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Absolute versus functional iron deficiency

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Key message

- Iron deficiency (ID), the most common cause of anemia, can be classified into absolute and functional types. Absolute ID is a state of low total body iron, while functional ID is a state of imbalance between iron demand and iron availability due to inflammation and/or infection.
- ID is diagnosed by serum ferritin and transferrin saturation levels.

Iron deficiency (ID), the most common cause of anemia, leads to iron-deficiency anemia (IDA), followed by inflammation leading to anemia of inflammation, better known as anemia of chronic disease.[1] IDA remains the most prevalent type of anemia globally, affecting children, pregnant and nonpregnant premenopausal women, and people in low- and middle-income countries.[2,3] ID is twice as prevalent as IDA, affecting more than 2 billion people globally.[4,5] As iron is necessary for erythropoiesis, myoglobin synthesis, and numerous cellular processes, ID can cause various physiological and cellular impairments, even without anemia.[3,4] In children and adolescents, it can cause failure to thrive, cognitive impairment, decreased school performance, breath-holding spells, restless leg syndrome, attention-deficit hyperactivity disorder, immune system dysregulation, and cardiac problems.[4,5] Therefore, controlling ID and IDA is a global health priority.[2-4]

Total body iron is distributed in the erythrocytes, muscles, and iron-dependent enzymes for cellular metabolism and stored in the liver, spleen, and bone marrow.[2,3,6] Total body iron is sourced predominantly from recycled iron scavenged from senescent erythrocytes by macrophages in the reticuloendothelial system (RES), while a smaller amount (1–2 mg/day) is sourced from dietary iron absorbed in the duodenum.[2,3,7] Hepcidin, a protein produced by hepatocytes, regulates systemic iron homeostasis by degrading ferroportin, the key iron exporter expressed on macrophages and duodenal enterocytes.[1-4] Ferroportin exports iron from macrophages, duodenal enterocytes, and hepatocytes to the plasma. Hepcidin production is suppressed by erythropoiesis, hypoxia, and absolute ID, decreasing ferroportin degradation and increasing plasma iron levels.[2,3] Hepcidin production is increased by high iron levels and inflammation.[2,3]

ID can be absolute or functional.[2,3] Absolute ID is due to low or depleted total body iron stores that causes iron-deficient erythropoiesis. Its etiologies include inadequate iron uptake (poor dietary iron nutrition, reduced iron absorption), increased iron requirements, increased iron loss, and exercise (Table 1).[2,3] Absolute ID suppresses hepcidin production and ferroportin degradation, upregulating iron absorption at the gastroduodenal junction using divalent meta-transporter 1 and iron export from macrophages and hepatocytes into the circulation.[2,3,6] Absolute ID is diagnosed as low serum ferritin (≤30 μg/L) and low serum transferrin saturation (TSAT; <20%) (Table 1).[2-5] The diagnostic threshold of serum ferritin (≤30 μg/L) has 92% sensitivity and 98% specificity for diagnosing ID, but inflammation and age-related factors should be considered since its levels increase with age.[2,4] Hepcidin is an emerging indicator of ID that can distinguish between types.[3] IDA is diagnosed at a hemoglobin (Hb) <13 g/dL in men, Hb <12 g/dL in women, and Hb <11 g/dL in pregnant women.[2] Indications for iron therapy in absolute ID include anemia, symptoms, premature birth, pregnancy, before surgery, uncorrected underlying factors (e.g., growth) in children, poor iron intake, and blood loss. Absolute ID can be treated with oral or intravenous (IV) iron therapy (Table 1).[2,5,8] Orally, 2–3 mg/kg of elemental Fe^{2+} iron in 1 or 2 doses/day taken 30 minutes before or after a meal or 3–5 mg/kg of elemental Fe^{3+} iron in 1 or 2 doses/day with meals (and juice or water since polymaltose is a sugar complex that must be dissolved in the gastric fluid) is recommended.[5] IV iron therapy improves Hb and serum ferritin levels in iron-resistant IDA with the *TMPRSS6* mutation.[5,8]

Functional ID is an imbalance between iron demand

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Table 1. Absolute iron deficiency versus functional iron deficiency

