REVIEW ARTICLE

MECHANISMS OF DISEASE

Iron Overload in Human Disease

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Iron-overload disorders are typically insidious, causing progressive and sometimes irreversible end-organ injury before clinical symptoms develop. With a high index of suspicion, however, the consequences of iron toxicity can be attenuated or prevented. Some iron-overload disorders are quite common (e.g., *HFE*-associated hereditary hemochromatosis and β-thalassemia), whereas others are exceedingly rare. An understanding of the pathophysiology of these disorders is helpful in directing the workup and in identifying scenarios that merit consideration of the less common diagnoses. Since many of the molecular participants in iron metabolism have been characterized only in the past several years, we first review the current understanding of iron metabolism[1] and then discuss specific iron-overload diseases.

Iron Metabolism

The four major cell types that determine body iron content and distribution are duodenal enterocytes (affecting dietary iron absorption), erythroid precursors (affecting iron utilization), reticuloendothelial macrophages (affecting iron storage and recycling), and hepatocytes (affecting iron storage and endocrine regulation). Each of these cell types plays an essential role in the homeostatic iron cycle (Fig. 1).

Enterocytes

Maintaining homeostatic balance requires only 1 to 3 mg of absorbed iron per day to offset losses from desquamated cells. Because there are no physiologically regulated means of iron excretion, dietary iron absorption is highly regulated. Dietary iron is absorbed primarily by duodenal enterocytes. After the iron is reduced at the apical membrane, it is taken into the cell through the divalent metal transporter 1 (DMT1). Heme iron is taken up through mechanisms that are incompletely characterized. Much of the iron taken up from either source is stored in the form of ferritin and is lost on sloughing of the senescent enterocyte. Export of iron from enterocytes to plasma occurs through the basolateral transporter ferroportin.

Regulation of each step (reduction, absorption, storage, and transfer) is mediated by signals reflecting oxygen tension in enterocytes, intracellular iron levels, and systemic iron needs.[2] Enterocyte tension regulates iron absorption through its effects on the transcription factor hypoxia-inducible factor 2α (HIF-2α) and subsequent changes in transcription of DMT1 and ferroportin.[3,4] The enterocyte iron content regulates iron absorption through its effects on iron regulatory protein (IRP) types 1 and 2 and their subsequent effects on messenger RNAs (mRNAs) encoding DMT1, ferroportin, ferritin, and HIF-2α.[5] The IRPs bind to sequences (iron-responsive elements [IREs]) that influence mRNA translation (with respect to ferroportin, ferritin, and HIF-2α) or stability (with respect to DMT1).[6,7] Enterocytes also express alternative mRNAs for DMT1 and ferroportin that lack IREs and

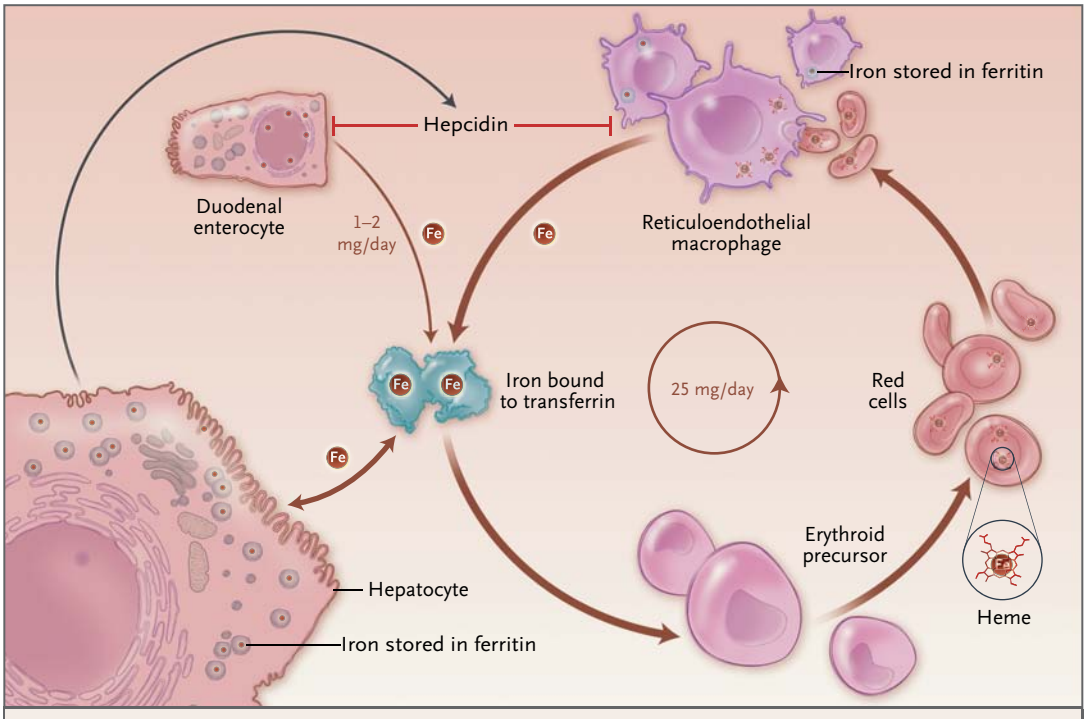

Figure 1. Iron Cycle.

