Iron is one of the most abundant elements in the earth’s crust and is the second most plentiful element in the body. It plays a role in respiration, oxygen delivery, host defense, and muscular activity. Not surprisingly, this vital element is carefully acquired, transported, and stored. In humans, iron concentrations are regulated by control of iron absorption and the subsequent trafficking of iron to cells via transferrin and the transferrin receptor, with any excess iron being stored in ferritin. In fact, a balanced economy regulates the amount of iron taken into the body and the amount lost, the latter being limited to obligatory losses from shedding of epithelial cells or, in a pathophysiological condition, by bleeding. Most of the iron is directed for the synthesis of hemoglobin. The careful recycling of iron derived from hemoglobin and its reutilization for synthesis of new red blood cells underpins one of the most carefully controlled systems in the human body.

The consequences of iron deficiency are not limited to anemia and the reduced oxygen-carrying capacity; another is diminished exercise tolerance. Many proteins that contain iron will be deficient and lead to muscle dysfunction and fatigue. For example, decreased concentrations of α-glycerophosphate dehydrogenase impair the ability of rats to exercise when they are iron deficient [1]. In children, cognitive function and attention span can be affected by iron deficiency, even without any significant decrease in hemoglobin concentration [2, 3]. Many other signs of iron deficiency (including changes in the nails, tongue, and esophagus) can be attributed to the loss of iron for the metabolism of these epithelial cells.

More than a billion people worldwide are anemic and as many as half of them have iron deficiency as the cause [4]. Thus, diagnosing iron deficiency and understanding iron metabolism have considerable implications for world health. In this issue of Clinical Chemistry, Hastka et al. report their examination of laboratory tests of iron status [5]. Stages of iron deficiency delineated by these laboratory tests range from diminished stored iron through iron-deficient erythropoiesis to severe anemia. Fairbanks [6], reviewing the history of laboratory testing for iron status, noted that “the proper interpretation of iron status is made from gestalt or the pattern of clinical and laboratory findings rather than any single test.” Tests ranging from examination of blood smears and determination of erythrocyte indices, which were introduced at the turn of the century, through more recent tests such as serum ferritin or erythrocyte zinc protoporphyrin all must be scrutinized in relationship to the stages of the total body iron stores and the iron economy.

Hastka et al. define three stages of iron deficiency—iron depletion, iron-deficient erythropoiesis, and iron-deficiency anemia—by utilizing a variety of tests, including hemoglobin concentration, red cell indices, serum ferritin, serum transferrin saturation, and erythrocyte zinc protoporphyrin, as well as bone marrow hemosiderin and sideroblast count. In their Fig. 3 the authors clearly define the stages of iron deficiency and which laboratory tests define each stage. They conclude that there is no single best marker of iron deficiency. This echoes the comments of Richard Cabot over a century ago: “...not pathognomonic signs but links in a chain of evidence are what we are to expect from blood examination” [6]. These links in the chain include the laboratory tests defined by Hastka et al.

Finding patients with iron depletion and a normal hemoglobin value may be critical, especially in children, as noted above, given the critical role iron may play in muscle metabolism and various cerebral processes. Iron replacement in these patients when they do not have anemia can improve their performance. Unfortunately, Hastka et al. did not extend their findings to examining patients with thalassemia, anemia of chronic disease, and iron overload. For the clinician, deciding between the anemia of chronic disease and iron-deficiency anemia in diseases such as rheumatoid arthritis is still a quagmire. Until further studies demonstrate that erythrocyte zinc protoporphyrin is a superior “first-line” test for differentiating between these entities, the primacy of erythrocyte zinc protoporphyrin values relative to iron transferrin saturation and ferritin concentrations remains open to verification. Furthermore, we must consider the cost analysis of the use of erythrocyte zinc protoporphyrin relative to use of other tests as the front-line strategy for assessing iron status. Obtaining reimbursement for erythrocyte protoporphyrin analyses from third-party payers may also be an important issue. Investigators must also address the impact of implementing this test on the clinical laboratory’s workload, equipment needs, and finances.

Moreover, the critical role of iron excess in disease is becoming more and more evident. Not only is hemochromatosis a common disease in our population, but also excess iron has a role in heart disease and cancer [7, 8]. Clinical chemists and clinicians still need to have defined the best tests for determining iron overload. New tests to assess the iron content of serum ferritin (most of circulating serum ferritin is iron-poor) may help differentiate “true” iron overload from “inflammatory” increases in serum ferritin.

Thus, balancing the iron budget may require multiple tests to accurately determine the stage of iron deficiency. Balancing the costs of new laboratory tests for the diagnosis of iron status requires careful cost–benefit analyses—which, we hope, will be elucidated by further studies, not a constitutional amendment.

References

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