Iron: Impact on Health and Wellness

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Faculty

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Faculty Disclosure

Contributing faculty, Evangeline Y. Samples, MS, RDN, LD, EdD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses and allied health professionals in all practice settings.

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Course Objective

The purpose of this course is to provide nurses with information about the importance of iron for human health so they can identify patients at risk of iron deficiency and provide nutrition counseling and education about recommended iron intake.

Learning Objectives

Upon completion of this course, you should be able to:

1. Identify the functions of iron in the human body.
2. Discuss the underlying processes involved in maintaining iron homeostasis.
3. List the daily recommended intakes of iron by age, gender, and life stage.
4. Classify levels of iron deficiency and identify groups at risk for iron deficiency.
5. Describe iron toxicity and conditions that lead to iron toxicity.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The role of iron in human health and disease has long been recognized. Iron had early medicinal uses for Egyptians, Hindus, Greeks, and Romans [1]. During the 17th century, iron was used to treat chlorosis (the "green disease"), a condition that often resulted from iron deficiency [2]. In 1932, the importance of iron was settled when it was established that it was needed for hemoglobin synthesis [3].

This course will provide nurses and other healthcare professionals with information about the impact of iron on health and wellness, including its role in a variety of metabolic processes; how iron equilibrium is regulated; sources of dietary iron and recommendations for daily iron intake; the causes, signs, and symptoms of iron deficiency and identification of populations at risk for this condition; treatment recommendations for iron deficiency; and the dangers of iron toxicity.

FUNCTIONS OF IRON IN THE BODY

Iron participates in a variety of metabolic processes, including oxygen and electron transport and DNA synthesis. Iron is also necessary for proper function of the heart [4]. Studies have reported an increased incidence of heart failure in patients with iron deficiency [5; 6; 7].

The body requires iron for the synthesis of hemoglobin and myoglobin and for the formation of heme and other enzymes involved in electron transfer. Iron is also a cofactor for enzymes in the brain [8; 9]. Approximately 60% of the body's iron is found in hemoglobin in circulating erythrocytes; 25% is contained in a mobilizable iron store; and the remaining 15% is bound to myoglobin in muscle tissue [10; 11; 12].

Iron also plays a role in dopamine signaling. Iron deficiency is associated with a disturbance in dopamine metabolism, reduced activity of the dopamine transporter, and abnormal activity of dopamine D1 and D2 receptors in the basal ganglia of the brain [12; 13]. Dopamine regulates cognition and emotion and the reward and pleasure centers in the brain, and it controls the release of hormones. Dopamine is active in the prefrontal cortex to promote cognitive control of executive functions, such as planning, working, memory, and sustained attention [14].

IRON HOMEOSTASIS

The average adult's total body iron is 3–4 grams. The body absorbs 1 mg iron daily, but the internal requirement is 20–25 mg (20 mg for hemoglobin synthesis and degradation and 5 mg for other requirements). While most of this iron passes through the plasma for reutilization, iron in excess of these requirements is deposited in body stores as ferritin or hemosiderin [4; 15; 16]. The constant interaction between iron uptake, transport, storage, and utilization is required to maintain iron homeostasis [17].

Hepcidin, a hormone secreted by the liver, functions as master regulator of systemic iron homeostasis by coordinating iron use and storage with acquisition [18]. Ferroportin is an iron transporter expressed in macrophages, duodenal enterocytes, and hepatocytes [19]. Hepcidin acts by binding to ferroportin, causing its internalization and degradation [20; 21]. Loss of ferroportin from the cell surface prevents iron entry into plasma, resulting in low transferrin saturation and less iron delivered to developing erythroblasts. Conversely, decreased expression of hepcidin leads to increased cell surface ferroportin and increased iron absorption [18; 20]. Disturbances in this process are the basis for many iron-associated disorders, including anemia and iron-overload-related disorders [22; 23].

SELECT SOURCES OF DIETARY IRON (HEME AND NONHEME)		
Food	**Amount Per Serving**	**Percent Daily Value (DV)[a]**
Breakfast cereals, fortified with 100% of DV for iron	18 mg	100%
Oysters, 3 oz	8 mg	44%
White beans, canned, 1 cup	8 mg	44%
Beef liver, 3 oz	5 mg	28%
Spinach, boiled, ½ cup	3 mg	17%
Tofu, firm, ½ cup	3 mg	17%
Sardines, oil-packed, 3 oz	2 mg	11%
Beef, bottom round, 3 oz	2 mg	11%
Green peas, boiled, ½ cup	1 mg	6%
Chicken, roasted with skin, 3 oz	1 mg	6%
Cheese, cottage, 2% milk fat, ½ cup	0 mg	0%
Milk, 1 cup	0 mg	0%
[a]According to the U.S. Food and Drug Administration.		
Source: [26]		*Table 1*

IRON ABSORPTION AND LOSS

Iron in the diet is either heme or nonheme iron [15; 16; 24]. Heme iron, derived from hemoglobin and myoglobin of animal food sources (i.e., meat, fish, poultry), is the most easily absorbable form and contributes 10% or more of total absorbed iron. Nonheme iron is derived from plants and iron-fortified foods and is less well absorbed [24].

