

The diagnosis and treatment of iron deficiency and its potential relationship to hair loss

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Iron deficiency is the world's most common nutritional deficiency and is associated with developmental delay, impaired behavior, diminished intellectual performance, and decreased resistance to infection. In premenopausal women, the most common causes of iron deficiency anemia are menstrual blood loss and pregnancy. In men and postmenopausal women, the most common causes of iron deficiency anemia are gastrointestinal blood loss and malabsorption. Hemoglobin concentration can be used to screen for iron deficiency, whereas serum ferritin concentration can be used to confirm iron deficiency. However, the serum ferritin concentration may be elevated in patients with infectious, inflammatory, and neoplastic conditions. Other tests may be needed, such as erythrocyte zinc protoporphyrin concentration, transferrin concentration, serum iron concentration, and transferrin saturation. The cause of iron deficiency must be identified. If the patient is male, postmenopausal female, or has risk factors for blood loss, then the patient should be evaluated for sources of blood loss, especially gastrointestinal (eg, colon cancer). Several studies have examined the relationship between iron deficiency and hair loss. Almost all have addressed women exclusively and have focused on noncicatricial hair loss. Some suggest that iron deficiency may be related to alopecia areata, androgenetic alopecia, telogen effluvium, and diffuse hair loss, while others do not. Currently, there is insufficient evidence to recommend universal screening for iron deficiency in patients with hair loss. In addition, there is insufficient evidence to recommend giving iron supplementation therapy to patients with hair loss and iron deficiency in the absence of iron deficiency anemia. The decision to do either should be based on clinical judgment. It is our practice at the Cleveland Clinic Foundation to screen male and female patients with both cicatricial and noncicatricial hair loss for iron deficiency. Although this practice is not evidence based per se, we believe that treatment for hair loss is enhanced when iron deficiency, with or without anemia, is treated. Iron deficiency anemia should be treated. Treating iron deficiency without anemia is controversial. Treatment of nutritional iron deficiency anemia includes adequate dietary intake and oral iron supplementation. Excessive iron supplementation can cause iron overload and should be avoided, especially in high-risk patients such as those with hereditary hemochromatosis. Patients who do not respond to iron replacement therapy should undergo additional testing to identify other underlying causes of iron deficiency anemia. (J Am Acad Dermatol 2006;54:824-44.)

Iron deficiency is the world's most common nutritional deficiency and is associated with reduced work capacity, impaired behavior, diminished intellectual performance, and decreased resistance to infection.¹ In children, iron deficiency anemia (IDA) can cause developmental delays, whereas in pregnant women, the likelihood of preterm and low-birth-weight delivery is increased. Iron

Abbreviations used:

AA:	alopecia areata
AGA:	androgenetic alopecia
CBC:	complete blood cell count
CTE:	chronic telogen effluvium
FPA:	female pattern alopecia
HH:	hereditary hemochromatosis
IDA:	iron deficiency anemia
IDE:	iron-deficient erythropoiesis
MCV:	mean corpuscular volume
NHANES:	National Health and Nutrition Examination Survey
RDA:	recommended dietary allowance
TE:	telogen effluvium
TIBC:	total iron binding capacity

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deficiency can be defined as absent bone marrow iron stores (determined by bone marrow iron smears), an increase in hemoglobin concentration by more than 1.0 g/dL after iron supplementation

Table I. The spectrum of iron deficiency^{2,3}

Iron status	Body iron content			Laboratory test					
	Storage iron	Transport iron	Functional iron	Storage iron	Transport iron			Functional iron	
				Serum ferritin	EP	Tf conc/TIBC	Tf sat	Serum iron	Hb, Hct
Iron overload	↑	↑	NI	↑	NI	↓	↑	↑	NI
Normal	NI	NI	NI	NI	NI	NI	NI	NI	NI
Iron depletion	↓	NI	NI	↓	NI	NI/↑	NI/↓	NI/↓	NI
Iron-deficient erythropoiesis	↓	↓	NI	↓	↑	↑	↓	↓	NI
Iron deficiency anemia	↓	↓	↓	↓	↑	↑	↓	↓	↓

EP, Erythrocyte zinc protoporphyrin concentration; Hb, hemoglobin; Hct, hematocrit; Tf conc, transferrin concentration; Tf sat, transferrin saturation (ratio of serum iron to TIBC); TIBC, total iron binding capacity.

Modified from Figure 26-5 in Brittenham GM. Disorders of iron metabolism: iron deficiency and overload. In: Hoffman R, editor. Hematology: basic principles and practice. 3rd ed. New York: Churchill-Livingstone; 2000. p. 410. With permission from Churchill-Livingstone.

Also modified from Table 3 in Centers for Disease Control (CDC). Recommendations to prevent and control iron deficiency in the United States. Morb Mortal Wkly Rep 1998;47:6. In public domain.

therapy, or abnormal values of other biochemical tests (discussed later in this article).²

Total body iron is classically viewed as being distributed among 3 compartments: storage iron, transport iron, and functional iron (Table I). Storage iron represents the body's iron reserves that are bound to ferritin and hemosiderin and is best measured by serum ferritin concentration. Transport iron, the iron that is transported to the tissues, is bound mainly to transferrin and is measured by erythrocyte zinc protoporphyrin concentration, transferrin concentration/total iron binding capacity (TIBC), serum iron, and transferrin saturation. Functional iron consists of iron that is bound to hemoglobin, myoglobin, heme enzymes such as cytochromes, and nonheme enzymes such as ribonucleotide reductase. Functional iron is measured by hemoglobin concentration and hematocrit.^{2,3}

Iron deficiency can be viewed as a continuum: iron depletion, iron-deficient erythropoiesis (IDE), and IDA (Table I). In iron depletion, body iron stores are reduced, but functional and transport iron remain normal, leaving little or no reserves if the body requires more iron. In IDE, both storage and transport iron are decreased. Red blood cell production is diminished, resulting in insufficient iron for growth and function. Finally, in IDA, storage, transport, and functional iron are severely decreased and can lead to impaired function of multiple organ systems.²

According to the National Health and Nutrition Examination Survey (NHANES) 1999-2000, the prevalence of IDA is 2% to 5% above the 2010 national health objectives.⁴ The prevalence of iron deficiency in adolescent girls and women of childbearing age (16-49 years of age) is 12% to 16%, whereas the prevalence of IDA is 2% to 4%.⁴ In women 50 years of age and older, the prevalence of iron deficiency is

Table II. Common causes of iron deficiency^{2,16}

Increased demand for iron and/or hematopoiesis

- Rapid growth in infancy or adolescence
- Pregnancy and lactation
- Erythropoietin therapy

Iron loss

- Blood loss
 - Childbirth
 - Surgery
 - Gastrointestinal tract loss
 - Genitourinary tract loss
 - Respiratory tract loss
- Menstruation
- Blood donation
- Phlebotomy

Decreased iron intake or absorption

- Insufficient dietary intake
- Decreased absorption
 - Disease (eg, sprue, Crohn's disease)
 - Surgery (eg, gastric and intestinal surgery)
- Acute or chronic inflammation

Modified from Table 90-2 in Adamson JW. Iron deficiency and other hypoproliferative anemias. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2005. p. 589. With permission of the McGraw Hill Companies.

Also modified from Exhibit I in Centers for Disease Control (CDC). Recommendations to prevent and control iron deficiency in the United States. Morb Mortal Wkly Rep 1998;47:5. In public domain.

6% to 9%,⁴ whereas the prevalence of IDA is approximately 2%.⁵

In males aged 16 to 69 years, the prevalence of iron deficiency is 2%,⁴ whereas the prevalence of IDA is less than or equal to 1%.⁵ In men 70 years of age and older, the prevalence of iron deficiency is 4%, while the prevalence of IDA is 2%.⁵

Table III. Conditions *other than* iron deficiency and iron overload which cause changes in tests of iron status^{2,3}

Test of iron status	Conditions where increased	Conditions where decreased
Hb, Hct		Folate deficiency Vitamin B ₁₂ deficiency Thalassemia Sickle cell disease Infection Inflammation Chronic renal failure
Serum ferritin	Infection Inflammation Malignancy Liver damage	
EP	Infection Inflammation Lead poisoning	
Tf conc, TIBC	Pregnancy Oral contraceptive use	Infection Inflammation Malignancy Liver disease Nephrotic syndrome Malnutrition
Serum iron	Recent iron ingestion Aplastic anemia Sideroblastic anemia Ineffective erythropoiesis Liver disease Substantial circadian fluctuation (increased in the morning)	Infection Inflammation Malignancy Ascorbate deficiency Substantial circadian fluctuation (decreased at night)

EP, Erythrocyte zinc protoporphyrin; Hb, hemoglobin; Hct, hematocrit; Tf conc, transferrin concentration; TIBC, total iron binding capacity.

