Best Practice & Research Clinical Haematology
Vol. 18, No. 2, pp. 319–332, 2005
doi:10.1016/j.beha.2004.08.022
available online at http://www.sciencedirect.com

12

Diagnosis and management of iron-deficiency anaemia

James D. Cook* MD, MSc (Med)
Philips Professor of Medicine
Department of Medicine, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA

Anaemia is typically the first clue to iron deficiency, but an isolated haemoglobin measurement has both low specificity and low sensitivity. The latter can be improved by including measures of iron-deficient erythropoiesis such as the transferrin iron saturation, mean corpuscular haemoglobin concentration, erythrocyte zinc protoporphyrin, percentage of hypochromic erythrocytes or reticulocyte haemoglobin concentration. However, the changes in these measurements with iron deficiency are indistinguishable from those seen in patients with the anaemia of chronic disease. The optimal diagnostic approach is to measure the serum ferritin as an index of iron stores and the serum transferrin receptor as a index of tissue iron deficiency. The treatment of iron deficiency should always be initiated with oral iron. When this fails because of large blood losses, iron malabsorption, or intolerance to oral iron, parenteral iron can be given using iron dextran, iron gluconate or iron sucrose.

Key words: iron deficiency; iron-deficient erythropoiesis; ferritin; transferrin receptor; parenteral iron.

DEFINITIONS OF IMPAIRED IRON STATUS

Iron deficiency is defined as a reduction in total body iron to an extent that iron stores are fully exhausted and some degree of tissue iron deficiency is present. In epidemiological studies, it has been common practice to determine the prevalence of both mild iron deficiency without anaemia and more advanced iron-deficiency anaemia (IDA).

An important term that is not synonymous with iron deficiency is *iron-deficient erythropoiesis* (IDE). This refers to laboratory evidence of an impaired supply of plasma iron to the erythroid marrow for haemoglobin synthesis, either directly as a reduced iron saturation of plasma transferrin, or indirectly as signs of iron deficiency in circulating red blood cells. While IDE is a cardinal manifestation of IDA, it is also seen in

* Tel.: +1 913 588 6077; Fax: +1 913 588 3996.
E-mail address: jcook1@kumc.edu

1521-6926/$ - see front matter

a large variety of clinical disorders associated with inflammation or malignancy. Unlike IDA, in which iron stores are totally absent, IDE can occur with normal or increased amounts of storage iron resulting from the impaired release of iron to the plasma from the storage iron compartment.

Functional iron deficiency has been used more recently to describe a specific form of IDE seen in patients given recombinant human erythropoietin, a treatment that exaggerates any disparity between the influx of iron to the plasma from the storage compartment and the iron requirements of the erythroid marrow. The term has been used predominantly in the haemodialysis literature to emphasize the potential need for parenteral iron therapy despite laboratory evidence of residual storage iron.

LABORATORY DIAGNOSIS OF IRON DEFICIENCY

Textbook descriptions of iron deficiency commonly list various signs and symptoms, but these seldom lead to a diagnosis. Clinical features such as koilonychia, glossitis or dysphagia are seen rarely in modern clinical practice. The most important clinical clue is the symptom of chronic fatigue. While iron deficiency should always be included in the differential diagnosis of this symptom, it is of little screening value because 20–30% of patients seen in a primary care setting report fatigue as a major health problem.[1,2] Because clinicians rarely consider the diagnosis of iron deficiency in patients who are not anaemic, iron deficiency is invariably diagnosed in the laboratory.

The key to understanding the laboratory measurements of iron status is knowledge of the major internal iron circuit resulting from the removal and replacement of 30–40 mg haemoglobin iron in senescent red blood cells each day. Within a few minutes of the ingestion of aged red cells by macrophages in the spleen and bone marrow, iron is extracted from haemoglobin and returned to the plasma where it becomes tightly bound to its dedicated extracellular carrier, transferrin. Over the next hour or two, iron-containing transferrin attaches to specific receptors located predominantly on the surface of red-cell precursors in the bone marrow. The iron cycle is completed when the newly formed erythrocytes are returned to the circulation over the next 7–10 days. Other important communications exist between the plasma iron compartment and the intestinal mucosa and liver, although these pathways are small compared to the major erythroid iron circuit.

It is useful to classify the laboratory methods for identifying iron deficiency into two major categories of screening and definitive measurements (Table 1). *Screening* measurements identify IDE by demonstrating either a reduced supply of plasma iron or poor haemoglobinization of circulating red blood cells. *Definitive* tests identify IDA by measuring iron-related proteins derived from either the iron storage compartment in macrophages or the iron utilization compartment in red-cell precursors. It should be noted that a therapeutic trial of iron has been proposed as a convenient method to diagnose iron deficiency in an anaemic patient. While this is a reasonable approach in otherwise healthy individuals at high risk of deficiency—such as infants, teenage girls and pregnant women—it is preferable to make a definitive laboratory diagnosis at the outset.

Screening measurements

The haemoglobin determination has been the most widely used screening method for iron deficiency, but when used as the only laboratory measurement it has serious limitations for identifying iron deficiency because of its low specificity and sensitivity.