Approximately 2 mg of iron is absorbed daily in the duodenum and jejunum. This is balanced by losses resulting from desquamation of skin, sloughing of intestinal epithelial cells, and blood loss [16]. Losses also occur due to hemorrhage, problems absorbing iron, and other medical conditions (e.g., end-stage renal disease) [25].

Diminished absorption is commonly due to insufficient intake of absorbable dietary iron [15]. Most dietary iron absorption depends on the physical state of the iron atom. At physiologic pH, iron exists in the oxidized ferric (Fe3+) state. To be absorbed, it must be in the ferrous (Fe2+) state or bound by a protein such as heme. The low pH of gastric acid in the duodenum allows the ferric reductase enzyme, duodenal cytochrome B reductase (Dcytb), to convert dietary ferric iron to the more soluble ferrous state. The protein divalent metal cation transporter 1 (DMT1) (on the membrane of enterocytes) then transports iron across the membrane and into the cell. Ferrous iron then enters the iron pool, where it can be used for heme synthesis, sequestered into ferritin, or transported into the body [24].

DIETARY IRON

As stated, dietary iron may be heme or nonheme. The richest sources of dietary heme iron include lean meats and seafood. Dietary sources of nonheme iron include nuts, beans, vegetables, and fortified grain products. Dairy products, while recommended as part of a healthy eating pattern, are poor sources of iron (***Table 1***) [26].

RECOMMENDED DAILY ALLOWANCES FOR IRON				
Age	**Male**	**Female**	**Pregnancy**	**Lactation**
Birth to 6 months	0.27 mg[a]	0.27 mg[a]	—	—
7 to 12 months	11 mg	11 mg	—	—
1 to 3 years	7 mg	7 mg	—	—
4 to 8 years	10 mg	10 mg	—	—
9 to 13 years	8 mg	8 mg	—	—
14 to 18 years	11 mg	15 mg	27 mg	10 mg
19 to 50 years	8 mg	18 mg	27 mg	9 mg
51+ years	8 mg	8 mg	—	—
[a]For this age group, adequate intake (a level assumed to ensure nutritional adequacy) is used because evidence is insufficient to develop an RDA.				
Source: [29]				*Table 2*

FACTORS THAT PROMOTE/ INHIBIT IRON ABSORPTION

Nutritional adequacy depends on both intake and bioavailability, and the bioavailability of iron is higher when it comes from animal- versus plant-based foods [26]. The bioavailability of iron is approximately 14% to 18% from mixed diets that include substantial amounts of meat, seafood, and vitamin C (which enhances the bioavailability of nonheme iron), and 5% to 12% from vegetarian diets [27; 28]. Phytates (in grains and beans) and certain polyphenols (in cereals and legumes) have the opposite effect [28]. It is believed that calcium might reduce the bioavailability of both heme and nonheme iron. However, because the effects of iron absorption enhancers and inhibitors are often reduced by the mixed western diet, they have little effect on the iron status of most individuals [29].

A variety of medical conditions can decrease iron absorption, including celiac disease, inflammatory bowel disease, gastrointestinal (GI) surgery (e.g., bariatric/weight-loss surgery), and rare genetic conditions (e.g., TMRPSS6 gene mutation, which causes overproduction of hepcidin) [25]. While both men and women can inherit hemochromatosis (an autosomal recessive disorder associated with iron overload), women are typically diagnosed after menopause, as blood loss from menstruation yields a significant loss of iron [84; 85]. Infections and inflammation (e.g., from congestive heart failure) also may inhibit nonheme iron absorption [11].

RECOMMENDED DAILY ALLOWANCES FOR IRON

The recommended daily allowance (RDA) is the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals [29]. The RDA for iron varies by age, sex, and life stage. ***Table 2*** lists current iron RDAs for nonvegetarians. The RDAs for vegetarians are 1.8 times higher than for people who eat meat [29].

Total iron (heme and nonheme) bioavailability from the U.S. diet has been estimated to be 18% [30]. However, the results of at least one investigation found this figure to be much lower [30]. Using data from the National Health and Nutrition Examination Survey (NHANES) MyPyramid database, researchers found that the average unadjusted nonheme iron absorption for all participants (6,631) was only 3.7%. It was higher in females (5.6%) than in males (2.6%) and lower in non-Hispanic whites (3.5%) than in Mexican Americans (4.5%) and non-Hispanic blacks (4.4%) [30].

IRON DEFICIENCY

Iron deficiency affects the health of more than 1 billion people worldwide, with an estimated 10 million affected in the United States [31]. The greatest burden of disease occurs in lesser-developed countries among children and women of reproductive age and is the result of both nutritional and infectious causes [31]. Iron deficiency diminishes the capability of affected individuals to perform physical labor, and it diminishes growth and learning in children [15]. Iron deficiency is the main cause of anemia, which has an estimated global prevalence of 24.8% [32].

In developing countries, iron deficiency is caused by a combination of poor iron intake and parasitic infections, specifically malaria and hookworm [31]. Malaria causes intravascular hemolysis and the loss of iron from hemoglobin in the urine. Once in the GI tract, hookworms can stay for several years and release eggs into the stool. In the small intestine, adult hookworms ingest blood, rupture erythrocytes, and degrade hemoglobin, leading to anemia. Antiparasitic drugs can reverse iron-deficiency anemia caused by hookworm [11].

