (5 to 20 mg/d).

Clinical Applications

Recommended Intakes for Adults

The AIs for biotin are: 30 mcg for men and nonpregnant women and 35 mcg during pregnancy. A UL for biotin has not been established because there are no reports of biotin toxicity.58

Sources

Food sources of biotin include liver; smaller amounts are also found in other cuts of meat and in fruits.

Populations at Risk for Deficiency

Biotin deficiencies have been reported in association with long-term PN, in people with alcoholism, and in patients with partial gastrectomy.

Half-Life of the Nutrient in the Body

The half-life of biotin is 1.8 hours. Inadequate biotin intake manifests as deficiency within 2 to 4 weeks.

Assessment of Biotin Status

Commonly used methods for determining biotin status include measurements of serum biotin concentrations and 24-hour urinary excretion of biotin. The most valid indicators of biotin status are an abnormally decreased urinary excretion of biotin and an abnormally increased urinary excretion of 3-hydroxyisovaleric acid.95 Whole blood or serum biotin concentrations of less than 200 pg/mL indicate biotin deficiency but are not as reliable as urinary analysis. A urinary concentration of biotin less than 6 mcg/d is a better indicator of deficiency.5

Patients with biotin deficiency may exhibit a variety of clinical signs and symptoms. See Table 8-14 for details.

TABLE 8-14 Clinical Signs and Symptoms of Biotin Deficiency

System	Deficiency
Skin	Pallor, erythematous seborrheic dermatitis
Hair	Alopecia
Eyes	Vision problems
Mouth	Glossitis, cheilosis
Nervous system	Nervous instability, dementia, hallucinations, paresthesia in extremities, depression
Other	Hypotonia, anorexia, nausea, vomiting, lethargy, muscle pain, ketolactic acidosis, elevated cholesterol

Source: Data are from references 14 and 93.

Nutrient-Nutrient Interactions

No nutrient interactions with biotin have been identified.

Medication-Nutrient Interactions

Carbamazepine (antiepileptic) decreases serum biotin.7

Treatment Considerations

Patients with biotin deficiency who are given 3 to 20 mg/d usually improve. Even at high intakes of biotin, no evidence of toxicity was observed when patients with biotin-responsive, inborn errors of metabolism or acquired biotin deficiency were treated with daily doses of either 200 mg of biotin orally or 20 mg intravenously.14,58

Pantothenic Acid

Pantothenic acid (vitamin B5) is a component of the CoA molecule and the acyl carrier protein of fatty acid synthetase complex.14 Dietary CoA is hydrolyzed to pantothenic acid in the intestinal lumen. Absorption is either by passive diffusion or via a saturable, sodium-dependent active transport. Absorbed pantothenic acid is transported via the erythrocytes throughout the body.14 Most of the

pantothenic acid in the body tissues is in the form of CoA, which is hydrolyzed to pantothenic acid before excretion in the urine.14

Functions of Pantothenic Acid

As a component of CoA, pantothenic acid is involved in energy released from fat, carbohydrate, and ketogenic amino acids. In this form, pantothenic acid is also involved in gluconeogenesis, heme and sterol synthesis, and most acetylation reactions. As CoA, pantothenic acid is required for the synthesis of bile salts, cholesterol, steroid hormones, and fatty acids. It is also responsible for the transport of long-chain fatty acids into the mitochondria for catabolism through beta-oxidation. Signs and symptoms of a pantothenic acid deficiency have only been observed after the administration of metabolic antagonists (ie, omega methylpantothenate) or feeding a synthetic diet free of this vitamin.

Clinical Applications

Recommended Intakes for Adults

AIs for pantothenic acid are as follows:

- Men and women: 5 mg
- Pregnant women: 6 mg
- Lactating women: 7 mg

The UL for pantothenic acid has not been established because the available data were insufficient.14,58 Toxicity due to pantothenic acid is rare.58

Sources

Food sources of pantothenic acid include sunflower seeds, beef liver, mushrooms, peanuts, eggs, broccoli, and milk.

Populations at Risk for Deficiency

Pantothenic acid deficiency often occurs in conjunction with multiple other nutrient deficiencies or with conditions such as diabetes mellitus, inflammatory bowel disease, and alcoholism. Absorption of pantothenic acid is likely impaired with both inflammatory bowel disease and alcoholism.14 Individuals who ingest large amounts of ethanol may have an increased requirement for this vitamin.58

Half-Life of the Nutrient in the Body

The half-life of pantothenic acid is unknown.

Assessment of Pantothenic Acid Status

Pantothenic acid status is reflected by both whole blood assays and urinary excretion determined by a 24-hour urine collection. A blood value less than 1 mcmol pantothenic acid per liter is considered low.14 Urinary pantothenic acid excretion is a more reliable indicator of status because it is closely related to

dietary intake and is likely the easiest test to conduct and interpret. A urinary pantothenic acid concentration less than 1 mg/d (in adults) indicates a poor status or nutriture of the vitamin.5

Table 8-15 presents the clinical signs and symptoms of pantothenic acid deficiency and toxicity.5,14

TABLE 8-15 Clinical Signs and Symptoms of Pantothenic Acid Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Poor wound healing	None
Nervous system	Neuromuscular disturbances, numbness, parethesias, staggering gait, mental depression, listlessness, irritability, restlessness, malaise, sleep disturbances	None
Other	Muscle cramps, fatigue, nausea, abdominal cramps, vomiting, diarrhea, hypoglycemia, increased insulin sensitivity, compromised immune function, diminished engraftment	Rare mild gastrointestinal distress

Source: Data are from references 5 and 14.

Nutrient-Nutrient Interactions

Nutrient interactions with pantothenic acid have not been identified.

Medication-Nutrient Interactions

Tetracycline (antibiotic) may cause decreased serum pantothenic acid.7

Treatment Considerations

Although no UL has been set for pantothenic acid, diarrhea has been reported with supplementation more than 10 g/d. Supplementation less than 10 g/d seems to be nontoxic.58

Choline

Choline is found in a wide variety of foods. Nearly all dietary choline is in the form of choline phosphatides such as lecithin and sphingomyelin. Betaine, the oxidized form of choline, is also present in the diet, but it cannot be directly converted to choline.14 Dietary choline is absorbed by the small intestine, and uptake occurs via choline transporter proteins before it is delivered to the liver via the portal vein. Choline is primarily converted to the major phospholipid phosphatidylcholine (lecithin). When the body's choline supply is low, choline is recycled in the liver and redistributed from the kidneys, lungs, and the intestines to the liver and brain.96 Very small amounts of choline are excreted in the urine; excess choline is converted to betaine, a methyl donor providing methyl groups to compounds such as homocysteine (Figure 8-2).14

Functions of Choline

Choline is needed for neurotransmitter synthesis (acetylcholine), cell membrane signaling (phospholipids), and lipid transport (lipoproteins). Its by-product, betaine, is a methyl group donor and may act as a substitute for vitamin B12 in the regeneration of methionine from homocysteine.14,96,97

As such, choline is essential for cell membrane integrity, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and the transport and metabolism of lipid cholesterol.58 Endogenous de novo synthesis of choline occurs via the sequential methylation of phosphatidylethanolamine with S-adenosylmethionine as the methyl donor.14 However, this de novo synthesis of choline alone is insufficient to meet human needs. In sum, the demand for choline is influenced by methionine, folic acid, vitamin B12, and betaine, all of which are involved in metabolic methyl-exchange reactions.14

Observational research has linked choline deficiency with long-term PN support. Evidence indicates that choline deficiency may contribute to PN-induced liver dysfunction, causing hepatic steatosis and eventual hepatic failure. Humans who were given PN formulations without choline developed fatty livers and liver damage, which were corrected in part by giving choline.58,98 Reductions in plasma choline concentrations observed in long-term PN also correlate with abnormal hepatic aminotransferase levels.98 Individuals receiving PN secondary to short bowel syndrome who develop a choline deficiency are more susceptible to these hepatic consequences. Impairment of verbal and visual memory in choline-deficient PN patients may be related to insufficient acetylcholine synthesis. IV choline supplementation is needed for optimal long-term PN support to minimize fatty liver infiltration.98 The UL for choline is set to avoid the adverse effects of excessive intakes.14,58

Significant evidence demonstrates a relationship between choline deficiency and the development of diseases such as liver disease, atherosclerosis, cancer, and possibly neurologic disorders (eg, NTDs, Alzheimer's disease, and memory problems).96 The current literature suggests that the AI set for choline may be too low because some people develop organ dysfunction even at levels that meet the AI.99

Clinical Applications

Recommended Intakes for Adults

The AIs for choline are 550 mg for men and 425 mg for women. The UL for choline is 3.5 g.

Sources

Food sources of choline include milk, liver, eggs, and peanuts.

Populations at Risk for Deficiency

Whenever the demand for choline is high (during pregnancy, lactation, hypermetabolic states), sufficient choline intake becomes a critical concern. Postmenopausal women may be at risk for choline deficiency because de novo synthesis of phosphotidyl-choline diminishes with diminished estrogen.99 Patients on long-term PN support without choline are also at risk.

Half-Life of the Nutrient in the Body

The half-life of choline is unknown.

Assessment of Choline Status

Plasma choline levels reflect dietary intake, but they do not decline below 50% of normal levels, even following a short fast. Maintaining a plasma choline concentration of 10 mcmol/L is desirable in adults for optimal health throughout life.100 Table 8-16 notes signs and symptoms of choline deficiency and toxicity.

TABLE 8-16 Clinical Signs and Symptoms of Choline Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	None	Sweating
Mouth	None	Excessive salivation
Nervous system	Impairment of verbal and visual memory	None
Other	Hepatic steatosis	Hypotension, anorexia, fishy body odor, hepatotoxicity

Source: Data are from reference 14.

Nutrient-Nutrient Interactions

Choline in the form of its metabolite betaine can replace vitamin B12 to replenish methionine from homocysteine through methyl group donation.

Medication-Nutrient Interactions

Interactions between choline and medications have not been identified.