Table II lists frequent causes of iron deficiency. In premenopausal women, the most common causes of IDA are menstrual blood loss and pregnancy. The most common causes of IDA in men and postmenopausal women are gastrointestinal blood loss and malabsorption.⁶

According to the Continuing Survey of Food Intakes by Individuals, only one fourth of adolescent girls and women (ages 12-49 years) meet the 1989 recommended dietary allowance (RDA) for iron. Among all adults 20 years of age and older, only 38% of women meet the 1989 RDA for iron compared with 86% of men. In the same group, 25% of women and 16% of men report using iron supplements.⁷

TESTS OF IRON STATUS

Laboratory studies, such as hemoglobin concentration, hematocrit, serum ferritin concentration, erythrocyte zinc protoporphyrin concentration, transferrin concentration/TIBC, serum iron, and transferrin saturation, can be used to detect different stages of iron

deficiency (see Table D). However, these studies may be affected in other conditions (Table III). Bone marrow examination showing absence of stainable iron is the definitive method for diagnosing IDA. However, this is a painful and invasive procedure and is usually used as a last resort.⁸

Hemoglobin and hematocrit

Hemoglobin plays a major role in binding to oxygen within circulating red blood cells.⁹ The concentration of iron-containing hemoglobin in circulating red blood cells can be measured easily. Hematocrit is the percentage of blood that is occupied by red blood cells.²

Hemoglobin concentration and hematocrit are frequently used to screen for iron deficiency because of their low cost and wide standard availability. However, hemoglobin concentration and hematocrit are only decreased in full-blown IDA, not in iron deficiency. In addition, reduced hemoglobin concentration or hematocrit does not indicate the cause

of anemia. Reduced hemoglobin concentration and hematocrit can be found in many other conditions, such as folate deficiency, vitamin B₁₂ deficiency, thalassemia, sickle cell disease, anemia of chronic disease, and chronic renal failure.^{2,3}

As the prevalence of iron deficiency has declined since the 1970s, anemia has become a less effective predictor of iron deficiency. When anemia is used in women of childbearing age to diagnose iron deficiency, it yields a sensitivity of 37% and a specificity of 93%.²

Serum ferritin

Ferritin is a highly conserved protein complex that plays an important role in iron storage and is recognized as the main iron-binding protein in nonerythroid cells.¹⁰ Intracellular ferritin is synthesized by the smooth endoplasmic reticulum. Serum ferritin is synthesized by the rough endoplasmic reticulum and glycosylated by the Golgi apparatus before being secreted. Generally, serum ferritin is directly related to intracellular ferritin and thus total body iron stores.³

Only iron deficiency causes very low serum ferritin concentrations; therefore a low serum ferritin concentration is very specific for iron deficiency. Although many laboratories use serum ferritin concentrations of 10 to 15 ng/mL as the lower limits of normal based on reference sample groups, this only gives a sensitivity of 59% and a specificity of 99% for diagnosing iron deficiency.¹¹ In women of childbearing age, using a cutoff of 10 to 15 ng/mL yields a sensitivity of 75% and specificity of 98%.² A cutoff of 30 ng/mL yields a sensitivity of 92% and a specificity of 98%, while a cutoff of 41 ng/mL yields a sensitivity of 98% and a specificity of 98%.¹¹ Investigators consider serum ferritin to be the most powerful screening tool for iron deficiency. One large review concluded that serum ferritin had a greater predictive value than other tests of iron status, such as transferrin saturation and erythrocyte zinc protoporphyrin.¹² In iron overload, ferritin is increased.¹³ Ferritin is also an acute phase reactant and is elevated in anemia of chronic (disease discussed later in this article).¹⁴

Erythrocyte zinc protoporphyrin concentration

The final step in heme synthesis is the chelation of ferrous iron by protoporphyrin IX. When iron is not present, zinc is chelated instead, thus forming zinc protoporphyrin. Therefore, when there is a lack of iron, serum erythrocyte zinc protoporphyrin concentration is elevated.¹¹ This test detects IDE and IDA, but it does not detect iron depletion as consistently as serum ferritin concentration.¹² Infection,

inflammation, and lead poisoning also can elevate erythrocyte zinc protoporphyrin concentration.² Finally, unlike serum ferritin, erythrocyte zinc protoporphyrin is not useful in detecting iron overload.¹⁵

Transferrin concentration/TIBC

Transferrin is a major serum iron transport protein. The serum transferrin concentration, measured indirectly as TIBC, is usually increased in iron deficiency and decreased in iron overload. Levels also can be elevated with pregnancy and oral contraceptive use and decreased with infection, inflammation, malignancy, liver disease, nephrotic syndrome, and malnutrition.³ By itself, transferrin concentration/TIBC is not considered a consistently reliable indicator of iron deficiency.^{3,12}

Serum iron and transferrin saturation

Serum iron and transferrin saturation (the ratio of serum iron to TIBC) also can be used to assess iron status. In IDE and IDA, serum iron and transferrin saturation are decreased. In iron depletion, serum iron and transferrin saturation are normal to decreased. However, serum iron can also be decreased with infection, inflammation, malignancy, and ascorbate deficiency. Serum iron can be increased by recent iron ingestion as well as aplastic anemia, sideroblastic anemia, ineffective erythropoiesis, and liver disease.³ Significant circadian variation causes serum iron and transferrin saturation to increase in the morning and decrease at night. In women of childbearing age, using a lower cutoff point of 16% for transferrin saturation in detecting iron deficiency yields a sensitivity of 20% and a specificity of 93%.² In iron overload, serum iron and transferrin saturation are usually increased.¹³

DIAGNOSIS OF IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

Diagnosing iron deficiency and IDA involves several principles:

- Knowing when to suspect iron deficiency and IDA based on demographics, risk factors, and symptoms
- Knowing which populations do not normally have iron deficiency or IDA and, when anemia is found, searching for causes other than iron deficiency
- Properly using laboratory tests in a cost-effective manner

This article focuses on men and nonpregnant women 18 years of age and older. Infants (from birth to 12 months of age), preschool children (1-5 years of age), school-age children (5-12 years of age),

adolescents (12-18 years), and pregnant and lactating women have other special considerations.²

Populations at high risk for iron deficiency

A study of the NHANES III (1988-1994) data showed that in the United States, the prevalence of iron deficiency and IDA is highest in women of childbearing age. According to the report, in women of childbearing age, the prevalence is highest in blacks and Mexican Americans (US Bureau of the Census definitions), those who are poor (self-reported income in relation to federal poverty income guidelines), those who have had 12 or fewer years of education, and those who have given birth to 4 or more children.⁵ Similar findings were reported in a Centers for Disease Control and Prevention (CDC) study of the NHANES 1999-2000 data for age, gender, and race, although economic, educational, and parity subgroup analysis was not reported.⁴

Risk factors for iron deficiency include heavy menstrual blood loss (≥ 80 mL per month, affecting approximately 10% of women), use of an intrauterine device, history of IDA, and insufficient iron intake.² Any form of blood loss, including blood donation, childbirth, and surgery, as well as gastrointestinal, genitourinary, and respiratory tract blood loss, puts patients at increased risk for iron deficiency.¹⁶ A single milliliter of blood contains approximately 0.5 mg of iron. Occult blood tests for stool usually become positive after a loss of 20 mL/d. Therefore, a patient who tests positive for occult gastrointestinal blood loss may be losing iron at a rate of more than 10 mg/d.¹⁷

Screening for IDA. The 1998 CDC guidelines recommend screening all nonpregnant women for IDA every 5 to 10 years during childbearing years. Premenopausal women with risk factors for iron deficiency (see above) are recommended to be screened for IDA annually. In men and postmenopausal women, routine screening is not recommended.²

Signs and symptoms of iron deficiency and IDA

The classic symptoms of iron deficiency are similar to those of anemia and include fatigue and decreased exercise tolerance.¹⁶ Signs of severe anemia include skin and conjunctival pallor, tachycardia, and low blood pressure.⁹ Other dermatologic findings include chronic diffuse telogen hair loss,¹⁸ cheilosis, and koilonychia.¹⁶ It is important to note that patients with iron deficiency and even anemia may be completely asymptomatic.¹¹

Evaluation for iron deficiency and anemia

The 1998 CDC guidelines state that there is no single test that is universally accepted for diagnosing

iron deficiency. The guidelines state that in premenopausal women, a presumptive diagnosis of IDA can be made with a low hemoglobin concentration or hematocrit alone and then confirmed by a response to iron replacement therapy in 4 weeks. A response is defined as an increase in hemoglobin concentration greater than or equal to 1 g/dL or an increase in hematocrit greater than or equal to 3%.²

This approach has at least two limitations. First, other important causes of anemia initially can be missed. Second, if the response is mild, it may be difficult to distinguish among poor patient compliance, inadequate iron absorption, incorrect diagnosis, or multiple causes of anemia.¹¹

Therefore reasonable initial laboratory testing to diagnose iron deficiency and IDA include a complete blood cell count (CBC, including leukocyte count, hemoglobin concentration, hematocrit, and platelet count), red blood cell indices (including mean corpuscular volume—see below), ferritin, TIBC, serum iron, and transferrin saturation.¹¹ Another alternative, when there is a strong clinical suspicion of iron deficiency, is to order a CBC, red blood cell indices, and ferritin. Some laboratories allow “adding on” TIBC, serum iron, and transferrin saturation up to a week after the patient has given a blood sample without requiring the patient to return to the laboratory.