SIGNS AND SYMPTOMS OF IRON DEFICIENCY

Signs of iron-deficiency anemia include koilonychia, cheilosis, pale/sallow skin, and atrophic glossitis [25]. With koilonychia, the nails (usually fingernails) are abnormally thin and may be spoon-shaped or concave [33]. Cheilosis is an abnormal condition of the lips characterized by surface scaling and fissures in the corners of the mouth [34; 35]. Pale, sallow skin may be a result of low levels of hemoglobin. With atrophic glossitis, the tongue appears to be smooth and glossy with a red or pink background [36]. Each of these conditions is reversible with correction of the iron deficiency.

Symptoms of iron-deficiency anemia include [5; 14; 25; 32; 37; 38; 39]:

- Chest pain, irregular heartbeat (sign of a more serious deficiency)
- Fatigue
- Cognitive deficits
- Headache
- Dizziness
- Dyspnea
- Pica
- Restless legs syndrome

As noted, anemia is a common, serious comorbidity in heart failure, with a prevalence ranging from 10% to 79%. While the cause of anemia in heart disease is not fully understood, it is believed to be associated with iron deficiency, comorbid chronic kidney disease, and blunted erythropoietin production [37; 40; 41]. Fatigue and cognitive deficits are also common [14; 42; 43; 44]. As stated, iron deficiency impairs the metabolism of dopamine, leading to poor inhibitory control, poor executive functioning, and altered social-emotional behavior [14].

Pica, the compulsive consumption of non-nutritive food items (e.g., dirt, paper), is often associated with iron deficiency [45]. Pica is observed most frequently in children and is the most common eating disorder in individuals with developmental disabilities. It also has been observed in women during pregnancy; among high-risk pregnancies, 5.7% reported pica [46]. Physical signs and symptoms include nausea, vomiting, tearing of the stomach, and bowel obstruction. Dental manifestations (e.g., severe tooth abrasion) also may be present [45]. Approximately one-half of patients with moderate iron-deficiency anemia develop pagophagia, a particular form of pica characterized by the ingestion of ice, freezer frost, or iced drinks [15; 47; 48; 49].

Central hypoxia may lead to symptoms of headache, tinnitus, and vertigo in some patients with iron deficiency. Other patients may experience restless legs syndrome [32; 47; 50]. Patients with iron deficiency have been found to have a 30% higher frequency of restless legs syndrome than those without, and the severity of iron deficiency correlates with the severity of restless legs syndrome symptoms [50].

Anemia is a common manifestation and complication of inflammatory bowel diseases, such as Crohn disease and ulcerative colitis. Patients with inflammatory bowel disease are commonly found to have impaired iron absorption due to tissue inflammation and iron-deficiency anemia secondary to chronic blood loss. Not all patients with iron deficiency manifest signs and symptoms; therefore, it is important to regularly monitor hemoglobin levels in patients with inflammatory bowel disease [34].

DIAGNOSING IRON DEFICIENCY

Iron deficiency develops in stages. Stage 1 is characterized by decreased iron stores in bone marrow and serum ferritin levels <20 ng/mL. Iron absorption increases, causing an increase in transferrin level. Erythropoiesis is impaired in stage 2. Although transferrin level is increased, the serum iron level decreases and the transferrin saturation decreases. Anemia develops during stage 3 (with indices that appear normal). Microcytosis and then hypochromia develop in stage 4. In stage 5, iron deficiency affects tissues, with resulting signs and symptoms [51].

Laboratory studies are used to confirm iron deficiency. The World Health Organization (WHO) defines anemia as a hemoglobin level <13.0 g/dL in adult men, <12.0 g/dL in nonpregnant adult women, and <11.0 g/dL in pregnant women. Mild anemia is defined as a hemoglobin level of 11.0–11.9 g/dL in nonpregnant women and 11.0–12.9 g/dL in men [52].

Serum ferritin is an early and highly specific indicator of iron deficiency. The WHO defines low serum ferritin as 12 mcg/L for children younger than 5 years of age and 15 mcg/L for children older than 5 years of age [52]. Limited data suggest that a serum ferritin level of <15 mcg/L is a specific, but not sensitive, cutoff; however, there is considerable variation in serum ferritin cutoff recommendations [53]. Additionally, the concentration of serum ferritin increases with age and in the presence of inflammatory disease [54].

As noted, functional iron deficiency may be observed in infectious, inflammatory, and malignant diseases [55]. Serum ferritin is a commonly used diagnostic marker of functional iron deficiency [56]. A serum ferritin level <100 mcg/L in nondialyzed patients is associated with a high likelihood of iron deficiency and potentially good response to repletion with supplemental iron. A serum ferritin level <12 mcg/L indicates absent iron stores [55]. Mean cell hemoglobin and mean cell volume are useful at diagnosing functional iron deficiency over weeks or months but are of no use in assessing acute changes in iron availability secondary to therapy with erythropoiesis-stimulating agents. The percentage of hypochromic red cells is the best-established variable for the identification of functional iron deficiency [55].