Treatment Considerations

Currently, there are no parenteral supplements for choline. The dextrose and protein components of PN formulations contain no choline. However, choline is part of lipid emulsions in the form of phosphatidylcholine. A 20% emulsion contains 13.2 mcmol choline per mL.101

Trace Elements

Minerals are required for virtually all aspects of metabolism. Trace elements are defined as minerals required by humans in amounts less than 100 mg/d. The minerals discussed in this chapter include iron, zinc, copper, manganese, selenium, iodine, chromium, fluoride, and molybdenum. Absorption, transport, excretion, function, deficiency and toxicity characteristics, and requirements are reviewed, with emphasis placed on alterations in metabolism, transport, and excretion that occur with chronic and acute illnesses. The physiological changes sometimes associated with trace element deficiencies can be subtle, which often makes diagnosis difficult. In addition, trace minerals interact with each other and compete for receptor sites, and these activities may influence or interfere with the absorption of select minerals.

Iron

Iron (Fe) is a component of every living cell and has long been recognized to be essential for the maintenance of health. The amount of iron present in an individual varies based on age, sex, weight, and nutrition status. Total body stores contain about 2 to 4 g, with differences between the sexes. On average, menstruating women have 40 mg iron per kg of body weight, whereas the average for men is 50 mg/kg.14

Normal iron balance is regulated via alterations in absorption. Iron in food occurs in a heme or nonheme form. Approximately 18.5% of iron in the typical diet is from heme iron derived from hemoglobin and myoglobin molecules found in animal flesh. Heme iron is more efficiently absorbed than nonheme iron, which is found primarily in plant foods. About 15% to 35% of ingested heme iron is absorbed.4 The amount of nonheme iron absorbed varies depending on other dietary constituents and is estimated at 2% to 20%.4 Factors that enhance nonheme iron absorption include the presence of organic compounds that increase acidity, such as vitamin C, HCl, lactic acid, and the acidic amino acids aspartic and glutamic acid. These components maintain iron in the ferrous form (Fe^{2+}), which is better absorbed compared to ferric iron (Fe^{3+}). Iron deficiency is another key factor that enhances absorption.

Absorption and Metabolism

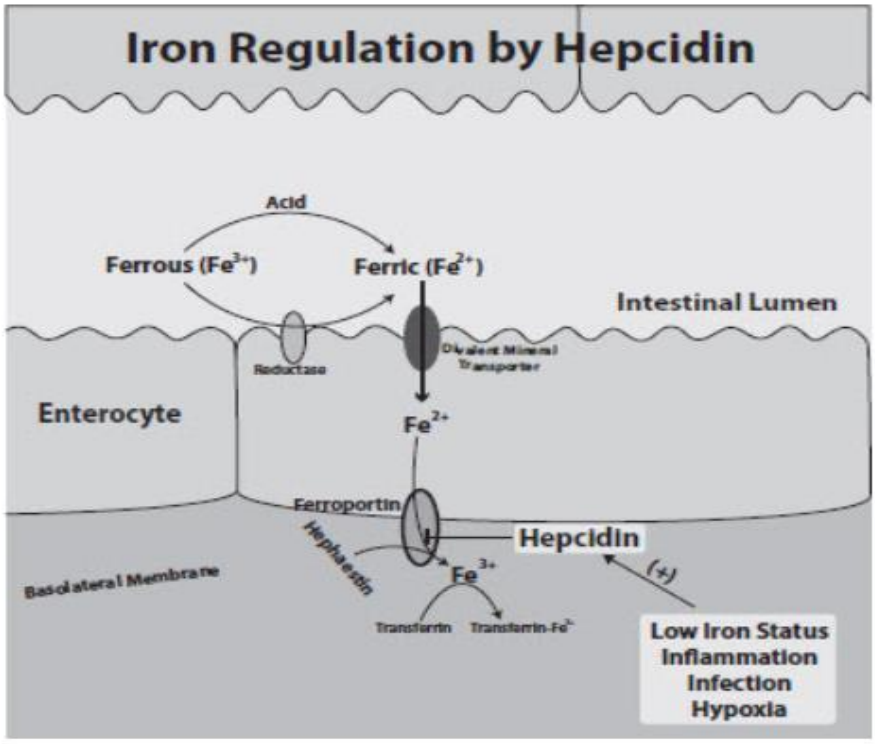
Absorption mechanisms differ for heme iron vs nonheme iron. Heme iron is absorbed intact into the enterocyte after the globin fraction is removed, and it is then hydrolyzed to ferrous iron by the intestinal cell. In the stomach, nonheme iron is released from food components, usually in the ferric form, and is then converted to ferrous iron via the action of gastric acid. This ferrous iron can traverse the intestinal cell's glycocalyx and brush border by binding to receptors. The primary sites of iron absorption are in the duodenum and jejunum.

Following absorption into the enterocyte and depending on the body's requirements, iron is transported out of the enterocyte by ferroportin into the bloodstream, where it is bound to transferrin, or it is stored in the intestinal cell, where it binds to apoferritin to form ferritin. Ferritin is a short-term form of iron storage. The iron incorporated into transferrin binds to transferrin receptors on the cell's surface. The number of transferrin receptors depends on the cell's iron requirement. An elevated need for iron increases the number of receptors on the cell's surface. Hence, the extent of iron stores in the body determines how much iron will be absorbed.14,102 When iron stores are adequate, all the iron-binding sites for transferrin are saturated and transport into the blood is inhibited. In contrast, when iron stores are low, transferrin receptors increase to allow for more iron binding, thus shifting iron directly from the intestinal cells into the blood. When the amount of iron in the body exceeds the storage capacity of ferritin, some of the ferritin is degraded to the insoluble iron-protein compound hemosiderin, which also acts as a long-term iron storage site. These mechanisms allow the body to control iron absorption. In addition, the body limits the amount of iron excreted per day. Because most iron is conserved and recycled, tight regulation of iron absorption is a necessity.

Hepcidin and Iron Regulation

Iron homeostasis is partially maintained by the peptide hormone hepcidin, which is synthesized in the liver. Hepcidin is a key homeostatic regulator of iron metabolism that senses iron status and is also involved in pathological regulation of iron in response to infection, inflammation, hypoxia, and anemia.102,103 During iron deficiency states, serum hepcidin concentrations are low, whereas concentrations are elevated in the anemia associated with the inflammation of chronic disease. Hepcidin enhances the degradation of the protein ferroportin, effectively blocking iron from exiting the cell for systemic circulation (Figure 8-3).5 Hepcidin regulates both plasma iron concentrations and tissue distribution via the inhibition of dietary iron absorption, iron recycling by macrophages, and the mobilization of iron from hepatic stores.103

FIGURE 8-3 Iron Regulation by Hepcidin



High hepcidin levels block the exit of iron from the enterocyte. Source: Data are from reference 5.

Iron and the Acute-Phase Response

The acute-phase response to injury and infection suppresses iron transport, at least partly due to the upregulation of hepcidin production.104 Clinically, serum iron levels are depressed, while serum ferritin levels are increased.105 Sequestration of iron into a storage form following injury and infection is thought to be physiologically protective to the host on several fronts. It reduces the availability of iron for iron-dependent microorganism proliferation.106 It may also reduce potential for free radical

production and oxidative damage to membranes and DNA.14,103 Iron is an essential component of hemoglobin, which is necessary for oxygen transport, and myoglobin, which is necessary for muscle iron storage. Iron is also an important component of cytochromes, which are necessary for the oxidative production of cellular energy as ATP.

Iron Deficiency

The diagnosis of iron deficiency and iron deficiency anemia is challenging. Iron deficiency is an anemia that is usually microcytic and hypochromic. Iron depletion and the development of iron deficiency occur in stages. An assessment includes several hematological indices: hemoglobin, plasma iron, iron-binding capacity, ferritin, transferrin, erythrocyte protoporphyrin, transferrin receptor, and MCV.14,107,108 These indices are examined in context with the nutrition-related and medical history. Early stages of iron depletion result in decreased transferrin saturation and are characterized by reduced plasma iron and elevated plasma transferrin. If depletion continues, serum ferritin, which reflects iron body stores, decreases to levels of less than 10 ng/mL in women and less than 20 ng/mL in men.

Ferritin is a positive acute-phase protein. Therefore, calculation of plasma ferritin concentrations must be adjusted to remove the effects of inflammation associated with chronic disease. It is recommended that ferritin and C-reactive protein are measured together to discern a more accurate ferritin concentration.14,105,107–110Another sensitive indicator of early iron deficiency is elevated levels of erythrocyte protoporphyrin. This iron measure has limitations because it is altered when hemoglobin synthesis is blunted, during situations of hemodilution, or in the presence of inflammation. Given these hematological changes, iron deficiency anemia is subsequently confirmed by a decreased MCV and a decreased hemoglobin concentration.107,108 The currently used indicators of iron status have limitations, some of which are related to the inflammation of chronic disease. However, serum hepcidin is emerging as a more useful indicator of deficient iron stores.111 This measure could significantly aid in the differential diagnosis of anemia of inflammation and iron deficiency anemia.

Clinical Applications

Recommended Intakes for Adults

The RDAs for iron are as follows:

- Men: 8 mg
- Premenopausal women: 18 mg
- Postmenopausal women: 8 mg
- Pregnant women: 27 mg
- Lactating women: 9 mg

The UL for iron is 45 mg.

Sources

Food sources of iron include meats, seafood, beans, dark leafy greens, broccoli, peas, bran, and enriched grain foods.

Populations at Risk for Deficiency

Individuals at risk for developing iron deficiency include women of childbearing age, patients hospitalized with excess blood sampling or blood loss, and individuals with decreased gastric acid production, including some older adults (gastric acid production diminishes with aging). The concomitant use of medications that reduce stomach acidity such as antacids, H2 antagonists, or PPIs can impair iron absorption. Ineffective iron absorption also occurs in malabsorptive states such as celiac disease, Crohn's disease, or pernicious anemia and during frank achlorhydria. In addition, reduced iron absorption occurs after Roux-en-Y gastric bypass or other GI surgery, after injury, or during inflammation.

