12 Minerals and Trace Elements

Michele A. DeBiasse-Fortin, MS, RD, LDN, CNSD

SIXTEEN mineral elements are considered essential nutrients for humans: calcium, phosphorus, potassium, sulfur, sodium, chlorine, magnesium, iron, zinc, selenium, manganese, copper, iodine, molybdenum, cobalt, and chromium. The first seven of these are classified as macronutrient minerals because they contribute more than 0.005% of body weight. They are discussed in Chapter 10 in detail. The remaining nine mineral elements are classified as micronutrients, or trace elements, because they are present in the body only in "trace" amounts (less than 0.005% of body weight).[1] The minerals discussed in this chapter include iron, zinc, copper, selenium, chromium, manganese, molybdenum, and aluminum. Each mineral's function, metabolism, characteristics of deficiency and toxicity, and requirements are reviewed, with an emphasis on the effect of critical illness. In addition, methods for assessment of status and guidelines for supplementation are presented.

Recommendations for supplementation of trace minerals fall under the guidelines of the recommended dietary allowances (RDAs) or the estimated safe and adequate daily dietary intakes (ESADDIs) both set by the Food and Nutrition Board. RDAs are "the levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy individuals."[2] When the data are sufficient to establish a range of nutritional requirements, but inadequate to set an RDA, the ESSADI may be recommended.[3] In both cases, these standards have been set for healthy persons. They are not requirements set for an individual, but for a population. In addition, they are established to prevent deficiency, not to affect potential therapy or disease prevention. Given the foundations of both the RDA and ESSADI, the clinician is often left with little guidance for prescribing vitamins and minerals to critically ill individuals, especially those receiving enteral and parenteral nutrition (PN) support. The savvy practitioner has a keen understanding of the functions, metabolism, deficiency and toxicity levels, and the safety and efficacy of the nutrients he or she "prescribes" and uses this information to guide the decisions for patients under his or her care.

Iron

Function

The most important function of iron is as a carrier of oxygen. Iron can be characterized as either functional or nonfunctional. Functional iron is present in hemoglobin, myoglobin, and in various iron-containing enzymes. Nonfunctional iron is found stored in the liver, spleen, and bone marrow.[1] Apotransferrin, a globulin produced by the liver, complexes with ferric iron to form transferrin, which is the main transport protein for iron.[4] In the cell, iron is stored on ferritin. Free iron, especially in the ferrous state, is toxic because it can significantly increase free oxygen radical production.

Metabolism

Iron stores have a strong regulatory influence on the amount of iron absorbed.[4] Absorption of iron rises slowly as stores decline and demonstrates a steep rise when stores reach depletion. Absorption also increases in iron deficiency anemia as iron requirements for erythropoiesis are unmet. Body iron content is regulated mainly through changes in the amount of iron absorbed by the intestinal mucosa.[5] The absorption of iron is regulated by the mucosal cells in the upper small intestine[6] and occurs mainly in the duodenum and proximal jejunum. Heme and nonheme iron are absorbed via different mechanisms.[5] Heme iron is highly bioavailable and readily absorbed (40% of that ingested).[1] Nonheme iron absorption is quite variable (10% to 50% of that ingested) and can be enhanced by several factors, including acid environment (from vitamin C, citric acid, lactic acid, hydrochloric acid, and acid amino acids) and the presence of animal tissue proteins.[1] Inhibitors of nonheme iron absorption include phytates, oxalic acid, polyphenols, calcium, reduced gastric acidity, and magnesium-based antacids.[1,5,7] Most investigators suggest that the absorption of iron is reduced after injury or during inflammation.[1] Apotransferrin, a globulin produced by the liver, complexes with ferric iron to form transferrin, which is the main transport protein for iron.[4] Transferrin binds to transferrin receptors on the surface of cells, and with the reduction of iron to its ferrous form, iron then readily crosses the cell membrane. In the cell, iron is stored on ferritin, or it can be used for the synthesis of iron-containing enzymes.

After injury or infection, iron transport is dramatically altered.[1] Within hours, serum iron is depressed and the storage form of iron is elevated. Transferrin concentrations and total iron-binding capacity (TIBC) demonstrate a more gradual decline. This shift in iron that occurs during the acute-phase response that follows injury or infection has been postulated to benefit the host by moving the exchangeable iron to a sequestered storage form, thereby reducing its availability to microorganisms; however, this theory has also been questioned.[8] In the absence of blood loss, iron is excreted in small amounts.[5] Basal obligatory losses of iron are primarily from

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Assessment of Status

The status of iron stores can be assessed by measuring the levels of serum ferritin, TIBC, and iron.[1,5] Reduced serum ferritin and iron concentrations, combined with elevated serum TIBC concentrations, indicate iron depletion. During the acute-phase response, serum iron, transferrin, and TIBC concentrations become depressed, and ferritin levels become elevated.[1] By obtaining each of these measurements, it is possible to differentiate iron deficiency resulting from need versus that resulting from stress or infection.