Fig 1 illustrates an approach to diagnosing iron deficiency and IDA. As described in Table III, care must be taken when interpreting tests of iron status because they can be influenced by multiple factors. It is especially important to consider iron ingestion. Iron ingestion may cause an increase in serum iron concentration and transferrin saturation.³ Serum ferritin concentration is related to iron stores and can also be elevated with iron ingestion.¹¹ Hemoglobin concentration and hematocrit also increase with iron supplementation in patients with IDA, but this occurs over several weeks.²

Initial tests should include at least a CBC and ferritin with or without TIBC, serum iron, and transferrin saturation. If the hemoglobin concentration and hematocrit are normal, then the patient does not have anemia. If the ferritin is normal, then the patient is iron replete. What constitutes “normal” or “low” ferritin is controversial. Many laboratories use serum ferritin concentrations of 10 to 15 ng/mL (sensitivity of 59% and specificity of 99% for diagnosing iron deficiency) as the lower limits of normal based on reference sample groups. A cutoff point of 30 ng/mL yields a sensitivity of 92% and a specificity of 98%, whereas a cutoff point of 41 ng/mL yields a sensitivity of 98% and a specificity of 98%.¹¹

If the hemoglobin concentration and hematocrit are normal and the ferritin concentration is low, then

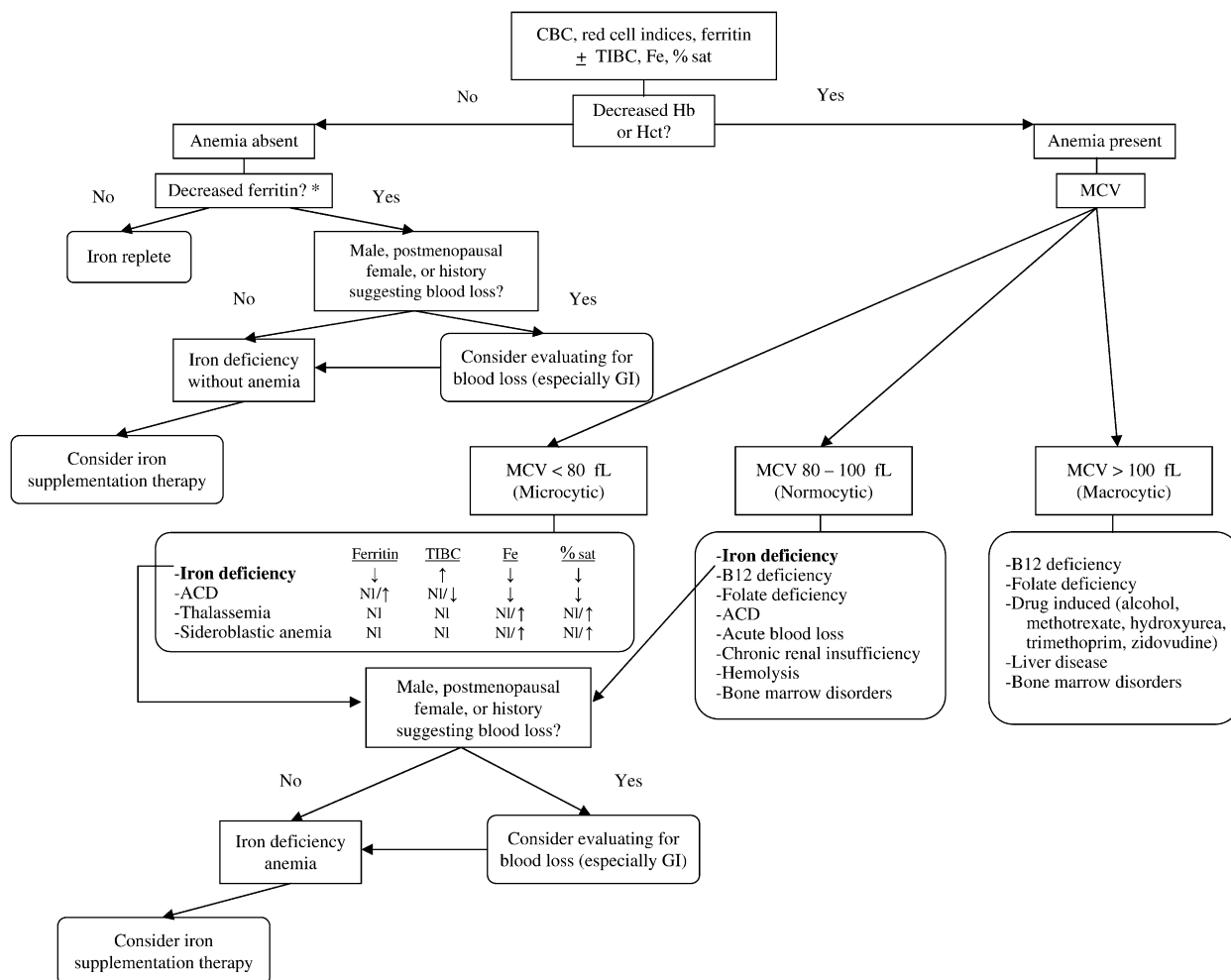


Fig 1. Approach to diagnosing iron deficiency and iron deficiency anemia.^{2,9,11,14,16,19,20}

% sat, transferrin saturation; ACD, anemia of chronic disease; CBC, complete blood count; Fe, serum iron concentration; GI, gastrointestinal; Hb, hemoglobin concentration; Hct, hematocrit; MCV, mean corpuscular volume; NI, normal; TIBC, total iron binding capacity.

*Lower of limit of serum ferritin concentration is 40 ng/mL (see text for discussion) or 10 to 15 ng/mL using most laboratory reference intervals.

Table on microcytic anemia modified with the permission of the McGraw-Hill Companies from Table 90-4, Adamson, JW. Iron deficiency and other hypoproliferative anemias. In: Kasper, DL, Braunwald, E, Fauci, AS, Hauser, SL, Longo, DL and Jameson, JL, eds. Harrison's principles of internal medicine, 16th ed. New York: McGraw-Hill, 2005. p. 586-92.

the patient has iron deficiency without anemia. If the patient is male, postmenopausal female, or has risk factors for blood loss, then the patient may be evaluated for sources of blood loss, especially from the gastrointestinal tract (eg, colon cancer). Table II shows other causes of blood loss.^{2,11}

If the hemoglobin concentration and hematocrit are decreased, then the patient has anemia. Anemia can then be classified according to the average size of the red blood cells, also known as the mean corpuscular volume (MCV). The normal MCV is approximately 80 to 100 fL (or 10⁻¹⁵ L). If the MCV is greater than 100 fL, then the anemia is macrocytic.

If the MCV is 80 to 100 fL, then the anemia is normocytic. If the MCV is less than 80 fL, then the anemia is microcytic. IDA is usually a microcytic anemia, although it can be normocytic. If other conditions that can make red blood cells macrocytic are present in addition to iron deficiency, then the anemia may be normocytic.¹⁹ If the patient has IDA and is male, postmenopausal female, or has risk factors for blood loss, then the patient should be evaluated for sources of blood loss.^{2,11}

Macrocytic anemia. Macrocytic anemias are most commonly caused by vitamin B₁₂ and folate deficiencies. Macrocytic anemias can also be

associated with drugs (alcohol, methotrexate, hydroxyurea, trimethoprim, zidovudine), liver disease, and bone marrow disorders. A workup should begin with serum vitamin B₁₂ and folate levels.²⁰ Additional workup may require white blood cell count and differential, peripheral smear, reticulocyte count, liver function tests, and possible bone marrow biopsy.²⁰

Normocytic anemia. Normocytic anemias are commonly due to nutritional deficiencies, including iron, vitamin B₁₂, and folate. Although iron deficiency is normally associated with microcytic anemia and vitamin B₁₂ and folate deficiencies are normally associated with macrocytic anemia, all three can also be found in normocytic anemia. Other causes of normocytic anemia include anemia of chronic disease (also associated with microcytic anemia), acute blood loss, chronic renal insufficiency, hemolysis, and bone marrow disorders. In addition to evaluating for iron deficiency, a workup should begin with serum vitamin B₁₂ and folate levels.^{19,20} Additional workup may require white blood cell count and differential, peripheral smear, reticulocyte count, hemolysis panel (lactate dehydrogenase, haptoglobin, conjugated and unconjugated bilirubin), renal function tests, and possible bone marrow biopsy.^{19,20}

Microcytic anemia. Microcytic anemias are associated with IDA, anemia of chronic disease, thalassemias, and sideroblastic anemia. Of these, IDA is the most common and in many cases can be confirmed with a low serum ferritin alone.²⁰ In cases in which history and physical examination suggest other causes of microcytic anemia, other tests may be ordered. These most commonly include TIBC, serum iron, and transferrin saturation.¹⁶