Category	Absolute iron deficiency	Functional iron deficiency
Definition	Low or depleted total body iron stores	Imbalance between iron demand and iron availability, despite adequate total body iron stores
Etiology	Poor dietary iron nutrition: low heme iron diet such as vegan diet; poverty; prolonged breastfeeding, milk preference Reduced iron absorption: GI diseases such as Celiac disease, atrophic gastritis, inflammatory bowel disease; bowel resection; high gastric PH due to antacid or proton pump inhibitor therapy or Helicobacter pylori infection; competition from other metals such as calcium, copper, lead or zinc; intrinsic erythrocyte defects; iron-refractory IDA due to mutation of *TMPRSS6* gene Increased iron requirements: growth, pregnancy, erythropoiesis-stimulating agent therapy Blood loss: GI blood loss, genitourinary blood loss such as heavy menstrual bleeding, pulmonary blood loss, trauma, phlebotomy, large vascular malformation Exercise: multifactorial	Inflammation and/or infection Anemia of chronic disease Anemia of inflammation: Autoimmune disease Cancer Chronic kidney disease (CKD) Congestive heart failure (CHF) Chronic pulmonary disease Inflammatory bowel disease Obesity Elderly Critical illness (accelerated course)
Pathophysiology	Low total body iron stores Iron-deficient erythropoiesis Suppressed hepatic hepcidin production Decreased ferroportin degradation Increased GI absorption of iron Increased iron export from macrophages and hepatocytes into plasma	Increased inflammatory cytokines (IL-6, IL-1β, IL-10, TNF-α, IFN-γ) IL-6, IL-1β, LPS induce hepatic hepcidin production Increased ferroportin degradation Reduced GI absorption of iron Increased iron sequestration in macrophages of RES Iron-restricted erythropoiesis IL-1β, TNF-α and IFN-γ inhibit renal production and activity of EPO; inhibit erythropoiesis through radical formation; promote hepatic and splenic erythrophagocytosis reducing erythrocyte survival
Diagnosis	Ferritin ≤30 μg/L (WHO: Ferritn <12 μg/L in children <5 years of age; Ferritin <15 μg/L in person over 5 years of age) TSAT <20% Normal to low Hb Increased sTfR CHr low <29 pg Normal to low MCV (<75 fL) and MCH RDW increased Hepcidin low Bone marrow (not recommended for routine screening): absent iron stores	TSAT <20% Ferritin <100 μg/L In CHF: ferritin <100 μg/L or ferritin <300 μg/L with TSAT <20% In CKD considering for iron therapy: ferritin ≤ 500 μg/L and TSAT ≤30% Mild to moderate anemia Normal sTfR CHr low <29 pg Normal to mild low MCV and MCH Hepcidin high relative to TSAT
Treatment	Heme iron in food Oral iron therapy IV iron therapy	Treatment of underlying diseases IV iron therapy Erythropoiesis-stimulating agents Blood transfusion Vitamin B9, B12, D, C
Novel therapeutics		Antagonists of hepcidin Agents that redistribute endogenous iron for erythropoiesis

GI, gastrointestinal; IDA, iron-deficiency anemia; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; LPS, lipopolysaccharide; RES, reticuloendothelial system; EPO, erythropoietin; WHO, World Health Oraganization; ferritin, serum ferritin; TSAT, transferrin saturation; IV, intravenous; sTfR, soluble transferrin receptor; Hb, hemoglobin; CHr, reticulate hemoglobin content; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width.

and availability despite adequate total body stores that causes iron-restricted erythropoiesis.[1-4] Its etiologies are inflammation and/or infection causing anemia of chronic disease or inflammation, including cancer, autoimmune disease, chronic kidney disease (CKD), congestive heart failure (CHF), chronic pulmonary disease, inflammatory bowel disease (IBD), and obesity (Table 1).[1] In functional ID, inflammatory cytokines such as interleukin (IL)-6, IL-1β, and lipopolysaccharide induce hepcidin production, causing ferroportin degradation and iron retention of macrophages in RES, decreased iron absorption at the gastroduodenal junction, and decreased bioavailability of plasma iron, ultimately resulting in iron-restricted erythropoiesis (Table 1).[1,3,4,6,9] Inflammatory cytokines such as IL-1, tumor necrosis factor-α, and interferon-γ inhibit renal erythropoietin production and activity, inhibit erythropoiesis by radical formation, and promote hepatic and splenic erythrophagocytosis, reducing erythrocyte half-life (Table 1).[1,2,4,9] Functional ID is diagnosed at a TSAT < 20% and serum ferritin level <100 μg/L, the former being more important.[1,2,4,8] In CHF, ferritin <100 μg/L, or ferritin <300 μg/L with TSAT < 20%, is used to diagnose ID (Table 1).[2] For patients with CKD, the Kidney Disease Improving Global Outcomes Guideline recommends considering iron therapy at ferritin ≤500 μg/L and TSAT ≤30% (Table 1), but in recent clinical trials in patients with CKD receiving dialysis, a ferritin level <200 μg/L or TSAT <20% was an indication for iron therapy.[2] Functional ID is best treated

with IV iron and/or erythropoiesis-stimulating agent (ESA) therapy with underlying disease correction.[1-5,8-10] IV iron with ESA therapy showed clinical and laboratory improvements in patients with malignancy and chemotherapy-induced anemia, CKD receiving dialysis, and IBD who were intolerant of oral iron therapy.[1-5,8-10] IV iron therapy improved the exercise capacity and quality of life of patients with CHF and ID.[3,8-10] For IV iron therapy in children, ferric sucrose is authorized from 3 years of age, while ferric carboxymaltose is authorized from 18 years of age in United States and from 14 years of age in Europe.[5,8,10]

Footnotes

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