Iron[1]

Iron (1) is an essential component of hemoglobin and myoglobin and thereby facilitates the transport, transitional tissue storage, and cellular use of oxygen. It also has important roles in cytochromes within mitochondria, mediating the transfer of electrons in the electron transport chain. Cytochrome P450 in the liver and intestine degrades endogenous compounds and environmental toxins. Iron is also part of heme-containing enzymes such as catalase, xanthine oxidase, and glutathione peroxidase and acts as an enzymatic cofactor for aconitase, NADH dehydrogenase, succinate dehydrogenase, and α-glycerophosphate dehydrogenase. Iron is absorbed as ferrous (2) iron via a divalent metal transporter 1 located on the apical membrane of the enterocyte. Heme iron can also be absorbed by heme-carrier protein 1 on the apical membrane after which iron is released by the action of lysosomal heme oxygenase. Iron that has entered the mucosal cell can be stored as ferritin or transferred through the mucosal cell and exported across the basolateral membrane by ferroportin. The exported iron is oxidized from ferrous to ferric (3) iron by ferroxidase hephestin located at the membrane. Transport of iron between tissues is mediated by transferrin, which carries up to 2 ferric (3) ions per molecule, and then delivers iron to the cell via transferrin receptors. Lactoferrin, present in human milk, plasma, neutrophils, and secretions, can reversibly bind iron. Iron is primarily stored in ferritin, a large protein that can bind as many as 4500 atoms of iron in the form of hydrated ferric oxide. In states of iron excess, iron can also be bound to hemosiderin or circulate as chelatable low molecular weight nontransferrin-bound iron. Considerable amounts of body iron are recycled by the breakdown of senescent red blood cells every day with limited normal basal (i.e., skin cells, hair) or blood losses. As a result, iron homeostasis is largely achieved through regulation of dietary iron absorption. This regulation is controlled by hepcidin, a peptide synthesized in the liver in response to increased iron stores or inflammatory signals. Hepcidin binds to ferroportin in the enterocyte and causes its degradation, which thereby blocks dietary iron uptake.

Deficiencies: Iron deficiency first leads to depletion of tissue iron stores (ferritin), during which clinical symptoms are minimal. As the magnitude of iron deficiency increases, functional consequences such as impaired immune function and lowered work capacity may become evident. Severe iron deficiency is manifested by a microcytic hypochromic anemia, which leads to listlessness/fatigue, labored breathing, palpitations on exertion, and reduced work capacity. Iron deficiency anemia has been associated with impaired behavior and cognitive development in infancy and early childhood and decreased resistance to infection, and impaired temperature regulation has been identified in iron deficiency anemia.

Diet recommendations: Dietary iron requirements are based on the maintenance of equilibrium between normal basal and menstrual iron losses and the variable iron demands over the normal life cycle that are associated with periods of growth and development during pregnancy, infancy, childhood, and adolescence (**Table 1**).

Food sources: Dietary iron is present in food in 2 forms: heme and nonheme iron. As a component of hemoglobin, heme iron is found in animal food sources such as meat, organ meats, fish, seafood, and poultry. Heme iron is efficiently absorbed from the diet, with an approximate absorption of 25%. Nonheme iron is present in plant-based foods as well as iron-enriched or iron-fortified foods (i.e., iron-fortified cereals). Multiple dietary and individual factors influence the degree of dietary nonheme iron absorption, with a mean absorption estimated to be ~17% in the United States. Individuals with adequate body iron stores will absorb less dietary nonheme iron compared with individuals with insufficient body iron stores. Other factors that influence dietary nonheme iron absorption include enhancing factors found in animal muscle tissue and foods containing vitamin C. Food factors that inhibit dietary nonheme absorption include phytates, tannins, calcium, polyphenols, and soybean proteins or possibly other soy components.