Laboratory values differ in patients with kidney disease. A serum ferritin level <200 mcg/L in patients undergoing chronic hemodialysis is associated with a high likelihood of iron deficiency and a potentially good response to iron therapy. However, due to extensive biologic variability, serum ferritin should be used with caution when guiding iron supplementation in patients with chronic kidney disease [56].

IRON DEFICIENCY IN WOMEN

More than 20% of women experience iron deficiency at some point in their reproductive lives, and blood lost during menstruation places women at risk for iron deficiency [57; 58]. Women with normal menses lose an average of 1 mg of iron per cycle. However, women with menorrhagia menstruate for an average of six days and lose an average of 5.2 mg of iron per cycle [58].

Iron-deficiency anemia has been found to influence cognitive function in women. In one cross-sectional study of healthy women 18 to 35 years of age, those with iron-deficiency anemia scored lower on measures of attention than those with no iron deficiency [42].

Iron Deficiency in Pregnancy

The estimated prevalence of iron deficiency in pregnant women is 18.6%; of these, 16.2% also have anemia [59]. One study of 1,311 pregnant women found that approximately 21% of women in their third trimester and 4% of women in their first trimester had anemia [60]. Factors that increase a pregnant woman's risk for iron-deficiency anemia include a diet lacking in iron-rich foods, GI disease, medications (e.g., antacids) that can decrease iron absorption, and a short interval between pregnancies. Non-Hispanic black and Mexican American women have higher prevalence rates of iron deficiency than white women [59]. Iron-deficiency anemia also is associated with adverse neonatal outcomes.

A hemoglobin level <11 g/dL in the first or third trimester or a hemoglobin level <10.5 g/dL in the second trimester indicates iron-deficiency anemia in the pregnant woman [61]. A maternal hemoglobin level <6 g/dL has been associated with abnormal fetal oxygenation resulting in non-reassuring heart tracings, low amniotic fluid volumes, fetal cerebral vasodilation, and fetal death [62; 63].

As noted, pregnant women require 27 mg of iron per day. However, one cross-sectional study found little difference between the food consumption of pregnant and nonpregnant women; inadequate intake of iron, folate, and calcium was observed in both groups [64]. Nonpregnant women consumed an average of 12.4 mg of iron per day, while pregnant women consumed an average of 13.6 mg of iron per day [64]. Another study performed among women in South Korea also found that iron intake from food was inadequate during pregnancy [65]. These results suggest that pregnant women are unlikely to meet their elevated iron needs from diet alone. The addition of daily prenatal vitamins is necessary, as these vitamins often include a low dose (30 mg) of elemental iron [59].

IRON DEFICIENCY IN THE PEDIATRIC POPULATION

Neonates

An essential goal of neonatal care is to deliver adequate oxygen to meet tissue demand. Increasing fetal hemoglobin by placental transfusion is an effective method of enhancing arterial oxygen content and improving oxygen delivery. Placental transfusion can increase the neonate's iron stores at birth, and it can be accomplished in one of three ways: delayed cord clamping; intact umbilical cord milking; and cut-umbilical cord milking [11; 62; 65; 66; 67].

Depending on the time of clamping and the infant's position relative to the mother's, the neonate can receive a placental transfusion of 20–30 mL/kg of blood (15–25 mg/kg of additional iron). In one study, a 30- to 120-second delay in clamping was found to improve iron status during the first two to three months of life in both full-term and preterm infants [62; 68].

With intact umbilical cord milking, the cord is grasped and blood is pushed, or stripped, toward the infant two to four times prior to clamping. Cord milking before clamping improves pulmonary blood flow immediately at birth and assists with lung expansion at the onset of respirations. If performed, it is recommended that the cord be milked five times for infants born at term and four times for preterm infants [65].

Cut-umbilical cord milking involves clamping and cutting a long segment of the cord immediately at birth and passing it and the baby to the pediatric provider who then untwists the cord and milks the entire contents into the neonate [65]. This practice is more commonly done in Asia. At least one study found that cord milking in preterm (born at less than 32 weeks' gestation) infants was associated with severe intraventricular hemorrhage [86].

One study was conducted to assess the effect of placental transfusion on serum ferritin levels in preterm neonates of 30 to 33 weeks' gestation. Interventions included delayed (by 60 seconds) cord clamping or cord milking compared with early (within 10 seconds) cord clamping [66]. The authors found that the median serum ferritin at discharge was significantly higher in the placental transfusion group than in the early cord clamping group, and that the incidence of anemia by 3 months of age was less in the placental transfusion group than in the early cord clamping group [66].

Infants and Children

Among infants, risk factors for iron deficiency include a mother with mild-to-moderate iron-deficiency anemia, low birth weight, premature birth, lead exposure, exclusive breastfeeding beyond 4 months of life, and weaning to whole milk and complementary foods without iron-fortified foods [62]. Low food security and low maternal education also may be associated with an increased risk of anemia in low-income family infants [69].

The American Academy of Pediatrics recommends universal screening for iron-deficiency anemia in all children at 1 year of age [70]. The Centers for Disease Control and Prevention also recommends screening children from low-income or newly immigrated families at 9 to 12 months of age. Preterm and low-birth-weight infants should be considered for screening before 6 months of age if they are not given iron-fortified formula [71].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in children ages 6 to 24 months.

(https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/iron-deficiency-anemia-in-young-children-screening. Last accessed November 28, 2022.)