Duodenal enterocytes absorb approximately 1 to 2 mg of iron per day to offset losses. Absorbed iron circulates bound to transferrin and is used primarily by erythroid precursors in the synthesis of heme. Reticuloendothelial macrophages clear senescent erythrocytes and release the iron from heme to export it to the circulation or store it in ferritin. Hepatocytes are another site of iron storage as ferritin and the principal site of production of the peptide hormone hepcidin. Hepcidin blocks the release of iron from enterocytes and reticuloendothelial macrophages by degrading the iron exporter ferroportin.

are regulated transcriptionally.[8] Systemic regulation of iron absorption is mediated by the hormone hepcidin. Hepcidin binds to the iron exporter ferroportin and induces its degradation, thus decreasing the transfer of iron from enterocytes to the circulation.[9,10]

CIRCULATING IRON

Iron released from enterocytes (and macrophages, see below) binds to free sites on the plasma iron-transport protein transferrin. Because transferrin-binding capacity normally exceeds plasma iron concentrations (normal transferrin saturation is approximately 30%), transferrin-bound iron is the only physiologic source available to most cells (reticuloendothelial macrophages are notable exceptions, as discussed below). Cells regulate the intake of transferrin-bound iron by altering the expression of surface transferrin receptor 1 (TfR1). In contexts in which transferrin becomes highly saturated, additional iron released into the circulation is bound to low-molecular-weight compounds (e.g., citrate).[11] This non–transferrin-bound iron (NTBI) is readily taken up by certain cell types, including hepatocytes and cardiomyocytes. The excess uptake of iron as NTBI contributes to oxidant-mediated cellular injury. A fraction of the circulating NTBI is redox-active and designated labile plasma iron.[12] Although there are methods for measuring serum NTBI and labile plasma iron, insufficient standardization and clinical correlation currently limit routine clinical use of them.

ERYTHROID PRECURSORS

Erythroid precursors are the major sites of iron utilization. These cells express high levels of TfR1, which mediates the entry of iron-bound transferrin (ferri-transferrin) into recycling endosomes. On acidification of the endosomes, the iron is released and then exported by DMT1. The IRE–IRP system plays an important role in ery-

throid precursors by regulating the stability of the mRNA for TfR1 and translation of the mRNA for erythroid-specific 5-aminolevulinate synthase, the first enzyme in heme synthesis.[13] This latter regulation ensures that levels of protoporphyrin IX (which is toxic) are in line with cellular iron availability. The production of heme requires transferrin-bound iron; NTBI cannot be used. Erythropoietic activity is an important regulator of hepcidin expression (see below).

RETICULOENDOTHELIAL MACROPHAGES

Reticuloendothelial cells serve as the major hepcidin-regulated iron repository. At equilibrium, these cells release approximately 25 mg of iron each day. Since the pool of circulating transferrin iron amounts to less than 3 mg, reticuloendothelial cells represent the most dynamic iron compartment, turning over about 10 times per day. Reticuloendothelial cells obtain most of their iron from the phagocytosis of senescent erythrocytes.[14] After release from heme, the iron can be stored as ferritin or exported into the circulation. Ferritin is an iron-storage protein complex composed of 24 ferritin monomers of two subtypes: "heavy" and "light" chains. The relative proportion of these ferritin chains in the complex varies across tissues.[15] Heavy-chain ferritin has ferroxidase activity, which is required for the efficient oxidation of incoming ferrous iron, whereas light-chain ferritin promotes efficient nucleation and mineralization.

The IRE–IRP system increases ferritin mRNA translation in response to cellular iron. Evidence suggests that temporal uncoupling of the synthesis of ferritin chains from the incorporation of iron results in secretion of an iron-poor form of ferritin.[16] This secreted ferritin provides a useful diagnostic tool, because serum levels reflect ferritin production and thus iron stores.[17] As observed in the duodenal enterocyte, iron export from reticuloendothelial cells is mediated by ferroportin and regulated by hepcidin[18] (see below). Because the rate of iron turnover by reticuloendothelial cells is quite high, hepcidin-mediated changes in iron export can result in rapid and marked changes in serum iron concentrations.

HEPATOCYTES

Similar to reticuloendothelial cells, hepatocytes are an important site of iron storage in the form of ferritin. NTBI is likely to be a major contributor to iron loading in hepatocytes under conditions of elevated transferrin saturation. Most important, hepatocytes serve a central role in iron homeostasis as the site of regulated production of the hormone hepcidin. Hepcidin functions as the "hypoferremia hormone" by down-regulating the ferroportin-mediated release of iron into the circulation. The consequent iron retention in duodenal enterocytes decreases dietary iron absorption; the iron retention in reticuloendothelial macrophages decreases iron turnover. Hepatocellular hepcidin production is regulated by signals reflecting inflammation, iron status, erythropoietic activity, and oxygen tension (Fig. 2).