Clinical uses: Worldwide, dietary iron deficiency is considered to be the most common nutritional problem. If dietary iron intake is insufficient to meet iron requirements, body iron stores will become depleted. If negative iron balance continues for a sufficient period of time, an advanced stage of iron deficiency or iron deficiency anemia will develop. Because dietary iron requirements correspond to growth and development demands, certain groups are at higher risk of iron deficiency anemia. These groups include infants, young children, adolescents, women of childbearing age, and pregnant or lactating women. Short- and long-term clinical consequences of iron deficiency anemia can include developmental delay, cognitive impairment, adverse pregnancy outcomes, and impaired quality of life and physical performance. These adverse outcomes justify oral iron supplementation when diet alone is anticipated to be insufficient to correct low body iron stores and facilitate hemoglobin production within a reasonable time. Supplemental oral iron is available as ferrous and ferric iron, with ferrous iron salts such as ferrous fumarate, ferrous sulfate, and ferrous gluconate being absorbed better than ferric iron. In cases in which oral iron supplementation is

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Table 1. Dietary reference intakes for iron (mg/d)[1]

Age	EAR Males	EAR Females	RDA Males	RDA Females	AI	UL
0–6 mo					0.27	40
7–12 mo	6.9	6.9	11	11		40
1–3 y	3.0	3.0	7	7		40
4–8 y	4.1	4.1	10	10		40
9–13 y	5.9	5.7	8	8		40
14–18 y	7.7	7.9	11	15		45
19–30 y	6.0	8.1	8	18		45
31–50 y	6.0	8.1	8	18		45
51–70 y	6.0	5.0	8	8		45
>70 y	6.0	5.0	8	8		45
Pregnant, ≤18 y		23		27		45
Pregnant, 19–50 y		22		27		45
Lactation, ≤18 y		7		10		45
Lactation, 19–50 y		6.5		9		45

[1]AI, Adequate Intake; EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; UL, tolerable upper intake level.

unsuccessful or severe iron deficiency anemia is present, parenteral iron sources such as iron dextran, sodium ferric gluconate, and iron sucrose are available.

Toxicity: Consequences of iron toxicity can be severe and are most commonly manifested in people with genetic disorders associated with iron metabolism or as a result of treatment for hereditary conditions requiring repeated blood transfusions. Hemochromatosis type 1 (HFE hereditary hemochromatosis) is an autosomal recessive disease resulting in increased intestinal dietary iron absorption and excessive tissue iron deposition that can precipitate cirrhosis or tissue necrosis and other serious complications. Genetic disorders such as sickle cell disease and thalassemia can lead to increased body iron loads as a result of the frequent need for blood transfusions as part of the clinical care of these disorders. Iron overdose with acute iron toxicity is possible from the accidental consumption of iron supplements, which is associated with vomiting, diarrhea, dizziness, confusion, and, in severe cases, death.

Recent research: Iron biology, metabolism, and nutrition over the life cycle and in different health contexts continue to be very active areas of research. The relatively recent identification of hepcidin and development of techniques to quantify concentrations have revealed that hepcidin is the main regulator of systemic iron homeostasis. Hepcidin has an important role in the development of anemia of inflammation or anemia of chronic disease that is associated with diverse conditions such as obesity, cancer, and infection. Further research is needed to determine the complex mechanisms that link iron homeostasis and these conditions.

Significant challenges to the comprehensive understanding of iron nutrition remain. Multiple known, and possibly yet to be identified, biomarkers of iron status exist. Because each biomarker is associated with different roles (i.e., transport, storage, enzymes, cofactors) and locations (i.e., blood, cells, total body iron), the choice and interpretation of iron status biomarkers for different research questions or when comparing studies that use different biomarkers for the same research question are complicated. Novel approaches to estimating total body iron have been proposed. Dietary iron content is not directly proportional to iron absorption, and consequently estimating the biological iron exposure from a given diet remains challenging. Advances in the development and refinement of dietary iron bioavailability algorithms that predict absorption based on dietary iron factors that enhance or inhibit iron absorption have been proposed, but a solution for how to predict individual dietary iron absorption that is indicative of internal dietary iron dose in large studies remains elusive.

Given the widespread global prevalence of iron deficiency and anemia, a considerable and active body of literature exists on strategies to resolve these significant public health problems. Ongoing research, development and evaluation of best practices for dietary diversity, and food fortification and iron supplementation programs continue. Because iron malnutrition frequently exists against a backdrop of multinutrient malnutrition, as well as high infectious disease burdens, a number of research projects are under way that will lead to improvements in our understanding of the biological mechanisms related to the apparent double-edged sword of dietary iron insufficiency and metabolic iron redistribution during infection, particularly for globally important diseases such as malaria, HIV/AIDS, and tuberculosis. The complexity of iron deficiency and anemia in a global context has prompted the development of guidelines calling for an integrated and multisectorial approach to address this challenging problem.

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