Deficiency and Toxicity

Iron deficiency is one of the most common nutritional problems in both developing and developed areas of the world.[6] Typically, iron deficiency results in microcytic, hypochromic anemia.[1] Signs and symptoms include tachycardia, fatigue, pallor, reduced work capacity, and alterations in mental and motor development. Impaired temperature regulation and decreased resistance to infection have also been reported.[9] Chronic iron overdosage can result in hemachromatosis,[4] a disorder characterized by cirrhosis, diabetes, and hyperpigmentation of the skin. Iron overload can also lead to increased oxidant activity as excess iron is released from its storage form. The result is the production of free radicals that can then lead to cell damage. Other features of iron overload include fatigue, sterility, changes in skin color, arthropathy, cardiac arrhythmias, hypothyroidism and testicular atrophy.[1] Of note, patients with infection tend to sequester exogenously administered iron in their lungs.[4]

Requirements and Supplementation

The RDAs for iron for adult men and women are 10 mg and 15 mg, respectively. In pregnancy, iron requirements are increased to 30 mg to allow for expansion of red cell mass, to provide iron to the fetus and placenta, and to replace blood loss during delivery.[5] Iron supplementation is used for the prevention and treatment of iron deficiency. It is important to recognize that iron supplementation will not correct erythropoietic abnormalities caused by conditions other than iron deficiency and is not indicated for the treatment of anemia resulting from causes other than iron deficiency; therefore, correct diagnosis of the cause of anemia is imperative.[5] The optimal method to replete iron stores is oral supplementation because it is safer, more convenient, and less expensive than other methods, and some evidence indicates that it is used more efficiently. Unfortunately, the use of large doses of iron orally may be complicated by nausea and therefore lead to noncompliance. Taking the supplement with food can reduce nausea. Ferrous sulfate (20% elemental iron), 320 mg twice daily is the standard supplemental oral dose.[1] Given the slow replenishment of iron stores, supplementation is generally required for 6 to 12 months to treat a deficiency.

Indications for the parenteral administration of iron (intramuscularly or intravenously) are limited. The parenteral use of iron dextran has resulted in fatal anaphylactic-type reactions and other significant side effects, and its use therefore should be restricted to situations in which the indication is clearly established, and the patient is not responsive to oral iron therapy.[5] Parenteral nutrition formulations have been used as a vehicle for the administration of iron dextran in both maintenance and therapeutic replacement doses.[10-12] In patients who are not iron deficient and require parenteral nutrition (PN) for a limited time, the supplementation of iron is clearly not indicated. In patients requiring long-term PN, because iron is not a component of the standard trace element preparation, the need for iron supplementation is less clear.[5] The use of maintenance doses of parenteral iron in patients receiving long-term PN is common practice among some clinicians, but it is not fully supported. Confusion involves the decision of whether or not to supplement with low, maintenance doses of iron in an effort to prevent deficiency or to wait and treat a deficiency when it occurs. Another recognized issue is the physical compatibility of iron dextran in parenteral nutrition formulations. In a study by Wan,[13] minimal changes were observed in a nonlipid-containing PN solution observed over an 18-hour period at room temperature after iron dextran was added at a concentration of 100mg/L. Unfortunately, PN solutions generally are infused over a 24-hour period, leaving further study necessary before this can be recommended. Studies of iron dextran added to 3-in-1 PN solutions (dextrose, amino acid, and lipid) demonstrate eye-apparent destabilization of the lipid fraction after 24 hours at room temperature, making this vehicle inappropriate for iron dextran administration.

Zinc

Function

Zinc is widely distributed in the body and is second to iron in total body content.[14] It is involved in many biochemical processes including cellular respiration, immune function, wound healing, membrane stability, antioxidant function, membrane transport of calcium, synthesis of proteins, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), carbohydrate metabolism, utilization of nitrogen and sulfur, cell division and growth, pituitary and adrenal gland function, enzyme detoxification of free radicals, and bone metabolism.[14-16] Zinc functions as a cofactor of more than 200 enzyme systems.[14,16] Zinc plays an important role in appetite regulation.[17] Zinc deficiency decreases appetite, while zinc supplementation increases appetite. It is postulated that this effect is the result of zinc-induced alterations in neurotransmitter metabolism. In a recent study by Mantzoros and others, serum zinc status was shown to affect serum leptin levels with the magnitude of change proportional to the changes in cellular zinc.[17] Zinc status has also been shown to have an effect on lipid metabolism, in that high levels of zinc supplementation have been shown to increase concentrations of total serum cholesterol, low-density lipoprotein cholesterol, and triacylglycerol.[18] In a recent study by Jern and colleagues, a positive correlation was observed between serum zinc concentrations and protein catabolic rate, such that supplementing the diet of hemodialysis patients with zinc led to an improvement in protein catabolic rate.[19] Parenteral zinc supplementation has also been shown to precipitate an exaggerated acute-phase response as evidenced by a significantly higher febrile response

in patients experiencing a mild acute-phase reaction.[20] Zinc can exist in several different valence states, but usually is divalent.[4]