IDA can also be associated with normocytic anemias. It is associated with low serum ferritin concentration, increased TIBC, and decreased serum iron and transferrin saturation. The most common diagnostic challenge is distinguishing IDA from anemia of chronic disease.¹⁶

Anemia of chronic disease is the second most common anemia after IDA.¹⁴ Classically, anemia of chronic disease is found in patients with infectious, inflammatory, and neoplastic conditions.²¹ Infectious conditions include those due to viruses (including HIV), bacteria, parasites, and fungi. Inflammatory conditions include rheumatoid arthritis, systemic lupus erythematosus, as well as connective-tissue diseases, vasculitis, sarcoidosis, and inflammatory bowel disease. Neoplastic conditions include both hematologic and solid organ malignancies. Patients with chronic rejection after solid-organ transplantation as well as chronic kidney disease have been reported to have anemia of chronic disease.¹⁴ Actual total body storage iron is normal or increased in

anemia of chronic disease.²¹ The pathogenesis of anemia of chronic disease is still unclear but appears to be related to sequestration of iron into cells of the reticuloendothelial system and decreased utilization of this iron for hemoglobin synthesis, decreased red blood cell survival,²¹ impaired erythropoiesis, and blunted erythropoietin response to anemia.¹⁴

Anemia of chronic disease is associated with normal to increased serum ferritin concentration, normal to decreased TIBC, and decreased serum iron and transferrin saturation.¹⁴ Often, it may be unclear as to whether IDA is present in addition to anemia of chronic disease. Serum ferritin concentrations less than 50 ng/mL probably indicate IDA in the setting of anemia of chronic disease, whereas serum ferritin concentrations above 50 ng/mL make IDA unlikely.²¹ Others cite using a cutoff point for serum ferritin concentration of 60 ng/mL¹¹ or 100 ng/mL to exclude IDA in the presence of anemia of chronic disease.^{12,14}

Some laboratories can measure the soluble transferrin receptor (sTfR) concentration. The sTfR concentration is normal in anemia of chronic disease but is increased in IDA. In concomitant anemia of chronic disease and IDA, sTfR is normal to increased. The sTfR divided by the logarithm of the serum ferritin concentration (sTfR/log ferritin) can be useful in determining whether IDA is present in patients with anemia of chronic disease. If the sTfR/log ferritin is less than 1, then IDA is unlikely. If the sTfR/log ferritin is greater than 2, then the patient is likely to have IDA, even if she or he has anemia of chronic disease.¹⁴

Thalassemias are rare causes of microcytic anemias. Thalassemias involve either production of structurally abnormal globin chains (globin chains are subunits of hemoglobin) or decreased production of one or more normal globin chains.²⁰ Thalassemias are associated with normal serum ferritin concentration, normal TIBC, and normal to increased serum iron and transferrin saturation.¹⁶ Definitive diagnosis usually involves hemoglobin electrophoresis and possible genetic testing, including polymerase chain reaction–based DNA tests and Southern blot analysis.²⁰

Sideroblastic anemia is a rare cause of microcytic anemia that involves impaired hemoglobin synthesis. The term “sideroblastic anemia” refers to the ringed sideroblasts seen on bone marrow iron staining. Ringed sideroblasts are formed when iron is loaded into the mitochondria but cannot be incorporated into heme because of mitochondrial dysfunction, often due to myelodysplasia.⁹ Myelodysplasia, frequently caused by exposure to radiation, benzene, and cancer therapy (eg, radiation and radiomimetic alkylating agents such as busulfan, nitrosourea, and

procarbazine as well as DNA topoisomerase inhibitors), is a disorder of clonal hematopoietic stem cells commonly involving mutations of genes that control the cell cycle.²² Proliferation and differentiation of these stem cells are impaired. Sideroblastic anemia is associated with normal serum ferritin concentration, normal TIBC, and normal to increased serum iron and transferrin saturation.¹⁶ As stated previously, bone marrow biopsy often shows ringed sideroblasts.²⁰

THE RELATIONSHIP BETWEEN IRON DEFICIENCY AND HAIR LOSS

The relationship between iron deficiency and hair loss has been examined in several studies, some of which suggest that iron deficiency even in the absence of IDA may be associated with certain kinds of hair loss. Almost all of these studies have addressed women exclusively and have focused on noncicatricial hair loss. Many of these studies have different definitions of iron deficiency and IDA. Table IV provides an overview of these studies and their methodologies and definitions.

Alopecia areata

In a case-control study of 106 female subjects 18 to 70 years of age presenting with alopecia, the 17 subjects with alopecia areata (AA) had a significantly decreased serum ferritin concentrations compared with 11 female control subjects without common mutations in the *HFE-1* gene for hereditary hemochromatosis (24.9 vs 59.5 ng/mL, respectively; $P < .05$). The mean hemoglobin concentrations between the two groups did not differ. In a comparison of subgroups 40 years of age or younger (11 AA subjects vs 6 controls), the mean serum ferritin concentration was still lower in the AA subgroup compared with controls (23.3 vs 62.3 ng/mL, respectively; $P < .05$). In this age range, the mean hemoglobin concentrations between the two groups did not differ. However, 7 patients with alopecia totalis/alopecia universalis (classified separately from the AA patients) did not have a significant difference in either serum ferritin or hemoglobin concentrations compared with controls.²³

One cross-sectional study examined 21 women aged 18 to 72 years and 11 men aged 31 to 57 years who presented with AA. Of the female subjects, none had IDA and 24% had iron deficiency. The prevalence of iron deficiency in the female group was stated as being comparable to that expected in an apparently normal population, although no statistical comparison was reported. None of the male subjects had IDA or iron deficiency.²⁴

Another cross-sectional study examined 21 female subjects aged 6 to 63 years and 9 male subjects

aged 3 to 41 years who presented with AA. Of the female subjects, 14% had IDA and 71% had iron deficiency. The authors stated that there was an apparent increase in incidence of iron deficiency in the female group compared with a population-based study from Denmark, although no statistical comparison was reported. None of the male subjects had IDA or iron deficiency.²⁵

Androgenetic alopecia

In a case-control study of 106 female subjects aged 18 to 79 years and presenting with alopecia, the 52 subjects with androgenetic alopecia (AGA) had a significantly decreased serum ferritin concentration compared with 11 female control subjects without common mutations in the *HFE-1* gene for hereditary hemochromatosis (37.3 vs 59.5 ng/mL, respectively; $P < .05$). The mean hemoglobin concentrations between the two groups did not differ. In a comparison of subgroups with subjects who were 40 years of age or younger (16 AGA subjects vs 6 controls), the mean serum ferritin concentration was still lower in the AGA subgroup compared with controls (23.8 vs 62.3 ng/mL, respectively; $P < .05$). In this age range, the mean hemoglobin concentrations between the two groups did not differ.²³

A prospective cohort study of 194 female subjects aged 11 to 72 years presenting with diffuse telogen hair loss that had been present for 6 months or longer found that 12 subjects (6%) had serum ferritin concentrations less than or equal to 20 ng/mL. All of them had normal hemoglobin concentrations. Seven of these 12 patients had AGA as confirmed by histology. The AGA patients were treated with spironolactone 200 mg daily as well as iron supplementation (dose not specified) for 3 to 6 months until their serum ferritin concentrations rose to above 20 ng/mL. Four of the 7 AGA subjects had reduction of hair shedding and an increase in hair volume, whereas 3 subjects showed no improvement. The response rate of patients with AGA and serum ferritin concentrations less than or equal to 20 ng/mL were said to be similar to the response rate of the 108 patients with AGA and normal iron stores who were treated with spironolactone alone (no statistical analysis performed—cited as an unpublished observation).²⁶

Another case-control study by Aydingoz, Ferhanoglu, and Guney²⁷ compared 10 female subjects (mean age, 32 years) with female pattern alopecia (FPA—synonymous with AGA in this study), 33 patients with diffuse alopecia (defined in this study to be a variant of AGA), and 46 healthy control subjects. The study found no difference in the prevalence of depleted iron stores or in the prevalence of IDA in

Table IV. Studies examining the relationship between iron deficiency and alopecia