Inflammation

Hepcidin is a type II acute-phase protein that mediates the hypoferremia associated with infection and inflammation. This protein was originally identified as an antimicrobial peptide with structural properties similar to those of the defensins.[20] However, the antimicrobial activity of hepcidin requires substantially higher concentrations than those found in the circulation. The hypoferremic properties of hepcidin may represent an adaptation to evolutionary pressure from microorganisms, because hepcidin decreases the availability of circulating iron to invading microbes. The inflammatory signal up-regulating hepcidin expression is largely mediated by interleukin-6.[21]

Iron Status

Iron status regulates hepcidin expression by two mechanisms: liver iron stores and circulating iron levels. Liver iron stores influence the hepatic expression of the extracellular signaling molecule bone morphogenetic protein (BMP) 6 (BMP-6).[22-25] The interaction of BMP-6 with hepatocyte BMP receptors[26] initiates intracellular signal transduction through SMAD proteins,[27] increasing hepcidin transcription. BMP-6 signaling to hepcidin is enhanced by cell-surface expression of the BMP coreceptor hemojuvelin.[28-30] The circulatory iron signal regulating hepcidin is provided by transferrin, which, on binding iron, serves as a ligand for two hepatocellular receptors: TfR1 and transferrin receptor 2 (TfR2). Ferri-transferrin–mediated signaling appears to be modulated by the physical interaction of these two receptors with the hemochromatosis protein HFE.[31-35] HFE is a major histocompatibility complex class I–like molecule without iron-transport properties. Loss

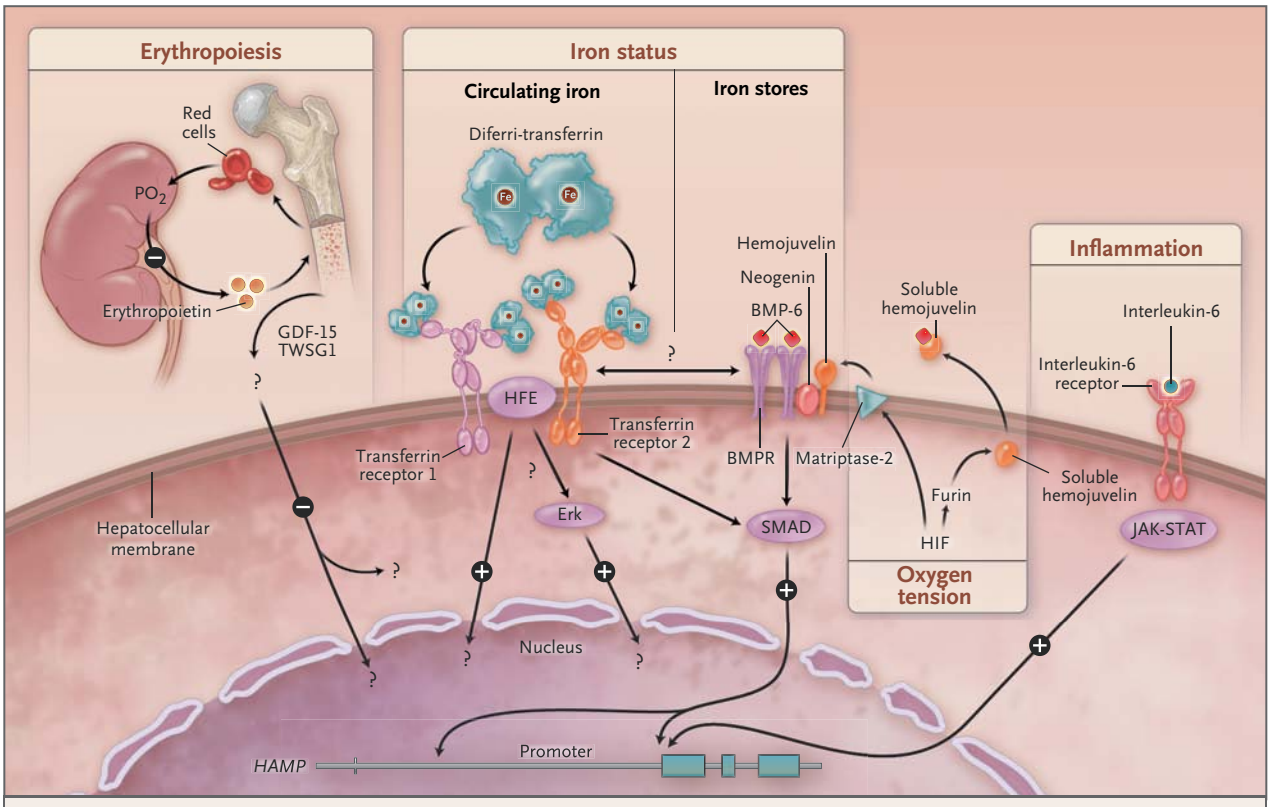

Figure 2. Regulation of Hepatocellular Hepcidin Expression.