Metabolism

Absorption of zinc occurs in the small intestine, especially the jejunum, via simple diffusion and specific ligands that transport zinc with them into the mucosal cells.[1,14] Zinc absorption from a supplement administered 3 or more hours after ingestion of a meal has been shown to range between 40% and 90%, while a supplement administered with a meal results in an absorption rate of 8% to 38%.[19] Animal proteins, amino acids, and unsaturated fatty acids enhance zinc absorption, whereas phytates; folates; high levels of copper, cadmium, and iron; and consumption of a high-calcium diet decrease zinc absorption.[14,21,22] With increasing amounts of zinc in a meal, the amount of zinc absorbed increases. Long-term zinc intake (i.e., zinc status) can also affect absorption of dietary zinc, in that prolonged low-zinc diets increase zinc absorption and retention.[21] In addition, protein-energy malnutrition results in an alteration in small intestine mucosal absorptive capacity for zinc, promoting zinc malabsorption. This can lead to a self-perpetuating cycle of poor zinc absorption, and further compromise of zinc stores.[23,24] Zinc is absorbed into the intestinal epithelial cells and transported via the plasma carrier proteins macroglobulin, albumin, transferrin, glycoprotein, and transthyretine.[1,14] Once in the blood, 80% to 90% of zinc can be found within the erythrocytes, 10% to 17% in the plasma, and 3% or less in white blood cells. From the circulation, zinc is taken up by the liver and other tissues[4] where zinc ions form complexes with metalloenzymes, membrane proteins, and metallothionein. Excretion of zinc is mainly via the bile, although a small amount is excreted in urine, sweat, desquamation of skin, and hair losses. Urinary zinc excretion is enhanced with the use of diuretics and in diabetic patients.[18,25] It is also increased after injury during the acute-phase response.[26,27]

Assessment of Status

Plasma zinc concentration, the most commonly measured index of zinc status, is insensitive and therefore unreliable.[4,16] Other methods for determining zinc status have been explored and include measurement of zinc concentrations in white blood cells, measurement of 5'NT activity, measurement of zinc kinetics, and determination of relationships between physiologic functions and zinc nutrition. Of these, measurement of zinc or 5'NT in white blood cells (or plasma) appears to be the most applicable to clinical situations.[16]

Deficiency and Toxicity

Because of zinc's role in cellular growth and differentiation, the effects of zinc deficiency are especially pronounced in tissues and organs with rapid turnover and during periods of rapid growth.[24] Organ systems known to be affected by severe zinc deficiency include the skin, GI tract, central nervous, immune, skeletal, and reproductive.[28] Symptoms of severe zinc deficiency include delayed wound healing, hair loss, diarrhea, growth failure, poor appetite, and impaired vision.[24,29] Secondary zinc deficiency can occur in many conditions including human immunodeficiency virus (HIV), chronic liver disease, diabetes, cancer, and chronic inflammatory diseases such as rheumatoid arthritis. Neurologic diseases such as Alzheimer's disease and Down syndrome are associated with redistribution or sequestration of zinc.[24] Zinc deficiency is common in the critically ill because of decreased intake, increased losses from the GI tract, and increased urinary losses resulting from hypoalbuminemia.[4] Zinc toxicity is uncommon and usually occurs in accidental intake or occupational exposure.[14,19] Symptoms include metallic taste, nausea, vomiting, stomach cramps, fever, diarrhea, and renal failure. Excess zinc can retard wound healing,[30,31] and it reduces both phagocyte and lymphocyte functions, thereby reducing immune responses.[1,32] Chronic zinc intake can lead to copper deficiency and anemia.[1,4] Recently, an association between high intakes of serum zinc and a faster disease progression and death in HIV-1-infected men has been shown.[33,34]

Requirements and Supplementation

The current RDA for zinc is 12 mg/day in adult women and 15 mg/day in adult men.[22,31] The RDA is lower for females because of their lower body weight. Current guidelines for parenteral trace elements recommend supplementing with the standard daily dose of 5 mg elemental zinc.[20] The American Medical Association (AMA) guidelines for parenteral zinc supplementation for catabolic patients include an additional 2 to 4 mg of zinc per day.[1]