Study	Type of alopecia	Study classification	Study subjects	Results	Comments
Kantor, et al ²³ (2003)	AA, AT, AU, AGA, TE	Case-control study	<ul style="list-style-type: none"> Total alopecia subjects: n = 106 (all female) ages 18-79 y AA: n = 17 AT/AU: n = 7 TE: n = 30 AGA: n = 52 Controls: n = 11 (all female) ages 24-52 y Control criteria: females without common mutations in <i>HFE-1</i> gene for hereditary hemochromatosis 	<ul style="list-style-type: none"> All alopecia subgroups did not have different Hb concentrations compared with controls In AA and AGA groups, mean serum ferritin concentrations (24.9 and 37.3 ng/mL, respectively) were significantly lower than in controls (59.5 ng/mL, $P < .05$) In TE and AT/AU groups, mean serum ferritin concentrations (50.1 and 52.3 ng/mL, respectively) did not differ from controls In pts with AA, TE, and AGA (n = 11, 4, and 16, respectively) who were ≤ 40 y of age, mean serum ferritin concentrations (23.3, 15.0, and 23.8 ng/mL, respectively) were significantly lower than in controls (n = 6, serum ferritin concentration = 62.3 ng/mL, $P < .05$) In pts with TE (n = 4) who were ≤ 40 y of age, Hb (12.0 g/dL) was significantly lower than in controls (n = 6, Hb = 13.8 g/dL, $P < .05$) 	<ul style="list-style-type: none"> Statistical analysis: <i>t</i> test with α correction, one-sided <i>P</i> values
Rushton ³⁰ (2002)	CTE	Double-blind placebo- controlled study	<ul style="list-style-type: none"> Total alopecia subjects: n = 12 (all female) Controls: n = 5/12 (all female) Ages not reported Control criteria: selection criteria were not stated 	<ul style="list-style-type: none"> 7 subjects received 72 mg iron and 1.5 g L-lysine daily for 6 mo 5 subjects received placebo Subjects receiving therapy experienced significant mean serum ferritin concentration increase from 41.3 to 68.9 ng/mL ($P < .05$), whereas controls had mean serum ferritin concentration increase from 26.0 to 28.4 ng/mL (NSS) Subjects receiving therapy experienced 31% reduction in amount of hair shed compared with 9% increase in controls (<i>P</i> value not reported) 	<ul style="list-style-type: none"> Statistical analysis: student <i>t</i> test (paired samples)

Rushton et al ³¹ CTE (2002)	Prospective cohort	<ul style="list-style-type: none"> • Total alopecia subjects: n = 22 (all female) • Ages not reported • Controls: none 	<ul style="list-style-type: none"> • All subjects received 72 mg iron and 1.5 g L-lysine daily for 6 mo • Mean percentage hair in the telogen phase significantly decreased from 19.5% to 11.3% ($P < .0001$) • Mean serum ferritin concentrations significantly increased from 33 to 89 ng/mL ($P < .0001$) 	<ul style="list-style-type: none"> • Statistical analysis: <ol style="list-style-type: none"> 1) Wilcoxon signed rank test (paired samples) for hair in telogen phase 2) Student <i>t</i> test (paired samples) for serum ferritin concentration
Rushton et al ³¹ CTE (2002)	Cross-sectional study	<ul style="list-style-type: none"> • Total alopecia subjects: n = 200 (all female) • Ages not reported • Control criteria: referred to standard reference ranges and definitions (see Results section) 	<ul style="list-style-type: none"> • 65% had serum ferritin concentration <40 ng/mL (lower limit of normal for males) • 95% had serum ferritin concentration <70 ng/mL (upper 99% confidence limit for iron staining in bone marrow—indicative of being iron replete) 	<ul style="list-style-type: none"> • Statistical analysis: calculation of percentage
Sinclair ²⁶ (2002)	AGA, CTE, DTHL Prospective cohort	<ul style="list-style-type: none"> • Total alopecia subjects: n = 194 with DTHL of ≥ 6 mo duration (all female) ages 11-72 y • Controls: none 	<ul style="list-style-type: none"> • 117/194 (60%) had AGA by histology • 12/194 (6%) had serum ferritin ≤ 20 ng/mL <ul style="list-style-type: none"> -All 12 pts had normal Hb concentrations -7/12 had AGA, 3/12 had CTE, 2 were indeterminate • All 12 pts given iron supplementation (dose not specified) for 3-6 mo until serum ferritin >20 ng/mL <ul style="list-style-type: none"> -AGA pts treated with spironolactone 200 mg/d -All 12 pts' serum ferritin concentrations rose to >20 ng/mL -4/7 AGA pts had reduction of hair shedding and increase in hair volume -3/7 AGA pts, 3/3 CTE pts, and 2/2 indeterminate pts had no improvement • Response rate of pts with AGA and serum ferritin ≤ 20 ng/mL were similar to response rates of 108 pts with AGA and normal iron stores who were treated with spironolactone (no statistical analysis reported) 	<ul style="list-style-type: none"> • Statistical analysis: none • All pts had two 4-mm biopsy specimens taken from vertex of scalp • One biopsy sectioned horizontally; if ratio of vellus to terminal hair <1:4, then diagnosed with AGA

Continued

Table IV. Cont'd

Study	Type of alopecia	Study classification	Study subjects	Results	Comments
Aydingoz et al ²⁷ (1999)	DA, FPA*	Case-control study	<ul style="list-style-type: none"> • DA: n = 33 (all female), mean age 24 y • FPA: n = 10 (all female) mean age 32 y • Controls: n = 46 (ages not reported) • Control criteria: healthy subjects (criteria not stated) 	<ul style="list-style-type: none"> • No significant difference in prevalence of depleted iron stores found in total subjects vs controls (32.5% vs 45.6%, respectively; $P = .61$, Kruskal-Wallis method—did not report statistical analysis of DA and FPA groups separately) • No significant difference in prevalence of IDA found in total subjects vs controls (16.2% vs 21.7%, respectively, $P > .05$, chi-square method—did not report statistical analysis of DA and FPA groups separately) 	<ul style="list-style-type: none"> • Statistical analysis: see Results section • IDA: serum ferritin <15 ng/mL and Hb <12 g/dL • Depleted iron stores: serum ferritin <15 ng/mL • Reduced iron stores: serum ferritin 15-30 ng/mL • Normal iron stores: serum ferritin >30 ng/mL
Boffa, Wood, and Griffiths ²⁴ (1995)	AA	Cross-sectional study	<ul style="list-style-type: none"> • Total alopecia subjects: n = 32 (21 women ages 18-72 y, 11 men ages 31-57 y) • Controls: none 	<ul style="list-style-type: none"> • Women: none had IDA; 5/21 (24%) had ID -Prevalence of ID in these patients reported as being comparable to that expected in an apparently normal population (no direct statistical comparison reported) • Men: none had IDA or ID 	<ul style="list-style-type: none"> • Statistical analysis: no formal analysis • IDA: ID and low Hb: women: Hb <12 g/dL, men: Hb <13 g/dL • ID: serum ferritin <15 ng/mL
White, Currie, and Williams ²⁵ (1994)	AA	Cross-sectional study	<ul style="list-style-type: none"> • Total alopecia subjects: n = 30 (21 females ages 6-63 y, 9 males ages 3-41 y) • Controls: none 	<ul style="list-style-type: none"> • Women: 3/21 (14%) had IDA, 15/21 (71%) had ID -When compared with population-based study from Denmark, appeared to be increased incidence of ID in AA patients (no direct statistical comparison reported) • Men: none had IDA or ID 	<ul style="list-style-type: none"> • Statistical analysis: no formal analysis • Used hematologist's assessment to describe IDA/ID; did not specify exact criteria • 2 pts (1 male, 1 female) younger than 10 y
Rushton and Ramsey ²⁸ (1992)	DAGA	Prospective controlled study	<ul style="list-style-type: none"> • Total alopecia subjects: n = 40 (all female) premenopausal subjects with DAGA, ages 18-47 y 	<ul style="list-style-type: none"> • 20 subjects were treated with CPA-EE₂ for 12 mo, 20 untreated (controls) 	<ul style="list-style-type: none"> • Statistical analysis: Wilcoxon signed rank test

			<ul style="list-style-type: none"> • Controls: n = 20 (all female) ages 22-42 y • Control criteria: same selection criteria as treatment group 	<p>-In each group, 10 had serum ferritin >40 ng/mL and 10 had serum ferritin ≤40 ng/mL</p> <ul style="list-style-type: none"> • Subjects treated with CPA-EE₂ with serum ferritin >40 ng/mL had significant mean increases in mean total (<i>P</i> < .01) and meaningful hair densities (<i>P</i> < .01) • Treated patients with serum ferritin <40 ng/mL did not have significant change in mean total and meaningful hair densities • The control group had significant decrease in mean total (<i>P</i> < .05) and meaningful hair densities (<i>P</i> < .05) <p>-In the control group, no correlation between serum ferritin concentration and hair loss was found</p>	<ul style="list-style-type: none"> • All pts with serum ferritin <40 ng/mL had Hb >11.0 g/dL
<p>Rushton, Ramsay, and James²⁹ (1990)</p>	<p>DA[†]</p>	<p>Case-control study</p>	<ul style="list-style-type: none"> • Total alopecia subjects: n = 100 (all female) premenopausal subjects with DA ages 14-54 y • Controls: n = 20 (all female) ages 17-49 y (see Results section) • Control criteria: regular menstrual cycles, unaware of increased hair shedding or changes in hair quality or quantity during previous 2 y; no illnesses longer than 7 days, menstrual irregularities, gynecological disturbances, or current pregnancy; no oral contraceptives in past 6 mo; never sought medical advice for acne, hirsutism, or scalp hair problems 	<ul style="list-style-type: none"> • 100 premenopausal females selected; of these, 50 consecutive females selected for biochemical and hematological investigation • 20 female controls selected; of these, 10 selected for biochemical and hematological investigation • 36/50 (72%) of tested pts had serum ferritin concentrations below that of lowest control subject (40 ng/mL) 	<ul style="list-style-type: none"> • Statistical analysis: calculation of percentage