Strength of Recommendation: I (Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)

Adolescents

Adolescents have an increased iron requirement due to increased demand resulting from expanded blood volume, myoglobin for higher muscular mass, and enzymes needed for growth [72; 73]. Iron requirements in girls begin to increase after menarche, with typical 30–40 mL blood loss and 15–30 mg iron loss during each menstruation. In boys, testosterone secretion and increased muscular mass development increase iron requirements [72; 73].

Iron deficiency is the most common cause of anemia in children and adolescents with inflammatory bowel disease, although the exact prevalence is unknown [74]. One small study sought to estimate the prevalence by following patients with inflammatory bowel disease for 15 years. The study included children 1 to 17 years of age; the average patient age at diagnosis of inflammatory bowel disease was 13.3 years. At diagnosis, 76.8% of patients had iron deficiency and 43.5% had iron-deficiency anemia. At one-year follow-up, 68.1% of the participants had iron deficiency and 21.7% had iron-deficiency anemia [74].

Persistent Effects of Early Iron Deficiency

Iron deficiency experienced early in life has persistent effects. Children who were iron-depleted at 12 months of age have lower developmental scores in self-help at 6 years of age [75]. Iron deficiency in infancy has been linked to deficits in attentional control at 10 years of age and heightened risk taking in adolescence [38]. Iron deficiency assessed in children soon after adoption predicts low intelligence quotient (IQ) scores and poor executive function performance [43].

In one study, participants with chronic iron deficiency in infancy were compared to those who were iron-sufficient before and/or after iron therapy [39]. Of those who were iron deficient in infancy, 58.1% did not complete secondary school, 76.1% were not pursuing further education, and 83.9% were single. In contrast, of those who were iron-sufficient, 24.4% did not complete secondary school, 33.8% were not pursuing further education, and 23.7% were single

[39]. Those with untreated iron deficiency early in life reported poorer emotional health, more negative emotions, feelings of dissociation and detachment, and physical symptoms of depression.

IRON DEFICIENCY IN OTHER POPULATIONS

Iron deficiency is also prevalent among athletes. Among male triathletes and runners, the incidence of a hemoglobin <14 g/L occurred at least once in 87.5% of triathletes and 31.3% of runners. A hemoglobin <12 g/L in women occurred at least once in 20% of triathletes, but 0% of runners [76]. Researchers also observed iron deficiency in 2,749 athletes from 25 different teams at one National Collegiate Athletic Association Division I institution [77]. Among girls/women, 30.9% had iron deficiency without anemia and 2.2% had iron-deficiency anemia. Among boys/men, 2.9% had iron deficiency without anemia and 1.2% had iron-deficiency anemia [77].

Iron deficiency also does not occur evenly throughout the world. In underdeveloped areas, there is an estimated fivefold increase in prevalence [11]. In some regions, the prevalence of anemia among young children is between 50% and 100% [78]. In these same regions, an estimated 40% to 50% of the entire population is anemic at all ages, with the exception of nonelderly men [79].

TREATMENT OF IRON DEFICIENCY

Treatment of iron-deficiency anemia depends on its cause and severity. Because the major cause of iron deficiency is overt or occult blood loss, the first step should be to identify and treat the source of the iron or blood loss, which should improve hemoglobin levels and symptoms of anemia. Any medications that may be blocking iron absorption should be discontinued. In cases of malnutrition or non-drug-induced impaired GI absorption of iron, supplementation may be indicated. Treatment may include oral supplementation or parenteral iron therapy [25]. Oral iron is the most common treatment, but it has a few adverse effects, including vomiting, constipation, darkening of the urine and stool, and staining of teeth and gums [59]. An oral therapy regimen of three to six months is typically required to replenish iron stores [25]. If oral therapy alone does not replenish body stores, or if the patient does not tolerate oral iron, parenteral therapy may be recommended [25; 59; 80]. Parenteral iron causes a more rapid therapeutic response and often takes only one or two sessions to replenish body iron stores; however, it can cause adverse effects, such as allergic or infusion reactions [54; 80]. Both oral and parenteral iron therapy should be continued for at least three months after the hemoglobin has normalized to replenish iron stores [87].

IRON TOXICITY

The tolerable upper intake level is the highest amount of a nutrient that healthy people can consume daily without adverse effects [29]. Beginning at 14 years of age and continuing through adulthood, the upper intake level for iron is 45 mg per day. In children from birth through 13 years of age, the limit for iron is 40 mg per day [81]. Iron may reach a toxic level in the body when ingested above the upper limit.

Iron poisoning is a significant cause of death among children, especially those younger than 6 years of age. In 2019, the American Association of Poison Control Centers (AAPCC) reported 4,858 single exposures to iron and iron salts and 8,898 single exposures to multiple vitamins with iron, with 82% in children younger than 6 years of age [82]. Iron supplements are routinely administered to postpartum women, and the presence of iron supplements in the home may place young children at risk for accidental iron toxicity via ingestion [83]. The toxic effects of iron may occur at doses of 10–20 mg/kg of elemental iron [83]. In children, diagnosis of iron toxicity is based on symptoms, imaging studies, and laboratory analysis. An abdominal x-ray will show if iron tablets were consumed [83].