Copper

Function

Copper is an essential trace element, third in total body content after iron and zinc. It is widely distributed throughout human tissues and organs, with the highest concentrations present in the liver.[35] Copper plays a role in many physiologically important pathways. It is required for proper erythropoiesis and leucopoiesis, skeletal mineralization, myelin formation, immune function, connective tissue synthesis, cardiac function, and glucose regulation.[35,36] All metaloenzymes of copper possess oxidative reductase activity. A number of the key enzymes include cytochrome-C-oxidase, required for energy production; superoxide dismutase, a key cytosolic antioxidant; and lysyloxidase, which catalyzes the oxidation of lysyl residues on collagen.[4,35] Copper is also an essential component of the oxidation enzyme ceruloplasmin, which oxidizes ferrous to ferric ion so it can be transported on ceruloplasmin to other tissues.[4]

Metabolism

Copper is thought to be absorbed readily throughout the upper GI tract, including the stomach, duodenum, and jejunum by both an active and passive transport system.[35,36] The biologic availability of copper is enhanced significantly by dietary protein and decreased by high doses of zinc and vitamin C.[1,36] Copper transport from the intestinal mucosa to the liver and other tissues is poorly understood.[35] It is thought that once in the blood, copper is carried on transcuprein and albumin to the liver and secondarily to the kidneys.[37] In the liver, most plasma copper is bound to ceruloplasmin and is secreted into the blood for transport to other tissues or is excreted.[1] The primary route of copper excretion is via the biliary tract; therefore, conditions that lead to chronic biliary obstruction impair copper excretion and may promote hepatic accumulation. The amount of copper

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Assessment of Status

Traditionally, plasma or serum copper concentration has been used to measure copper status. This is most likely the least reliable indicator of copper status, except in cases of severe copper deficiency.[38] Most changes observed in plasma copper concentrations are associated with changes in ceruloplasmin. As with plasma or serum copper concentration, ceruloplasmin concentrations are depressed during severe copper deficiency; however, in instances of marginal deficiency or in short-term studies of copper deprivation, ceruloplasmin responses are variable, rendering its measurement insensitive.[38] Currently, it appears that study of the copper-containing enzymes erythrocyte Cu/Zn superoxide dismutase and platelet cytochrome-C-oxidase may be better indicators of metabolically active copper and copper stores than plasma concentrations of copper or ceruloplasmin because the enzyme activities are sensitive to changes in copper stores and are not as sensitive to factors unrelated to copper status.[37,38]

Deficiency and Toxicity

Acquired copper deficiency is an extremely rare occurrence because of the ubiquitous nature of copper in various foods, but it has been described in patients receiving PN since 1972.[35,36] Low serum copper levels have also been described in patients recovering from major burn injury.[39,40] Copper deficiency is characterized by anemia; neutropenia; and rarely, thrombocytopenia.[36] Coronary artery disease has been observed in patients with the inherited form of copper deficiency (Menkes' syndrome), but it has not been observed in acquired copper deficiency. Toxicity from excess copper intake has not been well documented.[4] A recent study by Ford cites several studies, including his own, that have found elevated serum copper concentrations to be associated with cardiovascular disease, but it is unclear whether copper directly affects atherogenesis or is a marker of the inflammation associated with cardiovascular disease.[37]

Requirements and Supplementation

The ESSADI for copper is set between 1.5 and 3.0 mg/day.[38] This recommendation is based on copper requirements that have been estimated between 1.2 and 2.0 mg/day. The AMA recommendation for parenteral nutrition supplementation of copper is 0.5 to 1.5 mg/day.[41] Fleming[42] recommends reducing copper supplementation in PN to 0.155 mg/day when a patient develops chronic hyperbilirubinemia. Unfortunately, reduction of a single trace element in a PN solution is problematic because trace elements are usually added as a preparation that contains several trace elements. Fuhrman suggests that it may be more clinically feasible to reduce copper supplementation by providing a trace element preparation no more than three times per week when a patient develops chronic hyperbilirubinemia.[35]

Selenium

Function

Selenium functions within mammalian systems primarily in the form of selenoproteins. Selenoproteins contain selenium and selenocysteine and perform various physiologic roles.[43] Eleven selenoproteins have been identified and include both classical (cellular) glutathione peroxidase and plasma (extracellular) glutathione peroxidase. Selenium plays a vital role in the cellular antioxidant defense system. This system protects the integrity of the cell membrane and the immune system.[14] It is interesting to note that selenium can spare vitamin E and vice versa. As a result, the need for selenium declines as vitamin E intake increases.[1]

Metabolism

Selenium is well absorbed throughout the small bowel.[1,14] The organic forms of selenium are better absorbed than the inorganic forms. Absorption of selenium is probably by active transport, but the exact mechanism for absorption and transport is not well understood. Selenium is widely distributed in the body, with high concentrations in the liver, kidney, and testes. The primary route for excretion of selenium is via the kidneys,[14,43] although ingested selenium is also exhaled by the lungs.[14] Lower doses of selenium should be given when renal function is impaired.[43]