Four functionally defined hepcidin regulatory pathways are depicted: erythropoiesis, iron status, oxygen tension, and inflammation. Increased erythropoiesis is associated with decreased hepcidin expression by mechanisms that remain to be defined. Candidate signaling molecules from the marrow include growth differentiation factor 15 (GDF-15) and twisted gastrulation protein homolog 1 (TWSG1). Increased body iron status increases hepcidin expression through two mechanisms: a circulating-iron signal provided by ferri-transferrin and a cellular-iron-stores signal provided by bone morphogenetic protein 6 (BMP-6). The ferri-transferrin signal acts through transferrin receptors 1 and 2 and is modulated by the hemochromatosis protein HFE. The BMP-6 signal acts through its receptor and is modulated by the BMP coreceptor hemojuvelin and by neogenin. Decreased oxygen tension leads to decreased hepcidin expression by increasing the transcription of two genes, matriptase-2 and furin, that are responsive to hypoxia-inducible factor (HIF). Matriptase-2 cleaves hemojuvelin from the cell surface, preventing its function as a coreceptor. Furin cleaves hemojuvelin during processing to produce a soluble form that serves as a BMP-6 decoy. Infections and other forms of inflammation increase hepcidin expression by the cytokine interleukin-6. BMPR denotes bone morphogenetic protein receptor, *HAMP* hepcidin gene, JAK-STAT Janus-associated kinase–signal transducers and activators of transcription, and PO_2 partial pressure of oxygen. Adapted from Kroot et al.[19]

of HFE (or TfR2) attenuates SMAD-mediated signaling to hepcidin.[36,37] These molecules may also signal to hepcidin through a pathway involving mitogen-activated protein kinases.[38,39]

Erythropoietic Activity

Hepcidin expression is markedly decreased in contexts in which erythropoiesis is increased, such as phlebotomy, hemolysis, and administration of erythropoietin. The signal may be mediated by molecules released by erythroid precursors. Candidate signaling molecules, at least in the context of ineffective erythropoiesis, include growth differentiation factor 15[40-42] and twisted gastrulation protein homolog 1.[43] Erythropoietic activity has a greater influence on hepcidin expression than does body iron status.

Oxygen Tension

Under hypoxic conditions, HIF transcription factors up-regulate expression of the membrane protease matriptase-2,[44] which cleaves hemojuvelin from the hepatocellular surface[45] and attenuates BMP-6–mediated signaling to hepcidin. Hemojuvelin is also cleaved during processing to a secretory decoy receptor by the proprotein conver-

Table 1. Heritable Forms of Systemic Iron Overload According to the Pathophysiological Defect.*

Disorder	Gene and Inheritance	Age at Presentation	Neurologic Symptoms	Anemia	Transferrin Saturation
Impaired hepcidin–ferroportin axis					
HH type I	*HFE*, AR	Adult	No	No	High
HH type IIA	*HFE2*, AR	Child to young adult	No	No	High
HH type IIB	*HAMP*, AR	Child to young adult	No	No	High
HH type III	*TFR2*, AR	Young adult	No	No	High
HH type IVA (atypical HH)	*FP* (LOF), AD	Adult	No	Variable	Low initially
HH type IVB	*FP* (GOF), AD	Adult	No	No	High
Impaired iron transport					
Inadequate release to erythron: aceruloplasminemia	*CP*, AR	Adult	Yes	Yes	Low
Inadequate uptake by erythron					
DMT1 mutations	*DMT1*, AR	Child	No	Yes	High
Hypotransferrinemia	*TF*, AR	Variable	No	Yes	High
Ineffective erythropoiesis					
Thalassemia	*Globin*, AR	Child	No	Yes	High
Congenital sideroblastic anemia	*ALAS2*, XL; *SLC25A38*, AR; *GLRX5*, AR; *ABCB7*, XL	Variable	*ALAS2* and *SLC25A38*: no; *GLRX5* and *ABCB7*: yes	Yes	High
Congenital dyserythropoietic anemia					
Type I	*DAN1*, AR	Child	No	Yes	High
Type II	*SEC23B*, AR	Child	No	Yes	High
Type III	Unknown, AD	Child	No	Yes	High

* AD denotes autosomal dominant, AR autosomal recessive, GOF gain of function, HH hereditary hemochromatosis, LOF loss of function, and XL X-linked.

tase furin, which is transcriptionally regulated by HIF proteins.[46] Considerable overlap is likely in the regulation of hepcidin by hypoxia and iron. As mentioned above, HIF-2α translation is regulated by the IRE–IRP system. Iron also serves as a cofactor in the degradation of HIF proteins.[47]

Most iron-overload disorders reflect a dysregulation of either the iron-status signal or the erythroid signal, leading to inadequate hepcidin expression for maintaining normal homeostasis. If the resulting increased dietary iron absorption and iron release into the circulation from reticuloendothelial macrophages exceed the binding capacity of circulating transferrin, NTBI will appear in the circulation. Circulating NTBI is taken up by susceptible cell types, including hepatocytes, cardiomyocytes, and pancreatic islet cells, with consequent oxidant injury.