Continued

Table IV. Cont'd

Study	Type of alopecia	Study classification	Study subjects	Results	Comments
Hard ³² (1963)	DH	Cross-sectional, followed by prospective cohort	<ul style="list-style-type: none"> Total alopecia pts: n = 96 (all female) ages 3-75 y Controls: none 	<ul style="list-style-type: none"> Of 140 females with DH, 96 selected who had no skin disease to account for hair loss 18/96 (18.8%) had ID without anemia <ul style="list-style-type: none"> -All 18 pts with ID without anemia were given oral iron supplementation therapy (37-40 mg elemental iron 1 to 2 tablets 3 times daily) and were followed up between 2 mo and 2 y -In all 18 pts, hair loss ceased, and regrowth observed -In all 18 pts, serum iron levels rose to normal levels 	<ul style="list-style-type: none"> Statistical analysis: no formal analysis IDA: Hb <11 gram percent (Hb assayed for iron by cyanmethemoglobin determination) ID: serum iron below 60 gamma percent (serum iron analysis by method of Agner)

AGA, Androgenetic alopecia; AT, alopecia totalis; AU, alopecia universalis; CPA-EE₂, cyproterone acetate–ethinyl estradiol; CTE, chronic telogen effluvium; DA, diffuse alopecia; DAGA, diffuse androgenetic alopecia; DH, diffuse hair loss; DNPA, diffuse nonpatterned alopecia; DTHL, diffuse telogen hair loss; FPA, female pattern alopecia; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; NSS, not statistically significant; pts, patients; TE, telogen effluvium.

*DA was defined in this study as a variant of AGA; FPA was synonymous with AGA.

†DA in this study was synonymous with AGA.

hair loss subjects compared with control subjects. Table IV presents definitions and statistical methods. Statistical analyses of FPA and DA groups were not reported separately.²⁷

In a prospective controlled study, Rushton and Ramsay²⁸ studied 40 premenopausal female subjects aged 18 to 47 years with diffuse AGA. Twenty were treated with cyproterone acetate-ethinyl estradiol for 12 months, whereas the other 20 served as the control group. In both the treatment and control groups, half had serum ferritin concentrations greater than 40 ng/mL, and all had hemoglobin concentrations greater than 11.0 g/dL. A significant increase in mean total hair density ($P < .01$) and meaningful hair densities ($P < .01$) were found in patients in the treatment group with serum ferritin concentrations above 40 ng/mL. Treated patients with serum ferritin concentrations less than or equal to 40 ng/mL did not have a significant change in mean total and meaningful hair densities. The control group had a significant decrease in mean total density ($P < .05$) and meaningful hair densities ($P < .05$). In addition, no correlation between serum ferritin concentration and hair loss was found in the control group.²⁸

Rushton et al²⁹ studied 100 premenopausal female subjects aged 14 to 54 years who presented with diffuse alopecia (synonymous with AGA in this study) and 20 control subjects aged 17 to 49 years. Of these, 50 consecutive subjects were selected for biochemical and hematologic investigation. Thirty-six of these 50 patients (72%) had serum ferritin concentrations below that of the lowest control (40 ng/mL).²⁹

Telogen effluvium and chronic telogen effluvium

In a case-control study of 106 female subjects aged 18 to 79 years presenting with alopecia, the 30 subjects with telogen effluvium (TE) did not have a significantly decreased serum ferritin concentration compared with 11 female control subjects without common mutations in the *HFE-1* gene for hereditary hemochromatosis (50.1 versus 59.5 ng/mL, respectively). The mean hemoglobin concentrations between the two groups did not differ either. In a comparison of subgroups 40 years of age or younger (4 TE subjects vs 6 controls), the mean serum ferritin concentration was lower in the TE subgroup compared with the control group (15.0 vs 62.3 ng/mL, respectively; $P < .05$). In this age range, the mean hemoglobin concentration was also lower in the TE subgroup compared with controls (12.0 vs 13.8 g/dL, respectively; $P < .05$).²³

In a prospective double-blind, placebo-controlled study of 12 female subjects with chronic telogen

effluvium (CTE), 7 subjects received 72 mg of iron and 1.5 g of L-lysine daily for 6 months, whereas 5 subjects received placebo. Subjects receiving therapy experienced a mean serum ferritin concentration increase from 41.3 to 68.9 ng/mL ($P < .05$), whereas control subjects had a mean serum ferritin concentration increase from 26.0 to 28.4 ng/mL (not statistically significant). In addition, subjects receiving therapy experienced a 31% reduction in amount of hair shed compared with a 9% increase in control subjects (P value not reported). The age ranges were not reported.³⁰

Rushton et al³¹ followed 22 female subjects with CTE (age ranges not reported) after giving them supplementation with 72 mg of iron and 1.5 g of L-lysine daily for 6 months in a prospective cohort study. The mean percentage of hair in the telogen phase significantly decreased from 19.5% to 11.3% ($P < .0001$), and the mean serum ferritin concentration significantly increased from 33 to 89 ng/mL ($P < .0001$).³¹

A cross-sectional study by Rushton et al³¹ of 200 female patients with CTE (age ranges not reported) showed that 65% had serum ferritin concentrations less than 40 ng/mL and that 95% had serum ferritin concentrations less than 70 ng/mL. Interestingly, it was noted that 40 ng/mL is the lower limit of normal for males and that 70 ng/mL is the upper 99% confidence limit for iron staining in the bone marrow, an indication of being iron replete.³¹

A prospective cohort study of 194 female subjects aged 11 to 72 years presenting with diffuse telogen hair loss for 6 months or longer found that 12 (6%) had serum ferritin concentrations less than or equal to 20 ng/mL (mentioned above). All of them had normal hemoglobin concentrations. Three of these 12 patients had CTE. These three CTE subjects were treated with iron supplementation (dose not specified) for 3 to 6 months until their serum ferritin concentrations rose to above 20 ng/mL. None of these patients noted a change in hair status after treatment. There was no control group.²⁶

Diffuse hair loss

In 1963, Hard³² described a series of 140 female patients aged 3 to 75 years presenting with diffuse hair loss, 96 of whom had no "appreciable skin disease to account for the hair loss." Of these 96, 18 (18.8%) had iron deficiency without anemia. All 18 patients with iron deficiency without anemia were given oral iron supplementation therapy (37-40 mg elemental iron 1 to 2 tablets 3 times daily) and were followed up between 2 months and 2 years. In all 18 patients, hair loss ceased, hair regrowth was observed, and serum iron levels rose to normal

Table V. Recommended dietary allowances for iron*

Age (y)	Males		Females	
	Omnivore	Vegetarian/ vegan	Omnivore	Vegetarian/ vegan
14-18	11	20	15	27
19-50	8	14	18	33
≥ 51	8	14	8	14

*Units for iron are shown in milligrams per day. Note that the iron requirements for vegetarians and vegans are roughly 1.8 times higher than omnivores because of the bioavailability of ingested iron.³⁴

levels. IDA was defined to be hemoglobin less than 11 gram per cent (hemoglobin was assayed for iron by cyanmethemoglobin determination), and iron deficiency was defined to be serum iron below 60 gamma per cent (serum iron analysis by method of Agner).

Mechanism by which reduced iron stores may affect hair loss

The mechanism by which reduced iron stores affect hair loss is not known. Iron is a known cofactor for ribonucleotide reductase, the rate-limiting enzyme for the synthesis of DNA. Hair follicle matrix cells are among the most rapidly dividing cells in the body and may be exquisitely sensitive even to a minor decrease in iron availability, thus resulting in diminished hair growth in the presence of iron deficiency.^{23,33}

Summary

Of the studies that have examined the relationship between iron deficiency and hair loss, almost all have addressed women exclusively and have focused on noncicatricial hair loss. Some suggest that iron deficiency may be related to AA, AGA, TE, and diffuse hair loss, whereas others do not. Currently, there is insufficient evidence to recommend universal screening for iron deficiency in patients with hair loss. In addition, there is insufficient evidence to recommend giving iron supplementation therapy to patients with alopecia and iron deficiency in the absence of IDA. The decision to do either should be based on clinical judgment.