Normal serum iron levels are 50–120 mcg/dL. Mild-to-moderate systemic iron toxicity is possible when serum iron levels are 350–500 mcg/dL. Hepatotoxicity is usually observed at levels higher than 500 mcg/dL, and levels higher than 800 mcg/dL are associated with severe toxicity. Patients with serum iron levels exceeding 500 mcg/dL require age-appropriate intensive care, including chelation therapy with deferoxamine, but patients with symptoms of toxicity should be treated regardless of serum iron level [82]. Excessive iron has a corrosive effect on the GI tract leading to nausea, vomiting, diarrhea, melena, and hematemesis. Iron overload can damage organs, such as the liver, heart, and pancreas, as well as endocrine glands and joints.

CONCLUSION

Iron plays an essential role in human health by participating in a variety of metabolic processes. Constant interaction between iron uptake, transport, storage, and utilization is required to maintain iron homeostasis. Disruption of homeostasis is the basis for many iron-associated disorders and can lead to decreased absorption of dietary iron. Certain medical conditions can also inhibit iron absorption and lead to iron-deficiency anemia. The greatest burden of iron-deficiency anemia occurs in women of reproductive age and children and is usually caused by a combination of poor iron intake and parasitic infections, particularly in underdeveloped parts of the world. Persistent effects of early iron deficiency include lower than average developmental scores and poor executive functioning in children, and poorer emotional health in adults. Treatment of iron deficiency, either orally or parenterally, can replenish body iron stores and prevent the consequences of iron deficiency.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Beard JL, Dawson HD. Iron. In: O'Dell BL, Sunde RA (eds). *Handbook of Nutritionally Essential Mineral Elements*. New York, NY: CRC Press; 1997.
2. Guggenheim KY. Chlorosis: the rise and disappearance of a nutritional disease. *J Nutr*. 1995;125(7):1822-1825.
3. Yip R, Dallmann PR. Iron. In: Ziegler EE, Filer LJ (eds). *Present Knowledge in Nutrition*. Washington, DC: ILSI Press; 1996: 278-292.
4. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. *J Res Med Sci*. 2014;19(2):164-174.
5. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J*. 2010;31(15):1872-1880.
6. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013;165(4):575-582.
7. Cohen-Solal A, Damy T, Terbah M, et al. High prevalence of iron deficiency in patients with acute decompensated heart failure. *Eur J Heart Fail*. 2014;16(9):984-991.
8. Hurrell RF. Bioavailability of iron. *Eur J Clin Nutr*. 1997;51(Suppl 1):S4-S8.
9. McDowell LR. *Minerals in Animal and Human Nutrition*. 2nd ed. Amsterdam: Elsevier Science; 2003.
10. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc*. 2001;101(3):294-301.
11. Miller JL. Iron-deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med*. 2013;3(7).
12. Carlage CA, Ziegler EE. Iron deficiency in pediatric patients in long-term risperidone treatment. *J Child Adolesc Psychopharmacol*. 2013;23(2):101-109.
13. Pino JMV, da Luz MHM, Antunes HKM, de Campos Giampá SQ, Martins VR, Lee KS. Iron-restricted diet affects brain ferritin levels, dopamine metabolism and cellular prion protein in a region-specific manner. *Front Mol Neurosci*. 2017;10:145.
14. Lozoff B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. *J Nutr*. 2011;141(4):7405-7465.
15. Harper JL, Conrad ME. Iron-Deficiency Anemia. Available at https://emedicine.medscape.com/article/202333-overview. Last accessed November 17, 2022.
16. Wallace DF. The regulation of iron absorption and homeostasis. *Clin Biochem Rev*. 2016;37(2):51-62.
17. Lieu PT, Heiskala M, Peterson PA, Yang Y. The roles of iron in health and disease. *Mol Aspects Med*. 2001;22(1-2):1-87.
18. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. *Annu Rev Nutr*. 2006;26:323-342.
19. Abboud S, Haile DJ. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. *J Biol Chem*. 2000;275(26):19906-19912.
20. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306(5704):2090-2093.
21. Ward D, Kaplan J. Ferroportin-mediated iron transport: expression and regulation. *Biochim Biophys Acta*. 2012;1823(9):1426-1433.
22. Ganz T. Hepcidin and iron regulation, 10 years later. *Blood*. 2011;117(17):4425-4433.
23. Gozzelino R, Arosio P. Iron homeostasis in health and disease. *Int J Mol Sci*. 2016;17(1):130.
24. Ems T, Huecker MR. Biochemistry, iron absorption. *StatPearls*. 2019.
25. National Heart, Lung, and Blood Institute. Iron-Deficiency Anemia. Available at https://www.nhlbi.nih.gov/health-topics/iron-deficiency-anemia. Last accessed November 17, 2022.
26. Barré T, Perignon M, Gazan R, et al. Integrating nutrient bioavailability and co-production links when identifying sustainable diets: how low should we reduce meat consumption? *PLoS One*. 2018;13(2):e0191767.
27. Aggett PJ. Iron. In: Erdman JW, Macdonald IA, Zeisel SH (eds). *Present Knowledge in Nutrition*. 10th ed. Washington, DC: Wiley-Blackwell; 2012: 506-520.
28. Murray-Kolbe LE, Beard J. Iron. In: Coates PM, Betz JM, Blackman MR (eds). *Encyclopedia of Dietary Supplements*. 2nd ed. London: Informa Healthcare; 2010: 432-438.
29. National Institutes of Health. Iron. Available at https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/#h3. Last accessed November 17, 2022.
30. Armah SM, Carriquiry AL, Reddy MB. Total iron bioavailability from the US diet is lower than the current estimate. *J Nutr*. 2015;145(11):2617-2621.
31. Shaw JG, Friedman JF. Iron-deficiency anemia: focus on infectious diseases in lesser developed countries. *Anemia*. 2011;2603380.
32. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of iron-deficiency anemia. *Gastroenterol Hepatol*. 2015;11(4):241-250.
33. Kumar V, Aggarwal S, Sharma A, Sharma V. Nailing the diagnosis: koilonychia. *Perm J*. 2012;16(3):65.
34. Kaitha S, Bashir M, Ali T. Iron-deficiency anemia in inflammatory bowel disease. *World J Gastrointest Pathophysiol*. 2015;6(3):62-72.
35. Merriam-Webster. Cheilosis. Available at https://www.merriam-webster.com/medical/cheilosis. Last accessed November 17, 2022.
36. Reamy BV, Derby R, Bunt CW. Common tongue conditions in primary care. *Am Fam Physician*. 2010;81(5):627-634.