IRON-OVERLOAD DISORDERS

This section categorizes iron-overload disorders according to whether the underlying pathophysiological defect is in the hepcidin–ferroportin axis, erythroid maturation, or iron transport (Table 1). We also consider several less common disorders that do not fit into any of these categories.

DISORDERS OF THE HEPCIDIN—FERROPORTIN AXIS

Each of these disorders represents a form of primary iron overload and is a subtype of hereditary hemochromatosis. Of the six disorders in this group, five have a classic hereditary hemochromatosis phenotype (elevated transferrin saturation, elevated serum ferritin, normal hematocrit, and tissue iron overload). The pathophysiology of these five conditions is similar: inadequate or

ineffective hepcidin-mediated down-regulation of ferroportin.

By far, the most common disorder of the hepcidin–ferroportin axis is *HFE*-associated hereditary hemochromatosis (number 235200 in the Online Mendelian Inheritance in Man [OMIM] database). Nearly 10% of the white population carries the most prevalent C282Y *HFE* mutation. Although biochemical penetrance of homozygosity for this mutation is substantial (36 to 76%), disease penetrance is much lower: 2 to 38% among men and 1 to 10% among women. Polymorphisms in modifier genes, environmental factors, or both influence the risk of overt disease. Another common *HFE* allele, H63D, can cause iron overload when found in compound heterozygosity with a more consequential mutation.[48] Most patients with *HFE*-associated hereditary hemochromatosis do not present until middle age (and women not until after menopause). Mutations in *TFR2* cause a more severe form of hereditary hemochromatosis (OMIM number, 604250) with an earlier presentation.[49,50] Juvenile forms of hereditary hemochromatosis are due to mutations in genes encoding hemojuvelin[51] (OMIM number, 602390) or (in rare cases) hepcidin[52] (OMIM number, 613313). Combined mutations of *HFE* and *TFR2* are also manifested phenotypically as juvenile hemochromatosis.[53]

The fifth form of hereditary hemochromatosis with a classic phenotype is caused by mutations in ferroportin that interfere with regulation by hepcidin (OMIM number, 606069). These loss-of-regulation mutations cause excessive ferroportin-mediated iron export and are thus described as gain-of-function mutations.[54,55] As expected, the phenotype in affected patients is similar to that in patients with classic hereditary hemochromatosis, but with normal or elevated (rather than low) hepcidin levels. Iron overload in persons with loss-of-function ferroportin mutations, on the other hand, is primarily confined to reticuloendothelial cells, without elevated transferrin saturation, plasma NTBI, or liver injury. For unclear reasons, high urinary levels of hepcidin have been observed in the few reported cases in which it was measured.[56] Certain polymorphisms in the ferroportin gene are associated with African iron overload,[57] a condition that probably represents the combined consequences of excess iron intake and otherwise minor functional changes in ferroportin. As discussed below, iron overload in patients with classic hereditary hemochromatosis is managed with therapeutic phlebotomy.

DISORDERS OF ERYTHROID MATURATION

This class of disorders, representing forms of secondary iron overload, includes the so-called iron-loading anemias. Most are characterized by some degree of ineffective erythropoiesis — that is, apoptosis of certain erythroid precursors, failure of erythroid maturation, and secondary expansion of erythropoiesis. Hepcidin is down-regulated by signaling molecules associated with these events (and the consequent anemia, hypoxia, or both). The down-regulation of hepcidin persists despite iron overload.[58] Erythrocyte transfusions contribute substantially to the iron burden in patients with these disorders.[59]

Thalassemias

Worldwide, 15 million people have clinically apparent α-thalassemia (OMIM number, 604131) or β-thalassemia (OMIM number, 613985). Iron overload is a major cause of illness in patients with severe forms, whether or not they receive regular transfusions.[60] Currently, thalassemias are managed with chelation therapy; however, exogenous transferrin,[61] exogenous hepcidin,[61,62] or hepcidin signaling agonists[63] may be effective options in the future.

Congenital Sideroblastic Anemias

The sideroblastic anemias are heterogeneous disorders of heme synthesis with both primary (congenital and heritable)[64] and secondary causes. Syndromic and nonsyndromic forms have been identified. The best-characterized congenital forms are caused by mutations in genes required for the production of heme precursors (Table 1). Iron that would otherwise be incorporated into the final protoporphyrin IX ring accumulates in mitochondria, producing the characteristic ring sideroblasts. Certain congenital forms can be partially treated (e.g., with pyridoxine). Iron overload is managed with phlebotomy (when practical), chelation, or both.

Congenital Dyserythropoietic Anemias

The congenital dyserythropoietic anemias are a diverse group of disorders that result in defective erythrocyte production and often mild hemolysis.[65] Several forms have been identified (Table 1).

They are characterized by a macrocytic or normocytic anemia and low reticulocyte count from birth. The diagnosis is made on the basis of the characteristic erythroblast morphology. Management of the anemia may require repeated transfusions. Iron overload is treated with chelation.