Assessment of Status

Estimates of selenium status can be accomplished through a variety of means, including the measurement of specific selenoproteins; estimation of selenium intake; measurement of selenium concentrations in blood, tissues, or excreta; and determination of glutathione peroxidase activity in various blood components.[1,43]

Deficiency and Toxicity

Human selenium deficiencies are rare. The primary group who has developed selenium deficiency includes those who received PN for prolonged periods without selenium supplementation. Low selenium levels have often been reported in the critically ill.[44] Symptoms seen in this population include muscle weakness and pain.[1,43] Selenium toxicity has occurred in areas where soil concentrations of selenium are great or, in one case in the United States, when a manufacturing error of a selenium supplement resulted in a product that contained 182 times the amount of selenium declared on the label.[45] Signs of toxicity include nausea, vomiting, hair loss, peripheral neuropathy, fatigue, and changes in nails and teeth.[1,45]

Requirements and Supplementation

The recently published dietary reference intakes[46] fixed the new RDA for selenium at 55 μg/day for both men and women. This level was chosen because it was associated with the highest level of glutathione peroxidase activity.[47,48] Given the documented increased requirements for the critically ill, it is recommended that selenium supplementation be increased for this population.[4,44]

Chromium

Function

The metabolic functions for chromium are not well defined.[49] The biologic functions of chromium include its involvement in both carbohydrate and lipid metabolism. Specifically, chromium functions in the regulation of insulin by increasing

insulin binding to cells through increased insulin receptor numbers.[50] Chromium is thought to be the active component in glucose tolerance factor (GTF).[1] Chromium exists in several forms, of which hexavalent and trivalent are the most prevalent. The hexavalent form is recognized as toxic, whereas trivalent chromium is not.[51]

Metabolism

Chromium absorption and metabolism depend on its oxidation state, whether the chromium is complexed, and the intestinal contents. Very little of trivalent chromium is absorbed (less than 2% of the dose), although when complexed with picolinate or nicotinate, absorption is improved.[51] The exact mechanism of absorption is unclear, but factors such as oxalate intake, iron and zinc deficiency, and diabetes increase absorption, whereas phytate and aging decrease absorption. Following absorption, chromium is bound to transferrin; albumin; and, possibly, globulin proteins for transport throughout the system. Chromium is excreted mainly in the urine, and excretion increases as the result of a glucose load, stress conditions, strenuous exercise, physical trauma, pregnancy, and lactation.[1] Chromium excretion is also elevated in diabetics after insulin administration.[51] Hexavalent chromium is better absorbed, and blood levels are three to five times greater than those following administration of trivalent chromium. After absorption, hexavalent chromium enters the erythrocytes and binds to the globulin fraction of hemoglobin where it then becomes reduced to the trivalent form. Because trivalent chromium cannot cross the erythrocyte membrane, it remains irreversibly trapped in the cell.[51]

Assessment of Status

Currently no good method is available to determine chromium status. Plasma levels do not reflect tissue levels because tissue levels are ten times higher than plasma. In addition, balance studies show that there can be a negative chromium balance in the presence of raised plasma levels.[51] The best way to diagnose chromium deficiency currently is to observe whether the hyperglycemia and neuropathy that develop unexpectedly in patients on PN responds to chromium infusion.[1]

Deficiency and Toxicity

Signs of chromium deficiency include impaired glucose tolerance, increased levels of circulating insulin, elevated cholesterol and triglyceride levels, and decreased high density lipoprotein levels. No credible data or reports have shown adverse effects of trivalent chromium in humans. It is extraordinarily safe and has a wide margin of safety.[45] As previously mentioned, hexavalent chromium is recognized as toxic.

Requirements and Supplementation

The ESSADI for trivalent chromium is between 50 to 200 μg/day.[51] The reference dose set by the U.S. Environmental Protection Agency (EPA) for trivalent chromium is 1.47 mg/kg. This conservative estimate is 350 times the upper limit of the ESSADI, which is a much larger safety factor than almost any other nutrient.[50] Recommendations from the American Medical Association Panel suggest the daily administration of 10 to 15 μg of chromium per day in PN solutions. More recently, Fleming recommended 10 to 20 μg/day be added to PN.[42] Anderson, in his review article on chromium, suggests both amounts may not be adequate for severely stre patients, an assertion also made by Demling and DeBias their review of micronutrients in critical illness.[4,50] It should be noted that the basal chromium content of PN tions varies widely and should be monitored.[50]

Manganese

Function

Manganese is known to be involved in enzyme activation component of several metalloenzymes including argi pyruvate carboxylase, and manganese superoxide dismu Enzymes activated by manganese frequently can also be vated by magnesium.[1] As a component of various enzy manganese assists in energy release, fatty acid and choles synthesis, release of lipid from the liver, and production of collagen fibers and ground substance for wound healing.[1,