Half-Life of the Nutrient in the Body

Iron metabolism is a somewhat closed system. Unlike most nutrients, iron is regulated at the level of absorption, not excretion. Therefore, once iron successfully enters the body, it is very difficult to eliminate. Men and women lose approximately 1 mg iron per day by sloughed epithelial cells from intestines and skin. Premenopausal women lose an additional 0.3 to 0.4 mg/d on average from losses accrued during menstruation. There are very few other mechanisms of iron elimination in place, making iron potentially very toxic if it is consumed in excess.5

Assessment of Iron Status

To determine whether iron malabsorption is present, serum iron levels should be measured before and 2 to 4 hours after the patient is given 325 mg of oral ferrous sulfate. If the iron level does not rise above the pretreatment value, the result indicates poor iron absorption.14

The stages of iron depletion and deficiency are as indicated as follows:

- Stage 1: depleted iron stores—serum ferritin level 20 mcg/L or less
- Stage 2: non-anemia iron deficiency—transferrin saturation 15% or less and red blood cell protoporphyrin equal to or greater than 100 mcg/dL
- Stage 3: iron deficiency anemia—microcytic/hypochromic red blood cells (MCV equal to or less than 80 fL)

Iron toxicity or overload results from exposure to iron that exceeds the body's physiological protection mechanisms. A serum ferritin value great than 150 ng/mL in women and greater than 200 ng/mL in men suggests iron overload; values above 700 ng/mL are usually associated with symptomatic hemochromatosis.106 Hemochromatosis is a genetic disorder that increases the amount of iron absorbed from the diet. This increased iron is stored in the organs, especially the liver, and may cause organ damage over time. Iron therapy in patients with preexisting hemochromatosis is contraindicated.

Patients with iron deficiency exhibit a variety of clinical signs and symptoms. Signs of iron toxicity may occur in the skin or organs. See Table 8-17 for details.

TABLE 8-17 Clinical Signs and Symptoms of Iron Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Pallor	Skin pigmentation
Nails	Koilonychia	None
Eyes	Conjunctival pallor	None
Mouth	Glossitis	None
Nervous system	Impaired behavioral and intellectual performance	None
Other	Microcytic, hypochromic anemia; tachycardia; poor capillary refilling; fatigue; sleepiness; headache; anorexia; nausea; reduced work performance, impaired ability to maintain body temperature in cold environments; decreased resistance to infections; increased lead absorption; and adverse outcomes during pregnancy	Organ damage (ie, liver cirrhosis, heart enlargement, pancreatic damage)

Source: Data are from references 14 and 105–108.

Nutrient-Nutrient Interactions

Certain dietary factors reduce nonheme iron absorption by forming insoluble iron complexes. These factors include phytic acid in grain fibers; oxalic acid in spinach, chard, tea, and chocolate; polyphenols in coffee, tea, and cocoa; and other nutrients such as calcium, zinc, and manganese.14 Nutrient-nutrient interactions such as these have clinical significance, especially because increased doses of zinc and manganese are often standard recommendations in critical illness.107,108 Iron absorption may be competitively impaired when zinc or manganese supplements are provided via the GI tract; these can contribute to compromised iron status.107,108 Chromium toxicity can contribute to iron deficiency anemia because of chromium's receptor site competition with iron.5

Medication-Nutrient Interactions

Medications that decrease iron absorption include oral bisphosphonates (osteoporosis treatment), caffeine, phosphate binders, calcium polycarbophil (bulk-forming fiber therapy [Fibercon]), cholestyramine (bile acid sequestrant), magnesium hydroxide, miglitol (diabetes medication), oral contraceptives, PPIs, sodium bicarbonate (antacid), tetracyclines (antibiotic), and levothyroxine (thyroid hormone).7

Eltrombopag (thrombocytopenia medication) and vorapaxar (antithrombotic) decrease serum iron levels. Carbamazepine (antiepileptic) may decrease iron levels if taken long term.7

Epoetin alfa (erythropoietin) uses iron. Therefore, patients using this drug may require iron supplementation.7

Iron decreases the absorption of cefdinir (antibiotic), ciprofloxacin (antibiotic), levofloxacin (antibiotic), and dolutegravir sodium (HIV antiviral). Iron increases the absorption of methyldopa (antihypertensive).7

Treatment Considerations

The recommended treatment for iron deficiency is 150 to 200 mg elemental iron per day.113 Common oral preparations include ferrous sulfate, gluconate, and fumarate. Although the fumarate form has the highest absorption rate, the preferred forms remain ferrous sulfate and gluconate. These forms are relatively inexpensive and possess good bioavailability. Because oral iron is better absorbed in an acidic environment, it is recommended that iron supplements be taken with a source of ascorbic acid (eg, orange juice). Foods that reduce iron absorption (eg, tea tannins or phytates) or medications that increase the gastric pH (eg, antacids, PPIs, or H2 blockers) should be avoided.

Adverse effects of oral iron preparations include nausea, epigastric discomfort, and constipation. Enteric-coated, delayed release ferric compounds (eg, ferric bisglycinate) are often better tolerated but may be released in the GI tract distal to the site of optimal absorption.

Standard parenteral trace element products do not include iron, in part to avoid iron's potential contribution to microbial growth and damaging oxidative reactions. Parenteral iron preparations should be considered only when a patient cannot take anything by mouth or does not respond adequately to oral supplementation.107,109 Currently, 6 parenteral iron preparations are available: low–molecular weight iron dextran, high–molecular weight iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol, and soluble ferric pyrophosphate. Iron sucrose and ferumoxytol have been associated with lower rates of adverse effects.

Soluble ferric pyrophosphate (Triferic), a more recently introduced source of IV iron, has been shown effective in hemodialysis patients with end-stage renal failure whose iron needs are increased due to erythropoietin administration. Soluble ferric pyrophosphate is unique in that it is deliverable through the dialysate. Furthermore, it bypasses physiologic mechanisms of iron sequestration, making it more readily transported to the marrow to facilitate erythropoiesis.114

According to package insert information, no test dose is required by for iron sucrose (Venofer), ferric gluconate (Ferrlecit), ferumoxytol (Feraheme), or soluble ferric pyrophosphate (Triferic). A test dose of 0.5 mL is required for iron dextran to evaluate tolerance and avoid anaphylactic reactions.

The dextran formulation, or bound Fe, is the preferable form to add to PN.106 Iron dextran may be added to dextrose-amino acid solutions, but it should not be added to total nutrient admixtures because it can destabilize these emulsions. It seems to be safe, is devoid of lipid peroxide formation, and is preferred over free iron as a form of parenteral addition.

A parenteral administration of iron may contribute to oxidative reactions that exacerbate tissue damage. In addition, excessive amounts of circulating iron may also stimulate bacterial proliferation; therefore, parenteral use of iron is not recommended during acute illness or sepsis. During the recovery phase of stress, iron can be administered parenterally or otherwise with or without erythropoietin. For similar reasons, additional enteral iron is also not recommended during the acute-phase response to an infection.106

Zinc

Zinc (Zn) is involved in numerous aspects of cellular metabolism. It is hydrolyzed from amino acids and nucleic acids via the action of gastric HCl and other enzymes in the small intestine before absorption. A reduced gastric acidity can decrease zinc availability for absorption. Zinc is found bound to cellular proteins in virtually all cells in the body. More than 95% of the body's zinc content is intracellular.

Approximately 20% to 40% of ingested zinc is absorbed from the small intestine, primarily in the duodenum and jejunum and, to a lesser extent, in the ileum. Absorption occurs by a carrier-mediated (saturable) process and a nonmediated diffusion process.14 The transcellular movement of zinc into the mucosal cell is modulated by metallothionein, a protein responsible for the regulation of zinc absorption. If zinc is not transferred to the blood or zinc intake is high, metallothionein synthesis increases.

After the transfer from the intestine, zinc binds to albumin for transport to the liver. The liver releases zinc into the circulation bound to albumin (70%) or α-macroglobulins (approximately 30%).4 Diseases or physiological conditions characterized by hypoalbuminemia can impair hepatic release of zinc. Plasma zinc levels are also subject to a variety of stimuli including dietary zinc intake, fasting, and acute infections. During fasting, plasma zinc concentrations increase. However, during infections, zinc is redistributed, resulting in hypozincemia. Within hours after an injury, plasma zinc levels decrease by 10% to 69%; the extent and type of injury determine the duration and magnitude of this reduction.56

The stress of acute infection precipitates the secretion of cytokines such as interleukin-1 and interleukin-6, which act to increase the hepatic zinc uptake. These acute-phase responses are protective to the host and need to be considered when evaluating zinc status.

Various inhibitors of zinc absorption may deplete the zinc status. These include other minerals, vitamins, proteins, phytic acid, alcohol, physiological factors, and disease processes.14 Phytic acid and calcium supplements decrease zinc absorption by as much as 50%. Certain milk proteins may have a negative effect on absorption as well. In addition, the long-term ingestion of large amounts of zinc can compete with copper and iron for absorption. Key excretion routes include the GI tract, the kidneys, and the skin.

Functions of Zinc

The overall biochemical functions of zinc can be categorized as catalytic, structural, and regulatory in nature. Zinc is important as a catalyst for enzymes in all 6 enzyme classes, which include more than 200 enzymes.14 Examples of these enzymes include alkaline phosphatase, carbonic anhydrase, alcohol dehydrogenase, and the RNA polymerases I, II, and III. The structural role of zinc includes its function in metalloenzymes and in the zinc-finger motif in proteins (ie, zinc-finger proteins), through which zinc exerts a regulatory role in gene expression.14 Zinc is necessary for other physiological processes, such as lipid peroxidation, apoptosis, neuromodulation, cellular proliferation and differentiation, wound healing, insulin synthesis and glucose control, and immune function.14,115 Zinc may also have mild antimicrobial and anti-inflammatory properties.

The diagnosis of zinc deficiency is difficult, in part because of zinc redistribution during the acute-phase response to infection, inadequate biomarkers of zinc status, and the diversity of clinical symptoms. Zinc deficiency affects both the innate and adaptive immune systems and thus affects the immune response, resulting in lymphopenia, impaired phagocytic function, and natural killer cells coupled with an altered secretion of cytokines.115 Furthermore, zinc deficiency affects vitamin A metabolism via the following 2 mechanisms:

- Decreasing retinol mobilization from the liver
- Decreasing zinc-dependent enzyme conversion of retinol to retinal, which is critical to the vision cycle

A zinc deficiency could therefore precipitate a secondary vitamin A deficiency. Zinc deficiency also decreases the work capacity of muscles, which can have detrimental effects on respiratory muscle function, worsen hepatic dysfunction, and cause glucose intolerance. The underlying mechanisms for this problem have not been identified.115,116 Zinc deficiency may occur secondary to acrodermatitis enteropathica, a heritable disorder of zinc metabolism.

