Commentary: Iron deficiency and hair loss

Problems with measurement of iron

Dirk M. Elston, MD
Danville, Pennsylvania

See related article on page 1070

Iron is involved in many critical physiologic processes within the hair follicle, suggesting that iron deficiency could disrupt hair synthesis. However, studies of iron as a cause of hair loss have produced conflicting results. Some of the discrepancies may relate to limitations of assays for iron deficiency. This commentary discusses the sensitivity and specificity of available tests for iron deficiency and presents practical guidelines for testing and supplementation. (J Am Acad Dermatol 2010;63:1077-82.)

Key words: alopecia; ferritin; hair loss; iron.

In this issue of the *Journal*, St. Pierre et al[1] discuss the role of iron in hair growth as well as evidence for and against iron deficiency as a cause of diffuse hair loss. Despite decades of research, the debate about iron and hair loss continues. Why has this particular question proved so difficult to resolve? The most obvious reason is that human iron stores vary widely in different populations and ranges considered "normal" have traditionally been based on levels necessary to support hematopoiesis. Significant iron deficiency can exist in the absence of anemia,[2] and no studies have addressed minimal iron levels necessary for normal hair growth.

A second issue is that iron levels may be a poor marker for overall nutritional status or deficiency of other micronutrients. Correction of iron deficiency as an isolated intervention may not address other important etiologic factors. A third issue to be considered in any discussion of iron and hair loss is that laboratory methods used to detect iron deficiency have inherent weaknesses. This commentary will focus on the sensitivity and specificity of laboratory tests for iron.

Abbreviations used:

CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
RHC: reticulocyte hemoglobin content
sTfR: soluble transferrin receptor

LABORATORY TESTS FOR IRON DEFICIENCY

The majority of iron used for erythropoiesis is recovered from senescent erythrocytes, rather than coming directly from the diet. In the face of iron deficiency, iron stores decrease slowly. The earliest sign is a decrease in plasma ferritin, followed by a decrease in plasma iron and transferrin saturation.[3] Either by intelligent design or evolutionary pressure, we are built to make blood at the expense of hair when nutrients are scarce. This is well established in protein-calorie malnutrition and zinc deficiency,[4,5] but data remain mixed regarding isolated iron deficiency.

Tests for iron deficiency and their limitations are summarized in Table I. Both serum iron and ferritin have proved to be superior to red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean cell hemoglobin concentration, and cell morphology as markers of iron deficiency.[6] A study of patients with polycythemia vera treated by phlebotomy offers an interesting perspective on markers for iron deficiency. Although the study was small (11 patients evaluated at 90 points in time), it was unique in that it followed up 5 of these patients from normal iron status through various levels of therapeutically induced iron deficiency. In this population, serum ferritin

From the Departments of Dermatology and Pathology, Geisinger Medical Center.
Funding sources: None.
Conflicts of interest: None declared.
Reprint requests: Dirk M. Elston, MD, Department of Dermatology, Geisinger Medical Center, 100 N Academy Ave, Danville, PA 17822-5206. E-mail: Dmelston@geisinger.edu.
Published online October 1, 2010.
0190-9622/$36.00

doi:10.1016/j.jaad.2009.09.054

showed fewer false-negative results than serum iron, serum transferrin, or free erythrocyte protoporphyrin.[7]

FERRITIN IS PRONE TO FALSE-NEGATIVE RESULTS IN SOME PATIENT POPULATIONS

Although ferritin testing is widely used and has demonstrated excellent specificity, its sensitivity is variable. The most important cause of this variability is that ferritin behaves as an acute phase reactant, with significant elevations in patients with neoplasia, infection, and other inflammatory diseases.[8-12] This can result in paradoxically normal ferritin levels in the face of profound iron deficiency. This behavior as an acute phase reactant is apparent in population-based studies of iron deficiency. In a study of 1254 apparently healthy adults between the ages of 60 and 95 years, a serum ferritin cutoff of 22 μg/L was associated with a sensitivity of 89.5% and a specificity of 89.0% in the detection of iron deficiency.[13] In contrast, a study of 92 hospitalized patients showed that a serum ferritin below 60 ng/mL demonstrated sensitivity of only 69.6% and specificity of 97.1% when compared with bone-marrow aspirates.[14] It is likely that much of the loss of sensitivity relates to the prevalence of inflammation, infection, or neoplasia in the in-patient population.

In patients with lupus, serum ferritin parallels disease activity,[15,16] but in those with rheumatoid arthritis, serum ferritin may be an inaccurate indicator of iron deficiency even among those with clinically inactive disease.[17] In a study of 28 patients with rheumatoid arthritis, ferritin correlated better with the erythrocyte sedimentation rate (ESR) than with the presence of anemia. Soluble transferrin receptor (sTfR) and transferrin receptor-ferritin index (sTfR/logF) perform better than ferritin in this setting.[18,19]

A study of 81 patients compared the sensitivity and specificity of ferritin measurements in patients with and without HIV infection. Bone-marrow aspirates were used as the gold standard. In HIV-negative patients, ferritin testing demonstrated 90% sensitivity and 100% specificity. In contrast, in HIV-positive patients ferritin showed a sensitivity of only 20%, with specificity of 93%.[20]

Both C-reactive protein (CRP) and ESR have been paired with ferritin measurements as markers of chronic inflammation, and enzyme-linked immunosorbent sandwich techniques have been used to create inexpensive tests that provide a combined measurement of ferritin, sTfR, and CRP.[21,22] In a study of 96 patients on hemodialysis, serum ferritin was shown to correlate with CRP (P = .006).[23] Unfortunately, data regarding CRP are mixed, with some suggesting that CRP performs poorly in predicting elevations in ferritin as a result of inflammation.[24] There may be a better correlation between CRP and ferritin in synovial fluid than in serum.[25] Until more data become available, ESR remains the best marker of inflammation to couple with ferritin.

In the setting of chronic kidney disease, ferritin levels are even more problematic. Patients with chronic renal insufficiency may demonstrate a serum ferritin greater than 800 ng/mL, suggesting iron overload, whereas the transferrin saturation is less than 20%, demonstrating actual iron deficiency.[26] In this setting, total iron-binding capacity, transferrin saturation, reticulocyte hemoglobin content (RHC), and immature reticulocyte fraction are better markers of iron deficiency.[27-29]

CAPSULE SUMMARY

- It remains unclear whether isolated iron deficiency causes hair loss or whether iron supplementation is helpful.
- Hemoglobin, hematocrit, and red blood cell indices are poor screens for iron deficiency.
- Ferritin remains the most widely used test for iron deficiency, but is unreliable in patients with chronic inflammation, infection, neoplasia, or chronic kidney disease. Unreliable ferritin results also have been noted in patients with rheumatoid arthritis, even in the absence of clinically significant disease activity.
- Measurement of the erythrocyte sedimentation rate may indicate when ferritin is likely to be elevated as an acute phase reactant.
- Additional testing for soluble transferrin receptor, iron, and transferrin saturation, or a transferrin receptor-ferritin index may increase accuracy.
- Erythrocyte protoporphyrin studies and reticulocyte hemoglobin content have also been used as screens for iron deficiency, but no tests have been validated in the setting of alopecia.
- Iron replacement should be provided for those with iron deficiency, but iron supplementation for those with normal iron stores may increase the risk of coronary artery disease and malignancy.

OTHER AVAILABLE MARKERS OF IRON DEFICIENCY

Although some clinicians continue to use ferritin alone to screen for iron deficiency, a panel including