Metabolism

Relatively little is known about manganese absorption. total percentage of dietary manganese absorbed from a m small, with most studies suggesting that humans absorb than 5%.[52] High dietary iron has been shown to decrease ganese absorption and status in rats, and there is a strong ative association between ferritin status and the absorptio retention of manganese.[52] Once absorbed, manganese is b to α2-macroglobulin and transported to the liver wh portion of it is oxidized to Mn 3+, bound to transferri transported throughout the body.[1] Virtually 100% of m nese is excreted mainly in bile, although nonbiliary rou manganese excretion are known to exist.[53]

Assessment of Status

There is still no clearly defined method for assessing ganese status.[54] Many authors suggest that the concentrati manganese in red cells is a better indicator of manganese accumulation than plasma manganese concentrations.[53,54]

Deficiency and Toxicity

Descriptions of manganese deficiency in humans are no clusive. Some of the symptoms reported include neurom lar dysfunction, dermatitis, and hypocholesterolemia.[1] toxicity from dietary manganese has been reported,[1] number of studies have demonstrated significant neuroto and elevated blood manganese concentrations when ganese is provided in conjunction with parenteral nutrit patients with chronic liver and/or cholestatic disease.[1,53-5] earliest toxic phase is characterized by general sympto weakness, anorexia, apathy, and somnolence. This is fol by signs of basal ganglia dysfunction that resemble Parki disease. The final phase is characterized by muscular ri staggered gait, and fine tremor.[53,56] There is apparently a g susceptibility to manganese toxicity in elderly patients.

Requirements and Supplementation

The ESADDI for manganese has been established a 5 mg/day.[52,54] Manganese is routinely administered to p receiving PN at 100 to 800 μg daily. It is also contained

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Manganese

Function

Manganese is known to be involved in enzyme activation as a component of several metalloenzymes including arginase, pyruvate carboxylase, and manganese superoxide dismutase. Enzymes activated by manganese frequently can also be activated by magnesium.[1] As a component of various enzymes, manganese assists in energy release, fatty acid and cholesterol synthesis, release of lipid from the liver, and production of collagen fibers and ground substance for wound healing.[1,4]

Metabolism

Relatively little is known about manganese absorption. The exact percentage of dietary manganese absorbed from a meal is unknown, with most studies suggesting that humans absorb less than 5%.[52] High dietary iron has been shown to decrease manganese absorption and status in rats, and there is a strong negative association between ferritin status and the absorption and retention of manganese.[52] Once absorbed, manganese is bound to α_2-macroglobulin and transported to the liver where a portion of it is oxidized to Mn 3+, bound to transferrin and distributed throughout the body.[1] Virtually 100% of manganese is excreted mainly in bile, although nonbiliary routes of excretion are known to exist.[53]

Assessment of Status

There is no clearly defined method for assessing manganese status. Many authors suggest that the concentration of manganese in cells is a better indicator of manganese tissue status than plasma manganese concentrations.[53,54]

Deficiency and Toxicity

Signs of manganese deficiency in humans are not consistent. Symptoms reported include neuromuscular abnormalities, and hypocholesterolemia.[1,4] No toxicity from manganese has been reported,[1] but a study has demonstrated significant neurotoxicity with excessive concentrations when manganese is given in addition with parenteral nutrition to patients with cholestatic disease.[1,53-56] The toxicity is characterized by general symptoms of lethargy and somnolence. This is followed by symptoms that resemble Parkinson's disease characterized by muscular rigidity, tremor, and there is apparently a greater susceptibility in elderly patients.

Requirements and Supplementation

The ESADDI established at 2 to 5 mg/day is administered to patients receiving PN and is also contained in PN components in trace amounts.[56] Recently, there has been some suggestion that 100 µg/day should be the maximum amount provided in PN, and careful monitoring of manganese levels should be a part of the routine practice for those patients receiving PN for more than 30 days. In addition, manganese should be eliminated from the PN of patients with cholestasis[54,56] because trace amounts of manganese are associated with the components of the PN solution in amounts that will likely prevent deficiency.[56]

Molybdenum

Function

Molybdenum may exist in several oxidation states (+3, +4, +5, and +6), and as a result, it functions as a facilitator of electron transfer reactions.[14] Molybdenum serves as a cofactor for various enzymes, including xanthene oxidase, aldehyde oxidase, and sulfite oxidase. Xanthene oxidase catalyzes the oxidative hydroxylation of purines and pyrimidines. Aldehyde oxidase oxidizes purines, pyrimidines, and pteridines and may be involved in nicotinic acid metabolism. Sulfite oxidase, an enzyme essential to humans, catalyzes the oxidation of sulfite to sulfate. This reaction is necessary for the metabolism of sulfur amino acids.[57]