37. Beverborg GN, van Veldhuisen DJ, van der Meer P. Anemia in heart failure: still relevant? *JACC: Heart Fail.* 2018;6(3):201-208.
38. East P, Delker E, Lozoff B, Delva J, Castillo M, Gahagan S. Associations among infant iron deficiency, childhood emotion and attention regulation, and adolescent problem behaviors. *Child Dev.* 2018;89(2):593-608.
39. Lozoff B, Smith JB, Kaciroti N, Clark KM, Guevara S, Jimenez E. Functional significance of early-life iron deficiency: outcomes at 25 years. *J Pediatr.* 2013;163(5):1260-1266.
40. Terrovitis JV, Anastasiou-Nana M, Kaldara E, Drakos SG, Nanas SN, Nanas JN. Anemia in heart failure: pathophysiologic insights and treatment options. *Future Cardiol.* 2009;5(1):71-81.
41. Qaseem A, Humphrey LL, Fitterman N, Starkey M, for the Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013;159(11):770-779.
42. Cook RL, O'Dwyer NJ, Parker HM, et al. Iron-deficiency anemia, not iron deficiency, is associated with reduced attention in healthy young women. *Nutrients.* 2017;9(11):E1216.
43. Doom JR, Gunnar MR, Georgieff MK, et al. Beyond stimulus deprivation: Iron deficiency and cognitive defects in postinstitutionalized children. *Child Dev.* 2014;85(5):1805-1812.
44. Fugelstad AJ, Georgieff MK, Iverson SL, et al. Iron-deficiency after arrival is associated with general cognitive and behavioral impairment in post-institutionalized children adopted from Eastern Europe. *Matern Child Health J.* 2013;17(6):1080-1087.
45. Burke M, Soares NS. Pica. Available at https://emedicine.medscape.com/article/914765-overview. Last accessed November 17, 2022.
46. Santos AM, Benute G, Yamamoto Nomura RM, Santos NO. Pica and eating attitudes: a study of high-risk pregnancies. *Mat Child Health J.* 2015;20(3).
47. Leung AKC, Hon KL. Pica: a common condition that is commonly missed: an update review. *Curr Pediatr Rev.* 2019;15(3):164-169.
48. Borgna-Pignatti C, Zanella S. Pica as a manifestation of iron deficiency. *Expert Rev Hematol.* 2016;9(11):1075-1080.
49. Bhatia MS, Kaur N. Pagophagia: a common but rarely reported form of pica. *J Clin Diagn Res.* 2014;8(1):195-196.
50. Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. *Cochrane Database Syst Rev.* 2012;5:CD007834.
51. Merck Manual. Iron-Deficiency Anemia. Available at https://www.merckmanuals.com/professional/hematology-and-oncology/anemias-caused-by-deficient-erythropoiesis/iron-deficiency-anemia. Last accessed November 17, 2022.
52. World Health Organization. *Serum Ferritin Concentrations for the Assessment of Iron Status and Iron Deficiency in Populations.* Geneva: World Health Organization; 2011.
53. Daru J, Colman K, Stanworth SJ, DeLaSalle B, Wood EM, Pasricha SR. Serum ferritin as an indicator of iron status: what do we need to know? *Am J Clin Nutr.* 2017;106(Suppl 6):1634S-1639S.
54. Joosten E. Iron deficiency in older adults: a review. *Geriatr Gerontol Int.* 2018;18(3):373-379.
55. Thomas DW, Hinchliffe RF, Briggs C, et al. Guidelines for the laboratory diagnosis of functional iron deficiency. *Br J Haematol.* 2013;161(5):639-648.
56. Gaweda AE. Makers of iron status in chronic kidney disease diagnosing iron deficiency. *Hemodial Int.* 2017;21(Suppl 1):S21-S27.
57. Percy L, Mansour D, Fraser I. Iron deficiency and iron-deficiency anaemia in women. *Best Pract Res Clin Obstet Gynaecol.* 2017;40:55-67.
58. Napolitano M, Dolce A, Celenza G, et al. Iron-dependent erythropoiesis in women with excessive menstrual blood losses and women with normal menses. *Ann Hematol.* 2014;93(4):557-563.
59. Siu AL, U.S. Preventive Services Task Force. Screening for iron-deficiency anemia and iron supplementation in pregnant women to improve maternal health and birth outcomes: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2015;163(7):529-536.
60. Vandevijere S, Amsalkhir S, Van Oyen H, Egli I. Moreno-Reyes R. Iron status and its determinants in a nationally representative sample of pregnant women. *J Acad Nutr Diet.* 2013;113(5):659-666.
61. Rigby FB. Anemia and Thrombocytopenia in Pregnancy. Available at https://emedicine.medscape.com/article/261586-overview. Last accessed November 17, 2022.
62. Short MW, Domgalski JE. Iron-deficiency anemia: evaluation and management. *Am Fam Physician.* 2013;87(2):98-104.
63. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 95: anemia in pregnancy. *Obstet Gynecol.* 2008;112(1):201-207.
64. Sato AP, Fujimori AP, Szarfarc SC, Borges AL, Tsunechiron MA. Food consumption and iron intake of pregnant and reproductive aged women. *Rev Lat Am Enfermagem.* 2010;18(2):247-254.
65. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. *J Perinatol.* 2017;37(2):105-111.
66. Das B, Sundaram V, Kumar P, Mordi WT, Dhaliwal LK, Das, R. Effect of placental transfusion on iron stores in moderately preterm neonates of 30–33 weeks gestation. *Indian J Pediatr.* 2018;85(3):172-178.
67. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. *Semin Fetal Neonatal Med.* 2007;12(1):54-63.
68. van Rheenen P, Brabin BJ. Late umbilical cord-clamping as an intervention for reducing iron-deficiency anaemia in term infants in developing and industrialised countries: a systematic review. *Ann Trop Paediatr.* 2004;24(1):3-16.