Clinical Applications

Recommended Intakes for Adults

The RDAs for zinc are as follows:

- Men: 11 mg
- Women: 8 mg
- Pregnant women: 11
- Lactating women: 12 mg

The UL for zinc is 40 mg. This UL was set because observed copper deficiency is induced by excess zinc (see nutrient-nutrient interactions later in this section). Acute zinc toxicity was reported when 150 mg of zinc was administered daily. Death occurred when large IV doses (1.5 g zinc over 3 days) were given. Other toxicities have been associated with chronic oral intakes of 300 mg/d.14

Sources

Food sources of zinc include seafood, meats, greens, and whole grains.

Populations at Risk for Deficiency

Zinc deprivation has been reported in a variety of populations including older adults, people with alcoholism, postoperative patients, burn patients, patients with malabsorptive diseases or conditions (eg, intestinal bypass or resection), and patients with renal disease. Patients with liver disease may be at risk for deficiency.117 Zinc deficiency has also been known to occur in patients with sickle cell anemia, acrodermatitis enteropathica, or malignancy, and it may contribute to macular degeneration.14,51

Wound drainage or any clinical condition causing GI zinc losses can further contribute to a declining zinc status.

Half-Life of the Nutrient in the Body

The half-life of zinc is approximately 180 days.118

Assessment of Zinc Status

In healthy populations, plasma and urinary zinc have been confirmed as the most reliable biomarkers to assess zinc status.119 In a clinical setting, the measurement of serum or plasma zinc concentration presents a conundrum. During SIRS, serum zinc will fall to about half the normal level and remain depressed until resolved. This decline is secondary to zinc sequestration, which represents a host mechanism to control leukocyte cytokine production.56 Table 8-18 explains how to interpret plasma zinc levels.

TABLE 8-18 Interpretation of Plasma Zinc Levels

Status	Plasma Zinc Level, mcg/dL
Sufficient	>85
Marginal	>70 to ≤85
Low	≤70

In situations where SIRS is suspected, evaluating serum C-reactive protein, an acute-phase protein, may help differentiate between a declining serum or plasma zinc level related to an acute-phase response and a declining level associated with increased requirements.15,120 An elevated C-reactive protein level is consistent with the acute-phase reaction. Although an analysis of leukocyte zinc and lymphocyte 5'-nucleotidase activities provides more specific and sensitive indicators of zinc status, the current laboratory procedures are too tedious to perform. Table 8-19 lists clinical signs and symptoms of zinc deficiency and toxicity.14 Clinical manifestations of deficiency are noted at serum or plasma zinc levels less than 33 mcg/dL. These values should be interpreted cautiously with hypoalbuminemia because zinc transport depends on adequate albumin levels.

TABLE 8-19 Clinical Signs and Symptoms of Zinc Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Rash (periorificial, perianal, buttocks), impaired wound healing and epithelization	None
Hair	Alopecia	None
Eyes	Impaired night vision	None
Nervous system	Alterations in taste and smell	None
Other	Impaired immune function, hypogonadism, anorexia, diarrhea	Gastric distress, nausea, and dizziness; decreased immune function; decreased levels of high-density lipoprotein cholesterol

Source: Data are from reference 14.

Nutrient-Nutrient Interactions

Zinc deficiency can cause a secondary vitamin A deficiency. High levels of calcium or iron compete with zinc for binding to ligands and chelators necessary for zinc absorption. High levels of zinc (greater than 40 mg/d) may cause copper deficiency due to increased metallothionein production. Copper binds strongly to metallothionein and is effectively trapped in the enterocyte. See Practice Scenario 8-3 for further discussion of zinc-copper interactions.

Practice Scenario 8-3

Question: Besides inadequate iron intake, what other mineral deficiencies or excesses may create hematological indices consistent with iron deficiency anemia and why?

Scenario: A 28-year-old school teacher presents to the emergency department with toxic inhalation injury from smoke and heat exposure during a fire at her high school. Her medical history indicates that iron deficiency anemia was diagnosed 1 month ago and is being treated with oral iron supplementation. The patient's husband states that "she is constantly sucking zinc lozenges, 5 to 10 per day, to avoid getting sick." Because of her history of anemia, complete blood count and comprehensive metabolic panel are ordered along with serum ferritin. Laboratory test data reveal hemoglobin of 9 g/dL and serum ferritin of 10 mcg/L. Serum copper and ceruloplasmin tests are ordered to rule out copper deficiency anemia secondary to her potentially excessive zinc consumption. Both values are below normal: serum copper 0.8 mcmol/L; ceruloplasmin 28 mg/L. Within 2 hours of admission, the patient develops respiratory stridor, indicative of impending airway compromise. She is intubated and placed on mechanical ventilation.

Intervention: Within 1 week on enteral nutrition, patient's hemoglobin levels improve remarkably. Upon release, patient is instructed to continue her iron supplementation and stop consuming zinc lozenges until the anemia has resolved, at which point she should not use more than 2 lozenges per day.

Answer: Copper deficiency interferes with iron absorption and metabolism and thus effectively creates copper deficiency anemia (iron deficiency anemia in patients with iron replete status). Zinc toxicity creates a copper deficiency, initiating the same anemic mechanisms. Also, chromium toxicity can contribute to iron deficiency anemia due to its receptor site competition with iron.

Rationale: Zinc lozenges have been found effective in reducing the symptoms and duration of the common cold. These popular products are sold over the counter. One lozenge of the Cold-Eeze brand contains 13.3 mg of elemental zinc, and product labeling suggests that 1 lozenge can be taken every 2 to 4 hours until cold symptoms subside. Other zinc lozenge products contain up to 27 mg zinc. Considering the Tolerable Upper Intake Level (UL) of zinc consumption is 40 mg, patients taking zinc lozenges prophylactically may exceed the UL for zinc consumption for prolonged periods of time. High levels of zinc stimulate the increased expression of metallothionein, a protein that binds copper strongly, trapping it in the enterocyte. In this way, zinc toxicity leads to copper deficiency. Copper is necessary for the transport of iron out of cells. Iron is prepared for transport out of the enterocyte through oxidation by the copper-dependent enzyme hephaestin and out of other cells by ceruloplasmin. In copper

deficiency, iron is trapped inside the cell and iron absorption via the enterocyte ceases. The patient in this case study caused an iron deficiency status despite iron repletion by inducing a copper deficiency through excessive zinc consumption.

Medication-Nutrient Interactions

Tetracycline (antibiotic), ciprofloxacin (antibiotic), levofloxacin (antibiotic), phosphate binders, calcium polycarbophil (bulk-forming fiber therapy [Fibercon]), eltrombopag (thrombocytopenia medication), and ferrous salts decrease zinc absorption. Corticosteroids, (anti-inflammatory), hydrochlorothiazide (antihypertensive), and propofol (sedative) increase urinary zinc wasting. Oral contraceptives may decrease serum zinc levels. Zinc decreases absorption of dolutegravir sodium (HIV antiviral).7

Treatment Considerations

Zinc supplementation, although often indicated, can alter the status of other nutrients.116 Supplementation with 50 mg zinc per day increased urinary zinc excretion. Parenteral zinc doses of 30 mg/d induced an exaggerated acute-phase response.56 Zinc doses of 25 to 150 mg/d can induce a copper deficiency through the upregulation of metallothionein, which binds copper and prevents its ability to leave the cell.14 Additional zinc is recommended in patients with losses from thermal injury or hypermetabolic states such as traumatic brain injury, and in patients with excessive GI losses such as diarrhea, decubitus ulcers, and high fistula outputs.121 Doses of 80 mg zinc per day in combination with other antioxidant nutrients can reduce the development of age-related macular degeneration.120 Typical recommendations for wound healing are up to 40 mg zinc (176 mg zinc sulfate) for 10 days.14 The standard oral adult replacement dose is 220 mg twice daily (50 mg elemental zinc).122

Copper

Copper (Cu) homeostasis is maintained primarily by excretion rather than by absorption. Most of the copper in food is in the Cu^{2+} ionic state bound to organic compounds such as amino acids. Hence, digestion is necessary to free the copper before absorption. Gastric secretions, HCl, and pepsin assist in the release of bound copper in the stomach, which has some degree of copper absorption capacity. Most absorption, however, occurs throughout the small intestine, especially in the duodenum. Two mechanisms involved in copper absorption include a saturable, active transport system and a nonsaturable, passive diffusion.14 Like other transport systems, the active transport system for copper operates during low dietary copper intakes, whereas passive diffusion is activated during high dietary intakes. Typically, the intestinal absorption of copper ranges from about 12% to 75%, with higher intakes associated with low absorptive capacity. The reverse is true at low intakes. Hence, the amount of copper absorbed depends on dietary copper availability and the body's current copper status. The efficiency of copper absorption changes to regulate copper status, with changes in fecal excretion mediating the process. For example, as copper stores increase, biliary copper excretion increases. Dietary factors that negatively influence copper absorption include phytates, dietary fiber, zinc, iron, large doses of calcium gluconate, molybdenum, and large doses of vitamin C. Protein carriers, albumin, and specific copper transporters (CTR1, ATP7A) transport copper from the intestinal cell into the hepatocytes and Kupffer cells within the liver.14,123 Following hepatic uptake, copper is either incorporated into liver enzymes

(cytochrome c oxidase, superoxide dismutase) or the acute-phase protein ceruloplasmin, which is then either secreted into the blood for transport to extrahepatic tissues or excreted in bile.