Metabolism

Molybdenum is absorbed well in the GI tract by both passive and active transport.[14] Absorption of molybdenum is inhibited by copper, and increased molybdenum and sulfur levels decrease serum copper levels.[4] Molybdenum is transported in the blood bound to α_1-macroglobulin and is loosely associated with erythrocytes during transport. It is present in the highest concentrations in the liver, kidney, skin, and bones. Molybdenum is excreted primarily in the urine (90%) and to a lesser extent in the bile (10%).[14] A recent study by Turnlund and colleagues demonstrated that very little molybdenum is excreted into the GI tract (<1% per day), and urinary molybdenum appears to be the only point of regulation of molybdenum retention.[57]

Assessment of Status

No current method offers a good assessment of molybdenum status.[4] Neutron activation analysis would achieve the sensitivity needed to assess molybdenum status, but this technique is limited to facilities with nuclear reactors and is not widely available.

Deficiency and Toxicity

Molybdenum deficiency is difficult to diagnose because the low end of the reference range is not well defined.[14] Deficiency states are characterized by mouth and gum disorders, hypouricemia, hyperoxypurinemia, mental disturbance, and coma. Chronic exposure to molybdenum results in loss of appetite, listlessness, diarrhea, anemia, and slow growth.

Requirements and Supplementation

An ESADDI of 0.15 to 0.5 mg/day for adults was introduced in the ninth edition of the recommended dietary allowances. This level was revised downward to 0.075 to 0.250 mg/day in the tenth edition on the basis of newer reports of usual dietary intake.[14]

Aluminum

Function

Aluminum is the third most abundant naturally occurring element and the most common metallic element, composing approximately 8.8% of the earth's crust.[58] Aluminum has no known physiologic function in either humans or animals, and it is regarded as a potential toxin, particularly in patients with compromised renal function.[58,59] Although ubiquitous in nature, aluminum is largely insoluble, and the lungs, skin, and GI tract act as barriers to prevent it from entering the body. As a result, the estimated total body content of aluminum is less than 50 mg.[60]

Metabolism

The metabolism of aluminum in normal subjects has been studied by only a few investigators. Aluminum appears to be very poorly absorbed from the GI tract, such that only a small amount of aluminum has been found in the urine of subjects consuming a normal diet.[61] Aluminum absorption from the intestinal lumen is initially into the intestinal mucosal cells, and only a small proportion of this uptake continues into the blood.[62] Several factors have been shown to enhance aluminum absorption including citrate, pH, parathyroid hormone, 1,12-dihydroxyvitamin D_3, and uremia. Inhibitors of absorption include fluoride and calcium.[62]

The primary route of aluminum excretion is the kidneys, with only trivial amounts excreted in bile.[60,63] Several studies have shown that with the ingestion of large quantities of aluminum-containing antacids, urinary aluminum can be increased in normal subjects fivefold to fifteenfold.[60]

Assessment of Status

Blood levels of aluminum are not always predictive of tissue pathology and depend, among other factors, on length of time exposed and dose.[64] One source suggests that a plasma aluminum level greater than10 µg/dl put individuals at risk for aluminum toxicity.[58] In a special report published jointly by the American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN), it was suggested that determinations of aluminum content in fluid or tissues be performed by flameless or electrothermal atomic absorption spectroscopy or inductively coupled plasma emission spectroscopy.[63]

Deficiency and Toxicity

As stated previously, there is no known requirement for aluminum, and no deficiency has been reported. In contrast, toxicity states that result from the accumulation of aluminum have been noted in the literature since the mid-1970s. These first cases were observed in patients with end-stage renal disease who were receiving hemodialysis therapy when aluminum was found as a contaminant of the water used in the dialysis process. These patients exhibited a low-turnover vitamin D–resistant osteomalacic bone disease, and an encephalopathy with dementia that existed in conjunction with elevated tissue levels of aluminum and accumulation of aluminum at the mineralization front of bone.[63] Since that time, numerous studies have been published investigating the role of aluminum in bone disease and dementia states.[58-60,64-66] Many of these studies have focused on the role of long-term PN in inducing these

toxicity effects because metabolic bone disease was observed with significant frequency in this population. As a result, the aluminum content of parenteral nutrition solutions was evaluated, and it was discovered that casein hydrolysate amino acid solutions contained a significantly greater amount of aluminum than crystalline amino acid solutions. In one such study, the concentration difference was 100-fold.[60] These investigations lead to the use of deionized water for both hemodialysis and peritoneal dialysis for those patients with end-stage renal disease, and the substitution of crystalline amino acids for casein hydrolysate amino acids in parenteral nutrition solutions. Both interventions have resulted in decreased incidence of aluminum toxicity in the populations using these therapies.[63]

In addition to the previously listed disorders, microcytic hypochromic anemia has also been found to be a manifestation of aluminum toxicity.[64] Aluminum may also accumulate in the parathyroid gland, although its functional effects are unknown.[60]

Requirements and Supplementation

There is no known requirement for aluminum. The average adult dietary intake of aluminum is about 3 to 5 mg/day, of which only 15 µg (0.3% to 0.5%) is absorbed. There are no recommendations for aluminum supplementation.