Myelodysplastic Syndromes and Aplastic Anemias

Several congenital or acquired disorders characterized by ineffective hematopoiesis and peripheral cytopenias are associated with iron overload, particularly when exacerbated by multiple erythrocyte transfusions.[66]

DISORDERS OF IRON TRANSPORT

The common pathophysiological feature of these disorders is insufficient delivery of transferrin-bound iron for the synthesis of heme, despite iron stores. The consequent iron-restrictive erythropoiesis, anemia, or both contribute to low hepcidin levels and thus iron overload. Hypotransferrinemia (OMIM number, 209300) is a rare autosomal recessive condition in which functional transferrin concentrations are severely reduced.[67] Iron entering the plasma saturates the scant available transferrin and circulates as NTBI. Unlike ferri-transferrin, NTBI cannot be used in heme synthesis and cannot up-regulate hepcidin. The consequent anemia, combined with loss of the ferri-transferrin signal, results in low hepcidin levels, despite iron overload.[68,69] In patients with aceruloplasminemia[70] (OMIM number, 604290), the loss of ceruloplasmin ferroxidase activity decreases loading of iron onto transferrin, which in turn decreases ferroportin-mediated iron export from reticuloendothelial cells. As a consequence, iron delivery to the erythron is restricted. Presumably, ferroportin-mediated iron export from enterocytes is retained in these patients by the activity of the homologous cellular ferroxidase hephaestin. Mutations in *DMT1* (OMIM number, 206100) have been described that prevent normal delivery of transferrin-bound iron from the recycling endosome to the mitochondria for the production of heme. Although impaired DMT1 function would be expected to decrease the enterocyte uptake of dietary iron, most (but not all)[71] *DMT1* mutations appear to have less effect on dietary iron uptake than on erythroid iron delivery, and the net effect results in a low hepcidin state and iron overload.

NEONATAL HEMOCHROMATOSIS

Neonatal hemochromatosis is a severe form of systemic iron overload associated with newborn liver failure.[72] In contrast to other forms of hemochromatosis, the hepatocellular injury in this condition appears to be primary and the iron overload secondary. Nonetheless, excess iron possibly contributes to a cycle of further injury. Most cases are alloimmune-mediated — that is, they are caused by transplacental maternal IgG directed against an as-yet-unidentified fetal liver antigen.[73] Treatment with postnatal exchange transfusions and immune globulin may decrease the otherwise nearly universal requirement for liver transplantation.[74] Immune globulin administered in the mother during an at-risk pregnancy may also be beneficial.[75] Fetal myeloproliferative disorders, certain viral infections, and mutations in *AKR1D1* (OMIM number, 235555) or *DGUOK*[76] (OMIM number, 251880) are other causes of fetal liver injury that can be manifested as neonatal hemochromatosis.

LOCALIZED IRON OVERLOAD

Neurodegeneration with Brain Iron Accumulation

Several heritable conditions fall under the descriptive term "neurodegeneration with brain iron accumulation" (NBIA).[77,78] In most forms of NBIA, iron accumulates in the basal ganglia, and the condition is generally manifested as a progressive extrapyramidal movement disorder. Mutations in the pantothenate kinase–associated neurodegeneration gene (*PANK2*) are responsible for most cases[79] (OMIM number, 606157). Affected persons usually have a characteristic pattern of iron accumulation in the globus pallidus, identifiable by magnetic resonance imaging (MRI).[80]

Mutations in *PLA2G6* (OMIM number, 256600), *FA2H* (OMIM number, 612319), *ATP13A2* (OMIM number, 606693), and *DCAF17* (OMIM number, 241080) cause other autosomal recessive forms of NBIA. Mutations in the coding region of light-chain ferritin cause an autosomal dominant disorder (OMIM number, 606159) characterized by iron aggregates in the globus pallidus and late-onset extrapyramidal dysfunction (neuroferritinopathy).[81] Systemic iron status is unaffected. Aceruloplasminemia can be classified with this group of disorders; however, it differs from other forms of NBIA in that systemic iron status is also affected. An understanding of the basis of the localized iron accumulation in this class of

disorders may offer insights into more common acquired neurodegenerative disorders with localized excessive brain iron (e.g., Parkinson's disease).[82,83] Patients with some forms of NBIA appear to benefit from iron chelation.

Friedreich's Ataxia

Mutations in the frataxin gene are responsible for Friedreich's ataxia (OMIM number, 229300), the most common of the inherited ataxias. Frataxin appears to be required for normal mitochondrial iron (or iron–sulfur cluster) export.[84,85] The neurologic and cardiac manifestations of Friedreich's ataxia are the result of iron-mediated mitochondrial injury.[86] Serum iron concentrations in affected persons are normal.