Aside from transporting copper to cells via the specific ceruloplasmin cell surface receptor, ceruloplasmin acts as a scavenger of free radicals. It also catalyzes the oxidation of ferrous ion. Both serum ceruloplasmin and copper levels increase proportionally to the severity of the acute-phase reaction. Serum ceruloplasmin levels may rise during an infection to increase copper transport to stimulate cuproenzyme synthesis and inactivate inflammation-induced free radicals. These responses are considered a nonspecific host defense mechanism. Postprandially, 60% to 95% of circulating copper exists as a constituent of ceruloplasmin.14

Functions of Copper

Copper is involved in a myriad of biological processes. It primarily functions in oxidation-reduction and electron-transfer reactions involving oxygen (eg, cytochrome c oxidase).14 The 3 copper enzymes that have a role in antioxidant defense are superoxide dismutases, ceruloplasmin, and copper thioneins. Ceruloplasmin is also responsible for manganese (Mn^{2+}) oxidation and oxidation of ferrous iron (Fe^{2+}) to ferric (Fe^{3+}) iron. Select copper-dependent enzymes and their roles include lysyl oxidase, necessary for the formation of cross-linkages found in collagen and elastin; dopamine monooxygenase, necessary for the conversion of dopamine to norepinephrine; peptidylglycine α-amidating monooxygenase, necessary for the activation and deactivation of various peptide hormones; and other copper-containing enzymes, which are used for the formation and maintenance of myelin. In addition, copper is necessary for cholesterol metabolism, glucose metabolism, and the formation of melatonin pigment.14,123

Copper deficiency can lead to impaired absorption of iron. Iron must be in its ferric state to leave the enterocyte and bind to transferrin. Hephaestin, a copper-dependent protein catalyzes the oxidation of ferrous iron to ferric iron as iron leaves the enterocyte on the vehicle of ferroportin. In copper deficiency, iron cannot exit the enterocyte, causing a microcytic, hypochromic copper deficiency anemia.5

Clinical Applications

Recommended Intakes for Adults

The RDAs for copper are as follows:

- Men and women: 900 mcg
- Pregnant women: 1000 mcg
- Lactating women: 1300 mcg

The UL for copper is 10 mg.

Sources

Food sources of copper include liver, cocoa, beans, nuts, whole grains, and dried fruits.

Populations at Risk for Deficiency

Individuals at greatest risk for developing copper deficiency include patients with malabsorptive disorders such as celiac disease, patients recovering from undernutrition associated with chronic diarrhea, patients recovering from intestinal surgery, and those receiving hemodialysis where copper losses can be excessive. Individuals who have had bariatric surgery may also be at increased risk of deficiency. Copper deficiency can be a complication of celiac disease with hematological alterations and debilitating, often irreversible neurologic deficits.124

Copper toxicity is uncommon because the body regulates copper storage via biliary excretion. As a result, impaired biliary excretion or cholestasis may cause copper retention in the hepatocyte, leading to oxidative damage.14 Chronic ingestion of excessive copper amounts can result in liver cirrhosis in those with a genetic predisposition (eg, Wilson disease) with an accumulation of copper in the liver and other organs.

Half-Life of the Nutrient in the Body

The half-life of copper is 13 to 33 days.

Assessment of Copper Status

The preferred biomarker to assess copper status is serum copper concentration because it reflects changes in both depleted and repleted patients.127 Values less than approximately 0.7 mcg/dL represent the early stages of copper depletion. Serum ceruloplasmin levels are also useful data but may not reflect hepatic copper stores.127 A serum ceruloplasmin value less than 20 mg/dL is considered early copper deficiency.5 Serum ceruloplasmin levels, and subsequently serum copper levels, increase in response to SIRS; therefore, the identification of SIRS by the measurement of serum C-reactive protein concentration may assist in the interpretation of findings from laboratory tests of copper levels.127

Patients with copper deficiency or toxicity may exhibit an array of clinical signs and symptoms of the condition. See Table 8-20 for details.

TABLE 8-20 Clinical Signs and Symptoms of Copper Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	Hypopigmentation	None
Hair	Hypopigmentation	None
Eyes	Kayser-Fleischer rings (copper-colored ring around the iris)	None
Mouth	None	Metallic taste
Nervous system	Sensory ataxia, lower extremity spasticity, paresthesia in extremities, myeloneuropathy	None
Other	Hypochromic microcytic anemia, leukopenia, neutropenia, hypercholesterolemia, increased erythrocyte turnover, abnormal electrocardiographic patterns	Blood in urine, liver damage

Source: Data are from references 11, 14, 123, and 125.

Nutrient-Nutrient Interactions

Overzealous zinc supplementation can hamper copper absorption. Copper deficiency causes iron deficiency by decreasing release of iron from the enterocyte. (See Practice Scenario 8-3.) Excess molybdenum increases urinary copper wasting.

Medication-Nutrient Interactions

H2 antagonist or PPI medications decrease copper absorption. Oral contraceptives increase serum copper.

Treatment Considerations

Prophylactic copper supplementation is recommended for individuals with celiac disease when anemia or neutropenia is present.14 No clinically significant deleterious effects of copper ingestion have been observed with copper intakes equal to 0.5 mg/kg/d. Doses between 10 to 15 mg can cause a metallic taste, diarrhea, and vomiting. Because copper is excreted via the liver, it should not be administered, or should be administered with caution, in patients with hepatic dysfunction. There is a risk of iatrogenic hepatic copper overload in patients receiving PN, which has the potential to do irreparable harm to the liver.128 Autopsy reports for adult patients who received long-term PN have revealed alarming results concerning copper accumulation. Major elevations in copper (and manganese) were found, which suggests the current parenteral copper recommendations may need to be modified.129 Molybdenum, in the form of tetrathiomolybdate, is used in the treatment of copper toxicity because molybdenum induces urinary copper wasting.

Manganese

Manganese (Mn) is a ubiquitous mineral found in a wide range of oxidative states; however, in humans, it occurs only in the divalent state. Although the specific mechanism for manganese absorption is unclear, it seems to resemble the mechanism for iron absorption. Manganese is absorbed in the Mn^{2+} state throughout the small intestine.14 Approximately 1% to 5% of dietary manganese is absorbed. The absorption process is quickly saturated, such that absorption decreases when manganese intake is high, thus protecting the body against toxicity. Absorption of manganese can be influenced by iron because iron competes for common binding sites with manganese.

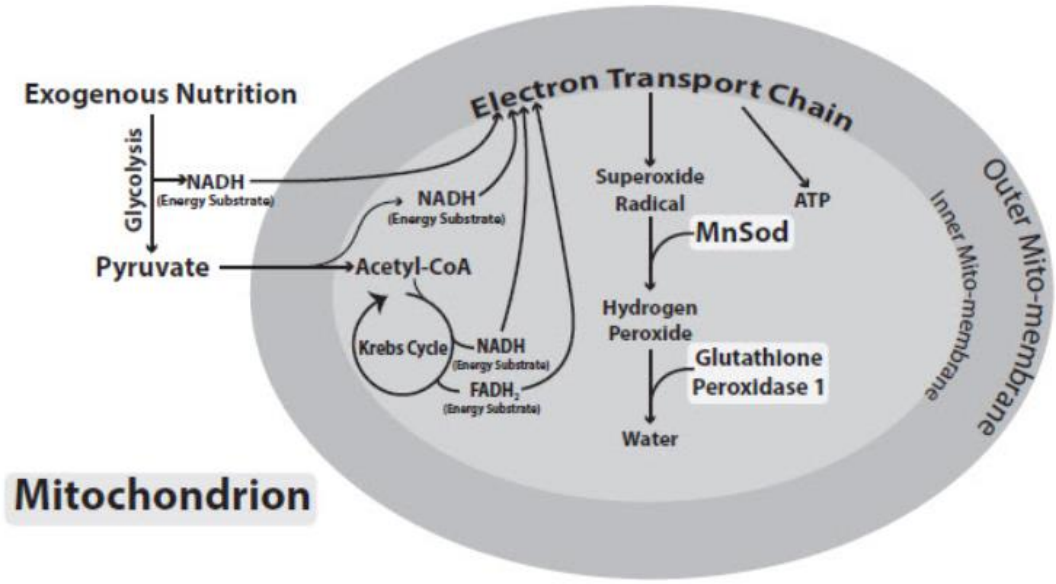
Manganese enters the liver via the portal circulation. In the liver, it is oxidized by ceruloplasmin to Mn^{3+}, possibly complexes with transferrin, and is delivered to extrahepatic tissues.130 Nearly 100% of manganese is excreted via the hepatobiliary system into the feces. Dietary excess is quickly excreted by the liver into bile to maintain manganese homeostasis and to prevent toxicity. Manganese toxicity can result in severe abnormalities of the central nervous system.

Functions of Manganese

Manganese functions as a constituent of various metalloenzymes and as an activator of certain enzymes. (See Figure 8-4.55) The manganese-containing metalloenzymes include arginase, which is

necessary for urea formation; pyruvate carboxylase, which is necessary for carbohydrate synthesis from pyruvate; and manganese superoxide dismutase, which provides the essential preparatory step in the neutralization of free radicals, produced from the electron transport chain, to water.55 Manganese also activates numerous enzymes such as glycosyltransferases, phosphoenolpyruvate carboxylase, and glutamine synthetase.

FIGURE 8-4 Management of Reactive Species by Manganese- and Selenium-Dependent Enzymes in the Mitochondria



ATP, adenosine triphosphate; CoA, coenzyme A; FADH2, flavin adenine dinucleotide; MnSod, manganese superoxide dismutase; NADH, nicotinamide adenine dinucleotide.

Source: Data are from reference 55.

Clinical Applications

Recommended Intakes for Adults

The AIs for manganese are as follows:

- Men: 2.3 mg
- Women: 1.8 mg
- Pregnant women: 2 mg
- Lactating women: 2.6 mg

The UL for manganese is 11 mg.

Sources

Food sources of manganese include nuts, oats, and other whole grains.

Populations at Risk for Deficiency or Toxicity

Manganese deficiency is rare unless the mineral is totally absent from the diet. Because manganese is almost exclusively eliminated via the hepatobiliary system, any patient with hepatobiliary disease, such as cholestatic liver disease, may be predisposed to manganese toxicity.132 Populations at risk for developing manganese toxicity include those receiving long-term PN (greater than 30 days) who develop obstruction of the biliary duct and are unable to excrete manganese.131,133 More than 50% of home PN patients have exhibited manganese toxicity coupled with clinically significant cerebral and hepatic complications.