TREATMENT

Primary prevention through diet

Primary prevention of iron deficiency is achieved through proper dietary iron intake. Table V presents the RDAs for iron. It should be noted that the iron requirements for vegetarians and vegans are approximately 1.8 times higher than for omnivores because

of the bioavailability of ingested iron (see below).³⁴ Information on how to achieve sufficient dietary iron can be found in "Nutrition and Your Health: Dietary Guidelines for Americans."³⁵ Lean meats, especially beef, have high iron contents that are highly bioavailable. Nonanimal foods that are high in iron include nuts, seeds, legumes, bean products, raisins, dark green leafy vegetables, whole grains, and iron fortified cereals (Appendix).^{36,37}

Absorption and bioavailability

Heme iron, found in meat, poultry, and fish, has a bioavailability of approximately 30% (ie, 30% of ingested heme iron is absorbed). Non-heme iron, found in plants and iron-fortified foods, has a bioavailability of less than 10%.³⁸ Iron in food is mostly ferric iron and is most soluble and best absorbed below a pH of 3. Ferrous iron, found in oral iron supplements, is soluble even at a pH of 7 to 8 and is more easily absorbed.³⁸ This may be important in patients with altered gastric environments such as achlorhydria (commonly affecting the elderly), gastric atrophy, and *Helicobacter pylori* infection.¹⁷

Enhancers of iron absorption include heme and ascorbic acid or vitamin C (found in broccoli, cauliflower, and many fruits). Tannins (found in tea and coffee), phytates (found in bran, cereal grains, flour, legumes, nuts, and seeds), and calcium (found in dairy products and many over-the-counter antacids) all inhibit iron absorption. Strategies to enhance iron absorption include drinking tea and coffee 1 to 2 hours after, rather than with, a meal; eating foods with high vitamin C content during meals; consuming dairy products as snacks rather than during meals; and eating foods containing inhibitors during meals with lowest iron content.³⁹

Treating iron deficiency and IDA

The need to treat IDA is well accepted.^{2,16,17,40} However, treating iron deficiency in the absence of anemia is controversial. The CDC currently does not recommend treating iron deficiency in the absence of anemia.² Iron deficiency without anemia can be associated with delayed cognitive development in children and adolescents and may respond to iron therapy. Iron deficiency without anemia may also be associated with reduced work capacity.¹⁷

Iron supplementation therapy. Iron can be supplemented orally, intramuscularly, and intravenously. Blood transfusions are sometimes required in severe cases.⁴⁰

Many oral iron preparations are available, both in tablet and elixir form. These include ferrous sulfate, ferrous fumarate, and ferrous gluconate. Extended-release, carbonyl iron, and polysaccharide-iron complex

formulations are also available. Table VI shows the elemental iron content of each preparation.⁴¹

The ferrous salts, including ferrous sulfate, ferrous fumarate, and ferrous gluconate, are all equally tolerated and effective.^{6,42} Of these, ferrous sulfate is the cheapest and is widely recommended as first-line therapy.^{6,17,40,42} Ferrous salts should be given on an empty stomach and should not be given within 2 hours of any inhibitor of iron absorption (see "Absorption and bioavailability" above).^{16,40} Some authors recommend taking ascorbic acid, 250 mg, along with ferrous salts to enhance absorption.⁴⁰

The most common complication of oral ferrous salt therapy is gastrointestinal upset, including abdominal pain, nausea, vomiting, and constipation. This can occur in 15% to 20% of patients receiving oral iron therapy.¹⁶ Alternatives include using extended-release iron preparations,⁴² liquid iron preparations,^{6,40} ferrous salts with lower elemental iron contents,⁴⁰ and taking iron tablets with meals.¹⁷

Although the CDC recommends prescribing 60 to 120 mg/d of elemental iron,² many authors recommend higher starting dosages, usually ferrous sulfate 300 mg (60 mg elemental iron) 3 to 4 times daily.^{16,17,40} Elemental iron ingested at 200 to 300 mg/d will result in iron absorption of approximately 50 mg/d.¹⁶

Iron can also be given parenterally, that is, as intramuscular (IM) and intravenous (IV) preparations. Both may be appropriate for patients who cannot tolerate oral iron as well as for patients with severe gastrointestinal bleeding, malabsorption, or both. Parenteral iron is available as iron dextran (IM or IV), ferric gluconate complex (IV), and iron sucrose (IV). Side effects of parenteral iron include local reactions (pain, muscle necrosis, and phlebitis) as well as anaphylaxis, fever, urticaria, and flare of rheumatoid arthritis.^{16,40} Advanced methods of maintaining iron balance such as using recombinant human erythropoietin along with parenteral iron therapy is usually used in patients with renal failure. We refer the reader to an excellent review on the subject.⁴³

Monitoring iron status and duration of therapy. At a minimum, the hemoglobin concentration should be checked 3 to 4 weeks after beginning oral iron supplementation therapy. If a patient with IDA takes ferrous sulfate 300 mg (60 mg elemental iron) 3 to 4 times daily, the hemoglobin concentration should rise approximately 2 g/dL after 3 to 4 weeks.^{6,40} If the rise in hemoglobin concentration is less, this may be due to poor compliance, misdiagnosis, malabsorption,⁶ coexisting cause of anemia in addition to IDA (eg, anemia of chronic disease, thalassemia), or continued blood loss.⁴⁰

If there is an appropriate response in hemoglobin concentration after 1 month, oral iron supplementation

Table VI. Selected oral iron supplements⁴¹

Class	Dose (elemental iron content), mg
Ferrous salts	
Ferrous sulfate	
Tablets (generic)	325 (65) 300 (60) 195 (39)
Solution (generic)	220 (44) per 5 mL 125 (25) per 1 mL
Dried	200 (65) Feosol*
Extended release	160 (50) Slow FE*
Ferrous fumarate	
Tablets (generic)	325 (107) 324 (106)
Ferrous gluconate	
Tablets (generic)	325 (38) 320 (37)
Carbonyl iron	
Tablets	45 (45) Feosol Caplets*
Suspension	15 (15) per 1.25 mL Icar Pediatric*
Polysaccharide-iron complex	
Tablets, film-coated	50 (50) Niferex*
Capsules	150 (150) Ferrex-150,* Fe-Tinic 150,* Hytanic,* Niferex- 150* (with benzyl alcohol and parabens)
Solution	100 (100) per 5 mL Niferex Elixir* (with alcohol 10%)

*Feosol, Feosol Caplets, GlaxoSmithKline, Pittsburgh, Pa; Slow FE, Novartis Consumer Health, Parsippany, NJ; Icar Pediatric, Hawthorne Pharmaceuticals, Madison, Miss; Nefirex, Niferex-150, Ther-Rx, Earth City, Mo; Ferrex-150, Breckenridge, Boca Raton, Fla; Fe-Tinic 150, Ethex, St. Louis, Mo; Hytanic, Hyrex Pharmaceuticals, Memphis, Tenn; Niferex Elixir: Schwarz Pharma, Milwaukee, Wis. Modified from "Iron preparations, oral." In: McEvoy GK, editor. AHFS (American Hospital Formulary Service) drug information 2005. Bethesda (MD): American Society of Health-System Pharmacists, Inc; 2005. p. 1403. With permission of the American Society of Health-System-Pharmacists.

should be continued until the hemoglobin concentration normalizes. This will depend on the degree of anemia and the rate of response to therapy. For patients who are at risk for or have had gastrointestinal bleeding, some authors recommend stopping iron supplementation once the hemoglobin concentration has normalized so that if there is further occult bleeding, this will cause IDA and can be quickly detected.⁴⁰ Others recommend continuing therapy until iron stores are replenished. This can take from 3^{6,17} to 6 months.^{16,40}

Reevaluating for iron deficiency after completion of therapy. In premenopausal women, a history of IDA is a risk factor for future iron deficiency. The 1998 CDC guidelines recommend annual screening of premenopausal women with risk factors for iron deficiency.² Therefore yearly reevaluation is a reasonable option for these patients.

The 1998 CDC guidelines do not make specific recommendations for reevaluating men and postmenopausal women who have had iron deficiency or IDA.² Further monitoring should be based on clinical judgment and the underlying cause of iron deficiency or IDA.