IRON-MEDIATED CELLULAR INJURY

Excess iron injures cells primarily by catalyzing the production of reactive oxygen species in excess of the capacity of cellular antioxidant systems. These reactive oxygen species cause lipid peroxidation, oxidation of amino acids with consequent protein–protein cross-links, protein fragmentation, and DNA damage. In most patients, cellular iron excess is a consequence of the uptake of circulating NTBI. Therapeutic phlebotomy removes iron from the body. The ongoing utilization of iron in hemoglobin production mobilizes iron from tissues, lowers transferrin saturations, and eliminates circulating NTBI. Chelators not only remove iron from the body but also scavenge and tightly bind labile iron to prevent the generation of reactive oxygen species.[60] Supplemental vitamin C should be avoided in patients with iron overload because it may increase the generation of reactive oxygen species and augment tissue damage.[87]

DIAGNOSIS OF SYSTEMIC IRON-OVERLOAD DISORDERS

The signs and symptoms of iron overload are insensitive and nonspecific. Thus, early diagnosis of iron overload requires consideration of this possibility when the physician is faced with such common findings as chronic fatigue, joint pain, impotence, osteoporosis, and diabetes. Scoring systems to identify patients at greatest risk for undetected systemic iron overload in the primary care setting are under development.[88]

Screening laboratory tests include measurements of the serum ferritin level and transferrin saturation. Ferritin levels above 200 ng per milliliter (449 pmol per liter) in women or 300 ng per milliliter (674 pmol per liter) in men who have no signs of inflammatory disease and transferrin saturation above 45% in women or 50% in men warrant additional testing.[89] Elevated ferritin concentrations without pathologic iron overload can be observed in acute or chronic inflammatory processes, autoimmune diseases, neoplasias, chronic renal insufficiency, hepatopathies, and the metabolic syndrome.[90] In these conditions, transferrin saturation is generally normal or decreased.[91] However, an increase in ferritin concentrations without an increase in transferrin saturation does not rule out an iron-overload disorder, since this combination can be seen, for example, in loss-of-function ferroportin mutations and in aceruloplasminemia. The importance of identifying the causative ferroportin mutations remains controversial, because the pathologic consequences and need for treatment are uncertain. Mutations in the iron-responsive element of the light-chain ferritin mRNA cause a syndrome of hyperferritinemia and cataracts (OMIM number, 600886), but without iron overload.[92]

The recognition of iron overload in patients with thalassemia who have not received a transfusion can be particularly challenging, because serum ferritin levels do not accurately reflect tissue iron in this context. This observation has led to the suggestion that liver iron concentrations be assessed every 1 to 2 years in patients with thalassemia intermedia.[93]

Algorithms to assist in the initial workup of systemic iron overload are shown in Figure 3. Identification of the underlying molecular defect is useful for genetic counseling and anticipation of the clinical course. Regardless of the underlying defect, therapeutic phlebotomy is indicated in patients with hemochromatosis who have high transferrin saturations and serum ferritin levels of more than 1000 ng per milliliter (2247 pmol per liter) and who do not have anemia.[94] Phlebotomy may also be considered for persons in whom ferritin levels are elevated but below this cutoff. Determining the severity of iron overload and monitoring the response to treatment may require a combination of tests: laboratory measurement of serum ferritin levels, MRI to assess liver and cardiac iron concentrations, and, in certain circumstances, liver biopsy (Table 2). Mea-