Half-Life of the Nutrient in the Body

The half-life of manganese is approximately 40 days.134

Assessment of Manganese Status

Reliable biomarkers for determining manganese status have not been identified. Consistent changes in blood or plasma manganese have not been seen in manganese-depleted and manganese-repleted human subjects.14 Magnetic resonance imaging (MRI) can detect toxicity; however, the procedure is expensive.14 Monitoring whole blood manganese levels is best to monitor trace element status because levels correlate well with MRI abnormalities. Normal blood levels for manganese range from 4.7 to 18.3 ng/mL.

Patients with manganese deficiency or toxicity may exhibit an array of clinical signs and symptoms of the condition. See Table 8-21 for details.

TABLE 8-21 Clinical Signs and Symptoms of Manganese Deficiency or Toxicity

System	Deficiency	Toxicity
Bones/joints	Abnormal bone and cartilage formation	None
Nervous system	Ataxia	Hyperirritability, violent tendencies, hallucinations, disturbances of libido, ataxia, manganese deposition in the basal ganglia secondary to perioperative parenteral nutrition support following gastrointestinal surgery, Parkinson-like motor dysfunction (ie, tremors, difficulty walking, facial muscle spasms)
Other	Poor reproductive performance, congenital abnormalities in offspring, abnormal bone/cartilage formation, growth retardation, and defects in lipid/carbohydrate metabolism	Immune system and reproductive dysfunction, nephritis, pancreatitis, hepatic damage, testicular damage

Source: Data are from references 14 and 67.

Nutrient-Nutrient Interactions

Iron competes for similar bindings sites with Mn^{2+} and may impair manganese absorption.130

Medication-Nutrient Interactions

Tetracycline (antibiotic) may chelate with manganese, decreasing manganese absorption.7

Treatment Considerations

As previously mentioned, both manganese and copper levels were elevated in the autopsies of home PN patients.129 Reports of manganese brain deposition have occurred with IV manganese administration of 1.1 mg/d. An oral manganese intake less than 10 mg/d is considered safe.

Selenium

The nonmetal selenium (Se) exists in ionic states as Se^{2-}, Se^{4+}, and Se^{6+}. Selenium content in food depends on soil concentration, which varies widely throughout the world. Most selenium in foods is complexed with derivatives of the amino acids methionine and cysteine. Selenomethionine, the primary dietary form, is derived from plant sources, and selenocysteine is derived from animal sources of food; both are called selenoproteins. The bioavailability of ingested selenium is approximately 50% to 100%.

Functions of Selenium

Following absorption, selenium is bound to the major plasma protein selenoprotein P. The role of selenoprotein P in selenium transport remains unclear, but it is thought to act as an antioxidant, particularly in the neutralization of the strongly oxidizing reactive species peroxynitrite.5 Selenium homeostasis is maintained almost equally through urinary and fecal excretion. The best understood biochemical function of selenium is as a required cofactor in glutathione, iodine, and thyroid metabolism. Some selenium-dependent enzymes include glutathione peroxidase and the iodothyronine deiodinases.

Glutathione peroxidase catalyzes reactions to eliminate hydrogen peroxide, a by-product of nutrient substrate processing at the electron transport chain (Figure 8-4). Iodothyronine deiodinase catalyzes the deiodination of iodine, triiodothyronine, and reverse triiodothyronine, thus playing a key role in the regulation of metabolism. Selenoprotein P is associated with oxidative defense properties.14,135,136 Approximately 50% of plasma selenium is found as selenoprotein P and 30% is found as glutathione peroxidase.

Available selenium is distributed to selenoproteins in a hierarchical fashion. Therefore, in deficient states, some selenium-dependent processes will continue to function while others are impeded.137 For example, glutathione peroxidase, which converts hydrogen peroxide to water, sits low on the selenium hierarchy and is likely affected early in selenium deficiency.

Clinical Applications

Recommended Intakes for Adults

The RDAs for selenium are as follows:

- Men and women: 55 mcg
- Pregnant women: 60 mcg
- Lactating women: 70 mcg

The UL for selenium is 400 mcg.

Sources

Food sources of selenium include fish, organ meats, eggs, milk, and shellfish.

Populations at Risk for Deficiency

Cardiomyopathy and skeletal muscle weakness have been reported in patients who received long-term PN without selenium supplementation and patients with thermal injury.14,114,136 Medications in the statin class of cholesterol-lowering agents inhibit the enzyme 3-hydroxy-3-methylglutaryl CoA reductase and can induce myopathy by interfering with the synthesis of selenoproteins.138 Depressed serum selenium levels in trauma patients postinjury have resulted in decreased thyroxine deiodination, which might explain the posttrauma changes observed in thyroid metabolism.139

Half-Life of the Nutrient in the Body

The half-life of selenium is approximately 100 days.

Assessment of Selenium Status

The plasma or serum selenium concentration reflects the recent intake of selenium, whereas the erythrocyte concentration indicates long-term selenium status. The measurement of plasma glutathione peroxidase reflects the functional status of selenium; erythrocyte values less than 10.5 U/mL denote deficiency. As a general guideline, plasma or serum concentrations of selenium greater than 100 mcg/L represent adequate selenium status,42 whereas 70 mcg/L tends to be the cut-off for deficiency.5 The plasma or serum selenium concentration can be assessed using a variety of methodologies.141 Table 8-22 lists clinical signs and symptoms of selenium deficiency and toxicity.14,135

TABLE 8-22 Clinical Signs and Symptoms of Selenium Deficiency or Toxicity

System	Deficiency	Toxicity
Skin	None	Skin lesions
Hair	None	Hair loss
Nails	None	Nail loss
Bone	None	Tooth decay
Nervous system	None	Peripheral neuropathy
Other	Increased susceptibility to mercury exposure, altered thyroid hormone metabolism, congestive cardiomyopathy secondary to Keshan disease, nausea, vomiting	Fatigue, irritability

Source: Data are from references 14 and 135.

Nutrient-Nutrient Interactions

The iodine-dependent selenoprotein deiodinases are necessary for the interconversion between the various forms of iodothyronine. Selenium deficiency decreases production of these deiodinases limiting this important role of iodine.

Medication-Nutrient Interactions

Eltrombopag (thrombocytopenia medication) decreases selenium absorption.7

Treatment Considerations

Clear recommendations for the treatment of selenium deficiency are lacking. However, studies performed in populations where selenium deficiency was prevalent found that participants needed approximately 75 mcg/d.

Selenium toxicity is known as selenosis. Due to the potential for selenosis, the consumption of less than 200 mcg of selenium per day or no more than 5 mcg per kg body weight per day has been recommended.14

Iodine

Iodine (I) can refer to the element in any ionic form but generally refers to iodide (I2), the molecular form. The iodide content in foods varies depending on the soil concentration and the amount of fertilizer used in plant cultivation. The predominant source of dietary iodide comes from iodized salt; other dietary sources are either bound to amino acids or are found free as iodate (IO3), which is reduced by glutathione to iodide during digestion. Iodide is rapidly absorbed in the stomach and the upper small intestine.14,142 Absorbed iodide appears in the portal blood, where most is rapidly taken up by the thyroid (70% to 80%) for the synthesis of thyroid hormones. Lesser amounts of iodide are found in the kidneys, salivary glands, and other tissues. The kidneys are the principal route of excretion.

Functions of Iodine

Iodine functions as an integral component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3).14 The metabolically active form of T3 regulates the rate of cell metabolism, as well as the activity and growth in multiple tissues, including fetal and neuronal tissues, and those in the periphery.14

When iodine is deficient, insufficient T4 is produced, thereby eliminating its negative feedback on thyroid-stimulating hormone (TSH). This lack of negative feedback results in a constant release of TSH from the pituitary gland, which causes hyperplasia of the thyroid gland (goiter) as an adaptation designed to more effectively capture iodide from the blood.

Iodine is generally well tolerated when thyroid function is normal. If iodine deficiency is present and iodine intake is increased too rapidly, normal control mechanisms are ineffective and thyrotoxicosis can occur. Clinical signs of this so-called Jod-Basedow phenomenon are described in later in this section in the discussion of assessment of iodine status. This phenomenon is especially problematic for older adults.

Clinical Applications

Recommended Intakes for Adults

The RDAs for iodine are as follows:

- Men and women: 150 mcg
- Pregnant women: 220 mcg
- Lactating women: 290 mcg

The UL for iodine is 1100 mcg.

Sources

Food sources of iodine include saltwater fish, seafood, and iodized salt.1

Populations at Risk for Deficiency

Iodine deficiency is a risk for individuals on low-salt diets, individuals who take salt from unfortified sources (eg, sea salt), and people from areas where the iodine level in the soil is low.

Half-Life of the Nutrient in the Body

The half-life of iodine is 66 to 80 days.

Assessment of Iodine Status

Assessment of iodine status focuses on both the physical examination and biomarkers (Table 8-23).142 Urinary iodine, measured in repeated 24-hour samples or in random samples, is a useful and reliable indicator of iodine status, and values correlate well with thyroglobulin concentrations, a biomarker for thyroid function.142 Data from field studies note that a mean urinary iodine value less than 5 mcg/L suggests a risk for iodine deficiency; also, in pregnant women, a value less than 2 mcg/L implies a serious risk that their infants will be born with cretinism.14,142 Iodine deficiency may also be indicated by elevated serum levels of total T3 (ie, greater than 24 ng/dL in adults ages 20 to 49 years; greater than 181 ng/dL in adults ages 50 to 90 years).

TABLE 8-23 Clinical Signs and Symptoms of Iodine Deficiency or Toxicity

System	Deficiency	Toxicity
Biochemical markers	Elevated TSH	Elevated TSH
Other	Jod-Basedow phenomenon: nodular goiter, weight loss, tachycardia, muscle weakness, skin warmth	Depressed thyroid activity

TSH, thyroid-stimulating hormone. Source: Data are from reference 142.