69. Metallinos,-Katsaras E, Colchamiro R, Edelstein S, Siu E. Household food security status is associated with anemia risk at age 18 months among low-income infants in Massachusetts. *J Acad Nutr Diet*. 2016;116 (11):1760-1766.
70. Baker RD, Greer FR; Committee on Nutrition, American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126(5):1040-1050.
71. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR*. 1998;47(RR3):1-29.
72. Urrechaga E, Izquierdo-Alvarez S, Llorente MT, Escanero JF. Prevalence of iron deficiency in health adolescents. *Ann Nutr Disord Ther*. 2016;3(2):1036.
73. Sekhar DL, Murray-Kolb LE, Wang L, Kunselman AR, Paul IM. Adolescent anemia screening during ambulatory pediatric visits in the United States. *J Community Health*. 2015;40(2):331-338.
74. Carvalho FSG, de Medeiros IA, Antunes H. Prevalence of iron-deficiency anemia and iron deficiency in a pediatric population with inflammatory bowel disease. *Scand J Gastroenterol*. 2017;52(10):1099-1103.
75. Thorisdottir AV, Gunnarsdottir I, Palsson GI, Gretarsson SJ, Thorisdottir I. Iron status and developmental scores in 6-year-olds highlights ongoing need to tackle iron deficiency in infants. *Acta Paediatr*. 2013;102(9):914-919.
76. Coates A, Mountjoy M, Burr J. Incidence of iron deficiency and iron-deficiency anemia in elite runners and triathletes. *Clin J Sport Med*. 2017;27(5):493-498.
77. Parks RB, Hetzel SJ, Brooks MA. Iron deficiency and anemia among collegiate athletes: a retrospective chart review. *Med Sci Sports Exerc*. 2017;49(8):1711-1715.
78. Lutter CK, Iron deficiency in young children in low-income countries and new approaches for its prevention. *J Nutr*. 2008;138(12):2523-2528.
79. Mclean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. *Public Health Nutr*. 2009;12(4):444-454.
80. Merck Manual. Anemia in Pregnancy. Available at https://www.merckmanuals.com/professional/gynecology-and-obstetrics/pregnancy-complicated-by-disease/anemia-in-pregnancy. Last accessed November 17, 2022.
81. Institute of Medicine Panel on Micronutrients. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press; 2001.
82. Spanierman CS. Iron Toxicity. Available at https://emedicine.medscape.com/article/815213-overview#a5. Last accessed November 17, 2022.
83. Holstege CP, Ross JA. Pediatric Iron Toxicity. Available at https://emedicine.medscape.com/article/1011689-overview. Last accessed November 17, 2022.
84. Porter JL, Bhimji SS. *Hemochromatosis*. Treasure Island, FL: StatPearls Publishing; 2017.
85. Geissler C, Singh M. Iron, meat, and health. *Nutrients*. 2011;3(3):283-316.
86. Katheria A, Reister F, Essers J. Association of umbilical cord milking vs. delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. *JAMA*. 2019;322(19):1877-1886.
87. Muñoz M, Gómez-Ramírez S, Besser M, et al. Current misconceptions in diagnosis and management of iron deficiency. *Blood Transfus*. 2017;15(5):422-437.

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