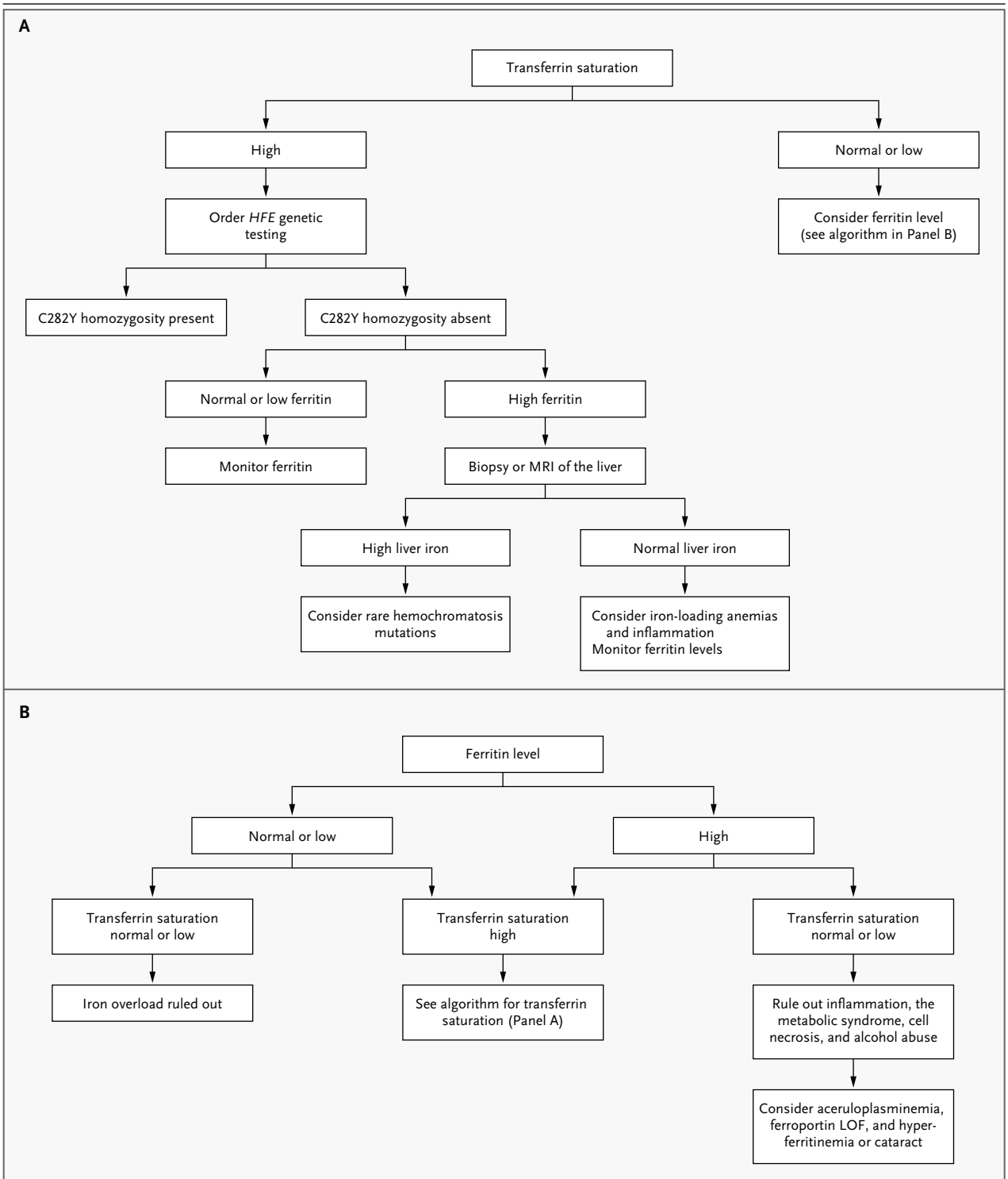

Figure 3. Algorithms for Diagnostic Workup of Iron Overload.

Panel A shows the suggested workup for iron overload in adults on the basis of serum transferrin saturation, and Panel B shows the suggested workup on the basis of the ferritin level. The combination of elevated transferrin saturation and a ferritin level above 1000 ng per milliliter in a patient without anemia is generally an indicator for therapeutic phlebotomy. Patients with a genetic diagnosis of hereditary hemochromatosis should have ferritin levels monitored and, if levels are more than 1000 ng per milliliter, should be considered for liver biopsy. LOF denotes loss of function. The algorithms were compiled, with modifications, from van Bokhoven et al.,[94] Bacon et al.,[95] and Camaschella and Poggiali.[91]

Table 2. Diagnostic Tests for Iron Overload.*

Test	Advantages	Disadvantages
Ferritin level	Inexpensive; identifies clinically significant iron overload	Low specificity; increased with inflammation or liver disease; underestimates iron load in thalassemia intermedia; cannot distinguish reticuloendothelial iron stores from tissue iron overload
Transferrin saturation†	Inexpensive; more sensitive screening test for HH than serum ferritin; identifies most conditions associated with NTBI-mediated iron toxicity	Low sensitivity as HH screening test in premenopausal women; serum iron shows diurnal variation and effects of recent dietary iron intake, increasing variability; because transferrin is a negative acute-phase reactant and is decreased in liver disease, it decreases TIBC
Liver biopsy	Direct measurement of liver iron concentration; validated reference standard; sensitive and specific; provides histopathological assessment of the liver; findings correlate with severity of illness and risk of death	Expensive; invasive; risk of sampling error; inadequate standardization across laboratories; impractical for longitudinal measurements
MRI	Liver and heart can be measured in parallel; entire liver measured; correlation with tissue iron content; longitudinal measurements useful	Indirect measurement of tissue iron content; requires specialized imager

* The table is adapted from Taher et al.[96] HH denotes hereditary hemochromatosis, MRI magnetic resonance imaging, NTBI non–transferrin-bound iron, and TIBC total iron-binding capacity.
† Transferrin saturation is calculated as the serum iron concentration divided by the TIBC, expressed as a percentage.

surement of serum hepcidin levels may someday prove useful in the diagnostic workup for iron overload, monitoring of affected patients, or both.[19] Assays have been developed but are not yet widely available.

FUTURE THERAPIES

The mainstays of treatment of systemic iron overload are iron removal by phlebotomy in the absence of anemia (applicable in most forms of hereditary hemochromatosis) and chelation in the iron-loading anemias. Phlebotomy, although inexpensive and generally well tolerated, will perpetuate the underlying low hepcidin state and excess iron absorption. Because dietary absorption of iron and certain other divalent metals occurs through the same transporter (DMT1), it is possible that homeostasis of these other metals[97-99] will be persistently abnormal in patients who undergo phlebotomy. Chelation is underutilized worldwide in the treatment of iron-loading anemias because of its inconvenience, cost, monitoring requirements, and untoward effects. Newer chelating agents and novel therapies, including exogenous transferrin,[61] exogenous hepcidin,[100-102] hepcidin analogues,[63] and hepcidin signaling agonists, might provide effective alternatives for this clinically consequential and common group of disorders.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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