Nutrient-Nutrient Interactions

The iodine-dependent thyroid hormones T3 and T4 depend on selenoprotein deiodinases to interconvert between active and inactive forms of thyroid hormone. Therefore, this major role of iodine is altered in the presence of a selenium deficiency. Furthermore, cruciferous vegetables contain

compounds that compete with iodide for entry into the thyroid gland. Such foods are termed goitrogens. In animal studies, diets exclusively high in goitrogenic foods caused goiter.5

Medication-Nutrient Interactions

Lithium (antimanic agent) inhibits thyroid hormone release from the thyroid.5

Treatment Considerations

In adults, iodine intakes between 50 and 1000 mcg/d are generally considered safe.67 Iodine requirements in adult patients receiving EN or PN range between 70 and 150 mcg/d.142 Parenteral micronutrient formulations currently available in the United States do not contain iodine. Hospitalized patients receive iodine primarily from iodine-containing antiseptic preparations absorbed via the skin.

Chromium

Chromium (Cr) is an essential trace metal required for glucose and lipid metabolism. It is ubiquitous within nature and in the food supply and can exist in several oxidation states from Cr2+ to Cr6+. The trivalent form seems to be the biologically relevant form. Most chromium in the food supply is in the trivalent form, which is the most stable. The Cr6+ compounds are strong oxidizing agents that are readily reduced to Cr3+ in an acidic environment.

Absorption and Transport

Absorption of dietary chromium within the intestines is rapid, yet poor, ranging from 0.4% to 3%, whereas the remainder is excreted in the feces.14 A dose-dependent relationship exists; as intake increases, absorption efficiency decreases. Absorption averages 2% at intakes of 10 mcg, whereas it decreases to 0.5% at doses of 40 mcg. Cr6+ is absorbed more readily than Cr3+.14,144 Some Cr3+ is soluble in the stomach and may form complexes with ligands in the acid environment. The remaining chromium is absorbed via nonmediated passive diffusion throughout the intestine, primarily in the jejunum.

Although little is known about the mechanism for Cr3+ absorption, the transport modality in the blood is more clearly understood. Trivalent chromium binds competitively with transferrin and is then transported into the blood along with iron. Consequently, chromium uses the iron transport system for movement from the blood into cells, where a rapid transfer from transferrin to the oligopeptide chromodulin occurs.14,144 Chromodulin, formerly called glucose tolerance factor, binds 4 Cr3+ molecules. Interestingly, increases in serum glucose are accompanied by increases in chromium excretion, which suggests that chromium stored or maintained in the blood is mobilized in response to increases in insulin concentrations and is ultimately excreted in the urine as chromodulin.

Functions of Chromium

Chromium potentiates the action of insulin; therefore, it has a role in glucose, protein, and lipid metabolism and, as such, is required for growth. The biologically active form of chromium is

chromodulin, which serves some role in insulin signaling, amplifying the tyrosine kinase activity of the insulin receptor. Conditions that lead to increased urinary excretion of chromium include type 2 diabetes and pregnancy. Individuals with these conditions may benefit from chromium supplementation.

Evidence for chromium deficiency in humans is sparse. Chromium deficiency can result in impaired glucose and amino acid use, increased plasma low-density lipoprotein cholesterol levels, and peripheral neuropathy. Chromium deficiency has been reported in adult patients who underwent massive bowel surgery and subsequently received PN. To date, the only cases of chromium deficiency reported in humans have been in patients receiving PN without an adequate chromium replacement.

Clinical Applications

Recommended Intakes for Adults

The AIs for chromium are as follows:

- Men younger than 50 years: 35 mcg
- Men age 50 years or older: 30 mcg
- Women younger than 50 years: 25 mcg
- Women age 50 years or older: 20 mcg
- Pregnant women: 30 mcg
- Lactating women: 45 mcg

The UL for chromium has not be set.

Sources

Food sources of chromium include whole grain products, egg yolks, beer, processed meats, mushrooms, and legumes.1

Populations at Risk for Deficiency

Patients receiving PN without chromium supplementation are at risk for chromium deficiency.

Half-Life of the Nutrient in the Body

Estimates regarding the half-life of chromium range from a few days to more than 1 month.145

Assessment of Chromium Status

Chromium status is difficult to determine because the mineral is present in the blood in extremely low concentrations, which approach detection limits.144 Normal serum, erythrocyte, and urine chromium values are less than 0.05 to 0.5 mcg/L, less than 20 to 36 mcg/L, and 0.1 to 2 mcg/L, respectively.146 Refer to Table 8-24 for signs and symptoms of chromium deficiency and toxicity.

TABLE 8-24 Clinical Signs and Symptoms of Chromium Deficiency or Toxicity

System	Deficiency	Toxicity
Nervous system	Peripheral neuropathy	None
Other	Weight loss, hyperglycemia refractory to insulin, glycosuria, elevated plasma free fatty acids	Muscle rhabdomyolysis,[a] liver dysfunction,[b] renal failure[b]

[a]Observed in patients taking 1200 mcg Cr3+ per day.

[b]Observed in patients taking 600–1200 mcg Cr3+ per day. Source: Data are from reference 144.

Nutrient-Nutrient Interactions

Iron status can be compromised with chromium supplementation because chromium and iron compete for binding sites on transferrin. Serum ferritin levels decrease at chromium intakes of 200 mcg/d.

Medication-Nutrient Interactions

Corticosteroids (anti-inflammatories) cause increased urinary chromium wasting.7

Treatment Considerations

The use of chromium supplements is probably unnecessary for the general population, and the use of certain chromium forms—such as Cr3+ picolinate (Cr[pic]3), the most common product—is potentially harmful.128 Cr[pic]3 causes liver dysfunction as well as renal and chromosomal damage at levels as low as 600 mcg/d.5,144 Intakes of 1200 mcg/d may cause muscle rhabdomyolosis.144

Glucose control improved in patients with type 2 diabetes taking 200 mcg Cr(pic)3 per day.147 Based on this evidence, individuals with altered glucose metabolism might benefit from pharmacological doses of chromium. However, safety issues related to Cr(pic)3 supplementation remain a concern.

Fluoride

Fluoride (F) is almost completely absorbed (50% to 100%) from the GI tract, and most is absorbed from the stomach.5 Absorption generally occurs via passive diffusion and is inversely related to pH. Therefore, factors that promote gastric acid secretion increase the absorption rate of fluoride. In contrast, factors that inhibit gastric acid secretion decrease absorption. Fluoride appears in the plasma promptly after absorption, primarily in the ionic form. Removal of fluoride from the circulation occurs via kidney excretion (50%) or by deposition in the calcified tissue (bone and developing teeth).

Functions of Fluoride

Although fluoride has not been proven to be an essential trace element in humans, it plays a role in bone mineralization and the hardening of tooth enamel.148 The major biochemical function of fluoride is to protect calcified tissues against pathological demineralization by forming fluorapatite crystals

rather than the usual hydroxyapatite crystals. Fluoride helps inhibit and reverse the initiation and progression of dental caries; for this reason, it is considered to be a "beneficial element for humans."148 Fluoride also stimulates new bone formation by stimulating osteoblasts, and it may reduce the risk for osteoporosis.12 Some studies suggest that it may inhibit the calcification of aorta and soft tissues.149

Unequivocal or specific signs and symptoms of fluoride deficiency in humans do not exist. When an individual is deficient in fluoride, he or she has an increased risk for developing dental caries.12

Acute fluoride toxicity may result in a variety of symptoms.149 Chronic excessive fluoride intake (eg, more than 5 mg/d) may result in enamel and skeletal fluorosis. Skeletal fluorosis has several stages. The preclinical stage (stage 1) is characterized by slight increases in bone mass and higher fluoride concentrations in the bone.148 Signs and symptoms of stage 1 include stiffness, joint pain, and some osteosclerosis of the pelvis and vertebra.148 Stages 2 and 3 involve the calcification of ligaments, osteosclerosis, exostoses, long bone osteoporosis, muscle wasting, and neurologic defects.148

The swallowing of fluoridated toothpaste represents a major source of fluoride toxicity. The American Dental Association recommends that children ages 2 through 6 years use only a pea-sized amount of fluoridated toothpaste when brushing the teeth and not swallowing.150 There are no recommendations for adults.

Clinical Applications

Recommended Intakes for Adults

The AIs for fluoride are 4 mg for men and 3 mg for women, including during pregnancy and lactation. The UL for fluoride is 10 mg.

Sources

Sources of fluoride include fluoridated water, toothpaste, and dental treatments; tea; and seaweed.

Populations at Risk for Lower Fluoride Intake

Populations with nonfluoridated water as their primary water source may have lower serum fluoride levels.

Half-Life of the Nutrient in the Body

Fluoride leaves the bloodstream for excretion or deposition in bone with a half-life of several hours. Due to its deposition in bone, its true half-life may be up to 2 decades.151

Assessment of Fluoride Status

Plasma and urinary fluoride levels may be monitored to detect toxicity. Normal ranges for ionic fluoride are 0.01 to 0.2 mcg/mL in the plasma and 0.2 to 1.1 mg per liter of urine. Serum fluoride concentrations greater than 190 ng/mL have been associated with skeletal fluorosis.5 Refer to Table 8-25 for clinical signs and symptoms of fluoride deficiency and toxicity.149

TABLE 8-25 Clinical Signs and Symptoms of Fluoride Deficiency or Toxicity

System	Deficiency	Toxicity
Eyes	None	Lacrimation
Mouth	None	Excessive salivation
Bone	Increased risk of dental caries	Enamel and skeletal fluorosis (mottled teeth)
Nervous system	None	Convulsions, sensory disturbances, paralysis, coma
Other	None	Nausea, vomiting, diarrhea, abdominal pain, pulmonary disturbances, cardiac insufficiency, arrhythmias, weakness

Source: Data are from reference 149.

Nutrient-Nutrient Interactions

Calcium and magnesium form insoluble complexes when combined with fluoride.

Medication-Nutrient Interactions

Phosphate binders and calcium polycarbophil (bulk-forming fiber therapy [Fibercon]) interfere with fluoride supplement absorption.7

Treatment Considerations

Fluoride treatment is not a part of nutrition care. For cases of toxicity, identifying and removing the source of fluoride intake (toothpaste, supplements) is key.