Conclusion

Table 12-1 contains a summary of each of the minerals presented in this chapter. When recommending supplementation of minerals and trace elements, it is important for the clinician to remember how closely regulated they are. While it is impor-

TABLE 12-1

Summary of Minerals and Trace Elements

Mineral	RDA/ESADDIs†	Deficiency Symptoms	Toxicity Symptoms	Laboratory Assessment	Oral Supplement	Parenteral Supplement
Iron	10-15 mg	Microcytic hypochromic anemia, pallor, fatigue, low serum iron and ferritin, high TIBC	Hyperpigmentation of the skin, cirrhosis, diabetes, sterility, arthropathy, cardiac arrhythmias	Serum iron, TIBC, and ferritin	Ferrous sulfate, 320 mg twice/day for 6 mo to 1 yr	Not supported
Zinc	12-15 mg	Diarrhea, hair loss, delayed growth and wound healing, impaired taste	Copper deficiency, microcytic anemia, reduced immune response, renal failure	WBC zinc concentration, 5'NT activity	Zinc sulfate, 20-40 mg/day	2-4 mg/day*
Copper	1.5-3.0 mg†	Microcytic hypochromic anemia, neutropenia	Vomiting, hepatic necrosis, ataxia, cirrhosis	Erythrocyte Cu/Zn superoxide dismutase and platelet cytochrome-C-oxidase activity	Cupric sulfate, 2 mg/day	0.5-1.5 mg/day
Selenium	55 µg/day	Cardiomyopathy, muscle pain, weakness	Hair loss, peripheral neuropathy, fatigue, nail and teeth changes	Selenoprotein measurement, serum selenium, glutathione peroxidase activity	Selenium sulfate, 50-200 µg/day	≤100 µg/day
Chromium	50-200 µg/day†	Glucose intolerance, elevated cholesterol and triglyceride levels, reduced HDL cholesterol	None reported from dietary intake	Glucose tolerance test	Chromium chloride, 200 µg/day	10-20 µg/day
Manganese	2-5 mg/day†	Dermatitis, hypocholesterolemia, neuromuscular dysfunction	Weakness, anorexia, somnolence, basal ganglia dysfunction, muscular rigidity, staggered gait, fine tremor	RBC manganese concentration	2-5 mg/day	≤100 µg/day
Molybdenum	0.075-0.250 mg/day†	Mouth and gum disorders, hypouricemia, hyperoxypurinemia, mental disturbance, coma	Anorexia, listlessness, diarrhea, anemia, slow growth	No good method	None specified	None specified
Aluminum	None	None	Vitamin D–resistant osteomalacic bone disease, dementia, microcytic hypochromic anemia	Flameless or electrothermal atomic absorption spectroscopy	None recommended	None recommended

HDL, High-density lipoprotein; *RBC*, red blood cell; *TIBC*, total iron-binding capacity; *WBC*, white blood cell.
*Amount to supplement in addition to the standard maintenance trace element preparation.
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Conclusion

Table 12-1 contains a summary of each of the minerals presented in this chapter. When recommending supplementation of minerals and trace elements, it is important for the clinician to remember how closely regulated they are. While it is important to provide appropriate individual mineral supplements, the interrelationship between the various trace minerals should not be forgotten. Caution should especially be used with the parenteral administration of minerals because the natural regulatory mechanism of the GI tract is bypassed. In addition, because many of these minerals are not readily excreted, there is a potential for toxicity. Supplementation regimens that fail to consider these facts can induce nutrient imbalances that could harm rather than benefit the patient.[1]

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Zinc	12-15 mg	Diarrhea, hair loss, delayed growth and wound healing, impaired taste	Copper deficiency, microcytic anemia, reduced immune response, renal failure	WBC zinc concentration, 5'NT activity	Zinc sulfate, 20-40 mg/day	2-4 mg/day*
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Manganese	2-5 mg/day†	Dermatitis, hypocholesterolemia, neuromuscular dysfunction	Weakness, anorexia, somnolence, basal ganglia dysfunction, muscular rigidity, staggered gait, fine tremor	RBC manganese concentration	2-5 mg/day	≤100 µg/day
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Aluminum	None	None	Vitamin D–resistant osteomalacic bone disease, dementia, microcytic hypochromic anemia	Flameless or electrothermal atomic absorption spectroscopy	None recommended	None recommended

HDL, High-density lipoprotein; *RBC*, red blood cell; *TIBC*, total iron-binding capacity; *WBC*, white blood cell.
*Amount to supplement in addition to the standard maintenance trace element preparation.
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