IRON OVERLOAD

One of the most important potential side effects of iron supplementation is iron overload.¹ The mechanism of iron toxicity involves the production of free radical species that can oxidize a wide array of lipids and proteins. This eventually leads to tissue damage and fibrosis.¹³ Normally, iron homeostasis is achieved through changes in gastrointestinal absorption. Although iron is lost via sweat, shed epidermal cells, and gastrointestinal and menstrual blood loss, the body cannot regulate iron excretion.⁴⁴ According to the Institute of Medicine, the upper limit of iron intake for men as well as pregnant and nonpregnant women 18 years of age or older is 45 mg/d.³⁴

Hemochromatosis is a condition involving excess iron absorption, excess iron tissue stores, and subsequent tissue injury. In hereditary hemochromatosis (HH), symptoms usually manifest in the fourth and fifth decades and include fatigue, depression, and arthralgias in early stages and increased skin pigmentation, hepatomegaly, polydipsia with polyuria, cardiomyopathy, arthritis, and hypogonadism in advanced stages.⁴⁴ Eventually, the accumulation of iron can cause liver failure, hepatocellular carcinoma, diabetes mellitus, amenorrhea, and hypothalamic or pituitary failure.⁴⁵

Long-term unnecessary iron supplementation in normal individuals can lead to hemochromatosis.⁴⁶ There is also some evidence that high dietary iron intake in normal individuals may lead to an increased risk of colorectal cancer, especially in the proximal colon.^{44,47} Patients who receive multiple blood transfusions may also develop iron overload.¹³

Patients with HH are most often homozygous for the C282Y mutation on the *HFE* gene. One in every 385 people in the United States has this genotype. Iron supplementation can exacerbate iron overload in HH patients.⁴⁴

Patients should be screened for HH if they have a first-degree relative with the condition.⁴⁸ Universal

screening, however, is controversial.^{2,48,49} If clinical suspicion is high for iron overload, serum ferritin concentration and transferrin saturation can be used. One study showed that using a transferrin saturation that is greater than or equal to 50% yielded a sensitivity of 58% and a specificity of 98% for detecting HH patients. The use of a serum ferritin level greater than 200 ng/dL yielded a sensitivity of 66% and a specificity of 85%. The definitive test for diagnosing iron overload is liver biopsy. Hepatic iron content greater than 71 $\mu\text{mol/L}$ of iron per dry gram of liver suggests iron overload.¹³ Genetic testing for specific genetic mutations is also available.⁴⁸

CONCLUSION AND RECOMMENDATIONS

- Hemoglobin concentration can be used to screen for iron deficiency, while serum ferritin concentration can be used to confirm iron deficiency. Although many laboratories use serum ferritin concentrations of 10 to 15 ng/mL (sensitivity of 59%, specificity of 99%) for diagnosing iron deficiency, a lower cutoff point of 41 ng/mL yields a sensitivity of 98% and a specificity of 98%.¹¹ Serum ferritin concentration can be elevated in anemia of chronic disease.¹⁴ Additional tests of iron status include erythrocyte zinc protoporphyrin concentration, transferrin concentration, serum iron concentration, and transferrin saturation.
- The cause of iron deficiency must be identified. If the patient is premenopausal and has no risk factors for blood loss, iron deficiency can initially be presumed to be caused by inadequate diet, menstrual blood loss, or both.² If the patient is male, postmenopausal female, or has risk factors for blood loss, then the patient should be evaluated for sources of blood loss, especially gastrointestinal (eg, colon cancer).^{2,11}
- Several studies have examined the relationship between iron deficiency and hair loss. Almost all have addressed women exclusively and have focused on noncicatricial hair loss. Some suggest that iron deficiency may be related to AA, AGA, TE, and diffuse hair loss, whereas others do not. Currently, there is insufficient evidence to recommend universal screening for iron deficiency in patients with hair loss. In addition, there is insufficient evidence to recommend giving iron supplementation therapy to patients with alopecia and iron deficiency in the absence of IDA. The decision to do either should be based on clinical judgment.
- It is our practice at the Cleveland Clinic Foundation to screen male and female patients presenting with hair loss, both cicatricial and noncicatricial, for iron deficiency by obtaining a complete blood cell

count, red blood cell indices, and serum ferritin concentration. We treat iron deficiency, with or without anemia, through dietary modification and, when necessary, oral iron supplementation. Although this practice is not evidence based per se, in our experience we believe that treatment for hair loss is enhanced when patients maintain a serum ferritin concentration greater than 70 ng/mL.

- IDA should be treated.^{2,16,17,40} Treating iron deficiency without anemia is controversial. In addition to adequate dietary intake, oral ferrous sulfate, 300 mg (60 mg elemental iron) taken 3 to 4 times daily is a widely accepted and cost-effective initial therapy,^{16,17,40} resulting in iron absorption of approximately 50 mg/d.¹⁶
- After oral iron supplementation therapy has begun, hemoglobin concentration should rise approximately 2 g/dL in 3 to 4 weeks.^{6,40} If the rise in hemoglobin concentration is less, this may be due to poor compliance, misdiagnosis, malabsorption,⁶ coexisting cause of anemia in addition to IDA (eg, anemia of chronic disease, thalassemia), or continued blood loss.⁴⁰
- Oral iron supplementation should be continued until the hemoglobin concentration normalizes. This will depend on the degree of anemia and the rate of response to therapy. Iron supplementation therapy may also be continued until iron stores are replenished. This can take from 3^{6,17} to 6 months.^{16,40}
- After oral iron supplementation therapy is complete, premenopausal patients who have had IDA may be rescreened yearly.² For men and postmenopausal women, further monitoring should be based on clinical judgment and the underlying cause of iron deficiency or IDA.
- Unnecessary long-term iron supplementation in normal individuals can lead to iron overload.⁴⁶ If clinical suspicion is high, serum ferritin concentration and transferrin saturation can be used to screen for iron overload.¹³

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APPENDIX

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Iron and Your Health

Patient Handout

What is iron?

Iron is a mineral that plays an important role in carrying oxygen to the entire body. Iron is essential for life.

How much iron should I eat?

Table 1 shows the U.S. recommended dietary allowances (RDA) for males and females ages 14 years and older.

Table 1. U.S. recommended dietary allowances (RDA) for iron.

Age (years)	Males (mg/day)		Females (mg/day)	
	Vegetarian and vegan		Vegetarian and vegan	
14 – 18	11	20	15	27
19 – 50	8	14	18	33
51 and older	8	14	8	14

Source: Institute of Medicine. *Dietary reference intakes (DRIs) for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington, D.C.: National Academy Press; 2002.

Which foods contain iron?

Good food sources of iron include red meats,* egg yolks,** green leafy vegetables, broccoli, nuts, beans, lentils, peas, fruits (apricots, prunes, and raisins), whole grain-enriched breads and cereals, and fortified meat alternatives. See Table 2.

How can vegetarians and vegans get enough iron in their diets?

Vegetarians and vegans need almost twice as much iron per day because the iron in meat and fish is more easily absorbed than in other types of food. It is important to include one to two iron-containing foods at each meal.

How can I make sure that my body absorbs the iron that I eat?

Vitamin C-rich foods, including broccoli, cauliflower, and many fruits such as oranges and berries can be eaten at each meal to enhance iron absorption.

If you drink tea or coffee, do so one to two hours after a meal since tea and coffee can interfere with iron absorption.

Should I take an iron supplement?

An iron supplement can help you if your body is deficient in iron. However, iron can be harmful even at over-the-counter doses if taken improperly. Talk to your physician to see if an iron supplement is right for you.

*Choose the leanest cuts

**Contains more than 200 mg cholesterol

Sample High-Iron Menu

For vegetarians and vegans, this menu assumes iron-fortified foods.

Breakfast

- Iron-fortified cream of wheat
- Scrambled egg** (almonds for vegetarians and vegans)
- Orange juice
- Skim milk (soy milk for vegans)

Lunch

- Bean soup
- Grilled chicken sandwich (grilled vegetarian burger for vegetarians and vegans) on enriched bread
- Tomato and lettuce
- Mustard
- Fresh strawberries
- Skim milk (soy milk for vegans)

Dinner

- Lean roast beef (tofu / black bean / potato casserole for vegetarians and vegans)
- Baked potato with margarine
- Tossed spinach salad
- Balsamic vinaigrette
- Apricot / raisin medley
- Fruit juice



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Table 2. Iron content of selected foods.

Food	Serving size	Calories	Iron (mg)
Cream of Wheat, instant, cooked	¾ cup	116	9.1
Liver, beef, cooked**	3 ½ ounces	161	6.8
Tofu, raw	½ cup	94	6.7
Lentils, boiled	1 cup	230	6.6
Post Raisin Bran Cereal	1 cup	190	6.3
Oysters, raw	6 medium	57	5.6
Navy beans, cooked	1 cup	258	4.5
Black beans, cooked	1 cup	227	3.6
Molasses, blackstrap	1 tablespoon	47	3.5
Spinach, boiled	½ cup	21	3.2
Prune juice	8 fluid ounces	182	3.0
Potato, baked, with skin	1 potato	220	2.8
Vegan burger	1 patty	75	2.7
Turkey, dark meat, without skin	3 ½ ounces	187	2.3
Beef, ground, lean, baked medium*	3 ½ ounces	268	2.1
Raisins	2/3 cup	300	2.1
Dried apricots	10 halves	83	1.7
Vegetarian burger	¼ cup	61	1.7
Pork tenderloin	3 ½ ounces	164	1.5
Broccoli, boiled	1 cup	44	1.4
Almonds, whole	1 ounce	170	1.3
Green peas, frozen, boiled	½ cup	62	1.3
Tuna, light meat, canned	3 ounces	99	1.3
Chicken, breast, without skin	3 ounces	143	0.9
Whole wheat bread, enriched	1 slice	69	0.9
Salmon, pink	3 ounces	99	0.7
Egg**	1 large	78	0.6

Source: Pennington, JAT. Bowes & Church's food values of portions commonly used. Philadelphia: Lippincott-Raven Publishers; 1998.

This handout is provided for informational purposes only and is not meant to substitute for the advice provided by your own physician or dietician. Information and statements have not been evaluated by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent any disease.

*Choose the leanest cuts

**Contains more than 200 mg cholesterol