Molybdenum

Molybdenum (Mo) is an ultratrace element because the estimated dietary requirement is less than 100 mg/d. Other ultratrace elements are discussed later in this chapter.

Molybdenum exists as the ionic states Mo4+ and Mo6+ and is generally bound to either sulfur or oxygen. Human absorption ranges from 85% to 93%. The absorption rate is highest in the proximal small intestine. The transport of molybdenum occurs by an active carrier-mediated process when molybdenum blood concentrations are low and via passive diffusion when blood concentrations are high. Molybdenum is transported as molybdate, which is loosely attached to erythrocytes, and tends to bind albumin and α-macroglobulin.152 After absorption, molybdenum elimination occurs as molybdate via the kidneys. High dietary intakes of molybdenum increase excretion. Hence, molybdenum regulation is controlled through excretion rather than absorption.

Functions of Molybdenum

Biochemically, molybdenum functions as a cofactor for the metalloenzymes aldehyde oxidase, xanthine oxidase, and sulfite oxidase, and it catalyzes the hydroxylation of various substrates.

Molybdenum deficiency is rarely caused by inadequate dietary intake alone. However, in at least one case, a patient with short bowel syndrome who received prolonged PN developed a syndrome of hypermethioninemia, hypouricemia, hyperoxypurinemia, hypouricosuria, and low urinary sulfate excretion, along with mental disturbances that progressed to a coma.14 Contributing factors included the loss of the molybdenum-dependent enzyme, sulfite oxidase activity, and inadequate molybdenum intake.

Excessive dietary intake (10 to 15 mg molybdenum per day) or exposure to an environmental molybdenum contamination may result in a gout-like syndrome with elevated blood levels of molybdenum, uric acid, and xanthine oxidase.14

Clinical Applications

Recommended Intakes for Adults

The AIs for molybdenum are 45 mcg for men and women; AIs increase to 50 mcg for women who are pregnant or lactating. The UL for molybdenum is 2 mg.

Sources

Food sources of molybdenum include beans, grains, and nuts.

Populations at Risk for Deficiency

Molybdenum deficiency is unlikely, but it has occurred in patients receiving long-term PN.

Half-Life of the Nutrient in the Body

The half-life of molybdenum is not documented. The half-time (time to clear 50% of molybdenum from the blood) is reportedly a few hours to a few days for small animals.

Assessment of Molybdenum Status

There is no standardized laboratory method for molybdenum analysis. Values in the literature on molybdenum blood levels vary widely, with normal molybdenum serum/plasma levels reported from 0.58 ± 0.21 to 0.8 ± 0.2 mcg/L.154 For the clinical signs and symptoms of molybdenum deficiency and toxicity, refer to Table 8-26.5,14

TABLE 8-26 Clinical Signs and Symptoms of Molybdenum Deficiency or Toxicity

System	Deficiency	Toxicity
Eyes	Dislocation of ocular lens, altered vision	None
Nervous system	Altered mental status, attenuated brain growth, neurologic damage	None
Other	Tachycardia, tachypnea, elevated methionine, headache, lethargy, nausea, vomiting	Rare: hyperuricemia, gout-like symptoms

Source: Data are from references 5 and 14.

Nutrient-Nutrient Interactions

Moderate doses of molybdenum (ie, 0.54 mg/d) are associated with copper wasting in the urine.14,154 The compound responsible, tetrathiomolybdate, is therefore used to treat copper toxicity (Wilson disease).

Medication-Nutrient Interactions

No medication interactions with molybdenum are known.

Treatment Considerations

In one case study, a patient with molybdenum deficiency secondary to 18 months of PN was successfully treated with 300 mcg ammonium molybdate (equivalent to 163 mcg molybdenum).

Ultratrace Elements

Ultratrace elements are defined as those elements with estimated dietary requirements less than 100 mg/d.5 The ultratrace elements include aluminum, arsenic, boron, bromine, cadmium, chromium, fluorine, germanium, lead, lithium, molybdenum, nickel, rubidium, selenium, silicon, tin, and vanadium. Research findings regarding the essentiality of these elements vary depending on the quality of the experimental evidence and should be interpreted with caution.8,154 However, research on boron suggests a relationship between adequate boron intake and health, perhaps making it a more relevant nutrition concern than previously thought.155 There is also substantial circumstantial evidence for the essentiality of arsenic, nickel, silicon, and vanadium.1 With the exception of molybdenum, the DRI process has not assigned RDAs or AIs to the ultratrace elements.

Parenteral Vitamins

In 2000, the FDA issued new parenteral multivitamin drug dosing requirements (Table 8-27).Dosages for thiamin, vitamin B6, vitamin C, and folic acid increased, and vitamin K was added to the multivitamin formulation. The addition of vitamin K raises some concern for patients who receive long-term parenteral multivitamin products and use oral anticoagulant therapy to maintain patency of their IV access devices. In these patients, regular monitoring of the INR is needed, and warfarin doses may need to be adjusted because of the vitamin K content in the multivitamin product. Two parenteral multivitamin products are currently available for adult patients, one with vitamin K and one without vitamin K, but both meet the FDA mandate. Other sources of IV vitamin K are found in ILE, but the amount varies from 0 to 290 mcg/L.44 Weekly IV supply of 250 to 500 mcg phytonadione, a synthetic form of phylloquinone, is adequate to preserve coagulation in PN patients.44 Clinicians should carefully consider the impact of the administration of parenteral vitamins outside of these FDA dosing requirements as well as what impact additional amounts have on other micronutrients.

TABLE 8-27 Parenteral Multivitamin Dosing Requirements

Vitamin	Amount Per Day
Fat-soluble vitamins	
Vitamin A (retinol)	1 mg
Vitamin D (ergocalciferol or cholecalciferol)	5 mcg
Vitamin E (α-tocopherol)	10 mg
Vitamin K (phylloquinone)	150 mcg
Water-soluble vitamins	
B_1 (thiamin)	6 mg
B_2 (riboflavin)	3.6 mg
B_6 (pyridoxine)	6 mg
B_{12} (cyanocobalamin)	5 mcg
Niacin	40 mg
Folic acid	600 mcg
Pantothenic acid	5 mg
Biotin	60 mcg
Vitamin C (ascorbic acid)	200 mg

Source: Data are from references 65, 156, and 157.

The parenteral multivitamin supplementation of certain other nutrients, such as vitamin D, can present clinical challenges. Vitamin D preparations for PN are challenging because high-dose parenteral formulas of vitamin D are unavailable or not recommended in the United States. Currently, US patients receiving PN receive a daily multivitamin infusion that contains 200 to 400 IU (5 to 10 mcg) of vitamin D. An intramuscular form of high-dose vitamin D is available outside of the United States, but it is not currently recommended in the United States because of solubility and absorption inconsistencies, unpredictable clinical response, and significant pain upon administration. Sun exposure and UVB radiation therapy from tanning beds are alternative and effective methods to ensure vitamin D status for long-term PN patients;158 however, these methods may increase the risk of skin cancer. For issues related to other parenteral vitamins, see the relevant sections earlier in this chapter.

Parenteral Trace Elements

The American Medical Association (AMA) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have published recommendations for daily parenteral intake of the trace elements zinc, copper, manganese, and chromium (Table 8-28). Selenium supplementation of 20 to 60 mcg/d is also now recommended for patients receiving PN therapy.Other information about parenteral dosing is found in sections on the various trace elements.

TABLE 8-28 Parenteral Trace Element Supplementation for Adults

	Dose per Day		
Trace Element	**Previous Recommendations (AMA, 1979)[14]**	**Current Recommendations (ASPEN, 2012)[159]**	**GI Losses**
Zinc	2.5–4.0 mg	2.5–5 mg[a]	Varies[b]
Copper	0.5–1.5 mg	0.3–0.5 mg	500 mcg/d
Chromium	10–15 mcg	10–15 mcg	20 mcg/d[c]
Iron	None	None	Not applicable
Manganese	150–800 mcg	60–100 mcg	Unknown
Selenium	None	20–60 mcg	Unknown

AMA, American Medical Association; ASPEN, American Society for Parenteral and Enteral Nutrition; GI, gastrointestinal.

[a]In hypermetabolic patients, increase dose by 2 mg zinc per day until 6–12 mg/d is achieved.

[b]An additional 12 mg zinc per liter of small bowel losses or 17 mcg zinc per kg of stool or ileostomy losses may be needed.

[c]Check glycated hemoglobin (A1C) every 6 months.

Source: Data are from references 14, 65, 156, and 159.

In 2009, ASPEN performed a review of commercially available parenteral products and found them to contain potentially toxic levels of manganese, copper, and chromium. Since the 1980s, studies have shown manganese toxicity, excess hepatic copper, and potentially nephrotoxic chromium levels in adults on long-term PN. The FDA has yet to issue recommendations for product reformulation despite these well-documented issues. Currently, ASPEN is working with the FDA to resolve this problem to improve the safety and effectiveness of PN support formulations.160

Enteral Vitamin and Mineral Adequacy

Data on the clinical implications regarding micronutrient stability in enteral formulations are limited. Variability in enteral feeding containers, light exposure, hang times, storage temperatures, and shelf life beyond 1 year can diminish micronutrient value.161,162 Specific nutrient losses of thiamin, riboflavin, and vitamins A and E have been reported at storage temperatures between 20°C and 30°C compared with 4°C. Storing EN for more than 9 months also results in a loss of these nutrients.163 Requirements that manufacturers include stability information in product information for EN formulas would help clinicians in product selection and administration. Adherence to the EN practice standards mitigates most of the stability issues.

Best Practice: The Clinician's Role in Micronutrient Management in Times of Shortages

During shortages of parenteral vitamins or trace elements, a professional practice consultation is critical. Clinicians involved in the delivery of specialized nutrition therapy should seek the recommendations on usage from ASPEN, the American Society of Health-System Pharmacists Drug Shortages Resource Center, or the FDA's Drug Shortage Program, and Current Drug Shortages bulletins. Some strategies

recommended include reassessing the indication of micronutrient supplementation, providing oral doses, and prioritizing the most vulnerable populations. To avoid micronutrient deficiencies in patients receiving EN or PN, clinicians collectively need to continually monitor and reassess the need for micronutrient supplementation.