

Iron Deficiency Anemia

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KEYWORDS

• Iron • Ferritin • Inflammatory bowel disease • Ulcers • TMPRSS6

KEY POINTS

- Iron deficiency can lead to symptoms independent of anemia.
- The serum ferritin is the most efficient test for iron deficiency.
- Oral iron is best given once a day with vitamin C.

INTRODUCTION

Iron deficiency anemia is the most common and most treatable of all anemias. There is an evolving understanding that iron deficiency can lead to symptoms independent of anemia and can be associated with a variety of diseases. This review covers iron metabolism as well as the epidemiology, diagnosis, and treatment of this common anemia.

IRON METABOLISM

Iron is found in a variety of foods, with meat being the richest source. Iron in food is largely in the ferric form (Fe^{3+}), which is reduced by stomach acid to the ferrous form (Fe^{2+}). In the jejunum, 2 receptors on the mucosal cells absorb iron. One receptor is specific for heme-bound iron and absorbs 30% to 40% of ingested heme iron. The other receptor, divalent metal transporter (DMT1), takes up inorganic iron but is 1% to 10% less efficient at absorption. Iron is exported from the enterocyte via ferroportin and is then delivered to plasma transferrin, the main transport molecule for iron. Transferrin can deliver iron to the marrow for use in red cell production or to the liver for storage, which is done by binding to the transferrin receptor on the red cell membrane. Ferritin is the storage protein for iron. The ferritin protein consists of 24 ferritin subunits that create a shell that can store up to 4500 iron molecules.¹ Iron that is contained in

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hemoglobin in senescent red cells is recycled by binding to ferritin in the macrophage. It is then transferred to transferrin for recycling into developing red cells or is sent to storage. This system is extremely efficient and loses less than 5% of the iron contained in total red cell mass.

The protein hepcidin controls iron absorption and iron's release from stores.¹ Hepcidin binds to ferroportin, leading to its degradation. When hepcidin degrades ferroportin, iron cannot be released from the enterocyte or hepatocytes, leading to both a lack of iron absorption and a halt in iron release to developing red cells. Hepcidin synthesis is upregulated not only by iron but also by inflammation. Levels are reduced by hypoxia, increased erythropoiesis, and iron deficiency.

Recommended dietary iron intake is 8 mg daily for adult men and 18 mg for premenopausal women, increasing to 27 mg daily during pregnancy.² Meats are rich in heme iron, and iron in meat is much more effectively absorbed. Nonmeat sources of iron are poorer in iron stores, the iron is less effectively absorbed, and it is difficult to ingest large enough amounts to meet iron requirements.

EPIDEMIOLOGY AND ETIOLOGIES

Given that there is no natural mechanism for the body to excrete iron, the predominant mechanism for iron deficiency is blood loss, most commonly from menstrual periods or from gastrointestinal bleeding (**Box 1**). The next major causes are issues with the absorption of iron. Both of these can be compounded by the influence of iron-poor diets. In the United States, the incidence of iron deficiency in men is approximately 1%, but is at least 11% and often higher in women.³

Women are at greater risk for developing iron deficiency due to obligate iron losses through menstruation, with an average loss of 35 mL of blood equivalent to 16 mg of iron per period.^{2,4,5} The average iron requirements per day in women average 1 to 3 mg, with higher needs for those with heavier periods. Compounding this iron loss is that dietary iron intake is often inadequate to maintain a positive iron balance.^{6,7} Several studies demonstrate high levels of iron deficiency in women, with the most

Box 1

Etiologies of iron deficiency

- Menstrual losses
- Pregnancy and delivery
- Gastrointestinal losses
 - Cancer
 - Gastritis
 - Helicobacter pylori*
 - Atrophic gastritis
 - Ulcers
 - Hookworm and other parasites
 - Inflammatory bowel disease
 - Meckel diverticulum
 - Vascular malformations
- Obesity
- Celiac disease
- Hematuria
- Bariatric surgery

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