Hemochromatosis can be classified as (a) primary, when it originates from a genetic disturbance that promotes the increase of iron absorption, or (b) secondary, when it relates to chronic diseases or to multiple transfusions. The distribution of iron accumulation differs between these two forms; therefore, they can be distinguished by using imaging methods in the majority of cases. Magnetic resonance (MR) imaging is the most sensitive and specific imaging modality in the diagnosis of hemochromatosis. The susceptibility effect caused by the accumulation of iron leads to signal loss in the affected tissues, particularly with the T2*-weighted sequences, which makes the diagnosis of iron overload possible. By using MR imaging techniques, it is possible to estimate the hepatic iron concentration in a noninvasive way, thereby avoiding repeated biopsies. Hemochromatosis can lead to complications, such as a higher frequency of neoplasia, particularly the development of hepatocellular carcinoma. Other neoplasms, such as colorectal tumors, are also associated. Complications related to the treatment of chronic anemia include the appearance of peliosis hepatitis and tumors, which can regress after the suspension of treatment with drugs. Knowledge of the disease and of the patterns of iron deposition in patients with iron overload enables not only diagnosis, but also treatment, follow-up, and the detection of possible complications by using imaging methods.

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Introduction
Iron is found in the body particularly in the composition of certain structures, such as the cytochromes, hemoglobin, and myoglobin. After being absorbed by the mucosa of the small intestine, iron is transported by transferrin and stored in another complex known as ferritin (1).

Medullary erythropoiesis requires around 20 mg of iron daily. However, only 1–2 mg of dietary iron is absorbed, which corresponds to 10% of the total amount ingested. Approximately the same amount is lost each day because of epithelial desquamation, menstruation, and other forms of blood loss. There is a good recycling mechanism through the reuse of iron found in old erythrocytes. Thus, the absorption is physiologically well controlled because there is no effective form of excretion (1,2).

Basically, iron is stored in the hepatic parenchyma and in the reticuloendothelial system. Excess iron can lead to toxicity because this element can catalyze the conversion of hydrogen peroxide into free radicals, causing damage to the cell membranes, proteins, and DNA (1).

The causes of iron accumulation in the body are numerous. The signs and symptoms of iron overload are highly nonspecific, which leads to (a) difficulty in developing a clinical suspicion that a patient has the condition and (b) a long period for correct diagnosis (3,4). The frequency of this disease varies according to the diagnostic methods used and the population studied (5).

The purpose of this article is to describe iron overload (hemochromatosis) and illustrate its appearance at magnetic resonance (MR) imaging, with an emphasis on detection, quantification, and related complications. After a general description of iron overload, the MR imaging methods and the patterns of iron deposition are presented, followed by the relationships of iron overload to other storage diseases and to various hepatic focal lesions.

Hemochromatosis
Iron overload (hemochromatosis) can be classified as primary or secondary. Primary hemochromatosis is a recessive autosomal genetic disorder that alters a protein involved in the regulation of iron absorption. Most of these patients are homozygous or heterozygous for this mutation and have iron absorption two or three times higher than that of the unaffected population (1,6). The results of studies indicate a global rate of occurrence of the gene of around 2%–5%, and primary hemochromatosis is considered the most common genetic disease in the white population (rate of disease, 0.2%–0.5% for homozygous disease and as much as 10% for heterozygous disease) (1,5,7).

Any other nongenetic cause of iron accumulation in the organs is classified as secondary hemochromatosis. The causes of secondary hemochromatosis include (a) another cause of increased absorption, such as cirrhosis, (b) myelodysplastic syndrome, (c) anemias related to ineffective erythropoiesis (eg, thalassemia), and (d) exogenous increase by ingestion, parenteral infusion, or multiple transfusions (2,3,8). The main differences between the primary and the secondary forms of hemochromatosis are shown in Table 1.

The disease is often clinically silent but can be diagnosed with imaging methods; therefore, radiologists should be aware of the MR imaging findings so that they can suggest the diagnosis. Moreover, the evaluation of the effects of clinical treatment can also be done in a noninvasive way.

Laboratory values used in the diagnosis of hemochromatosis include the ferritin level and the transferrin saturation index, both of which are generally increased in these patients. However, these tests have low sensitivity and specificity, with false-positive results found in alcohol abusers and with false-negative results found in young patients with hemochromatosis (1,9,10).

The genetic test can be done by using an inexpensive blood examination. The test, which consists of the identification of the genes associated with primary hemochromatosis, is used primarily in the evaluation of populations at risk or to confirm the diagnosis of primary hemochromatosis in patients with iron overload. However, the use of this test remains a topic of debate because identification of the defined mutations tests for only a subset of the patients with primary hemochromatosis and because other genetic mutations related to hemochromatosis have been identified. The overall costs and benefits of screening remain unclear (5–7,11).

Hepatic biopsy is considered the reference standard method for diagnosis because biopsy has the capacity to be used to quantify iron overload, to determine the prognosis on the basis
Figure 1. Appearance of the liver at CT. (a) Axial nonenhanced CT image of a normal liver (attenuation, 54–59 HU). (b) Axial nonenhanced CT image of a patient with secondary hemochromatosis shows increased liver attenuation (103–109 HU).

Table 1
Features of Primary and Secondary Hemochromatosis

<table>
<thead>
<tr>
<th>Primary Hemochromatosis</th>
<th>Secondary Hemochromatosis (Acquired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary autosomal recessive disease</td>
<td>Parenteral administration of iron (eg, repeated blood transfusions)</td>
</tr>
<tr>
<td>Increases intestinal absorption with normal dietary intake of iron</td>
<td>Dietary iron overload</td>
</tr>
<tr>
<td>Iron excess deposits in parenchymal cells, preferentially in the liver, pancreas, heart, pituitary gland, thyroid, and synovium</td>
<td>Iron is predominantly deposited in the reticuloendothelial system (spleen and Kupffer cells)</td>
</tr>
<tr>
<td>Leads to cellular damage, organ dysfunction, and malignancy</td>
<td>Less toxic</td>
</tr>
<tr>
<td>If untreated, may progress to cirrhosis, hepatocellular carcinoma, diabetes, and cardiac dysfunction</td>
<td>Secondary increased absorption of normal dietary iron intake: liver diseases (alcoholic hepatitis and hepatitis C), myelodysplastic syndrome, anemias, other chronic and oncologic diseases</td>
</tr>
</tbody>
</table>

of the level of hepatopathy, and to monitor the evolution of the disease and the effects of treatment. However, biopsy is an invasive procedure with known potential risks and is susceptible to sampling error because of the tiny amount of tissue taken from the edge of the liver (9,10,12).

**Imaging Methods**

Computed tomography (CT) and MR imaging can be used to detect iron overload. Nonenhanced CT shows a homogeneous increase in the attenuation of the hepatic parenchyma to 72 HU or more (13,14). CT has low sensitivity (63%) and high specificity (96%) for the diagnosis of iron overload.

Certain conditions, such as associated steatosis, can reduce the sensitivity still further by reducing the hepatic parenchymal attenuation. Other factors, such as Wilson disease, colloidal gold treatment, and long-term administration of amiodarone, also increase the hepatic parenchymal attenuation, which decreases the diagnostic specificity of CT (14–17) (Fig 1).
MR imaging is the best noninvasive method for measuring the level of iron in the liver for the purposes of confirming the diagnosis, determining the severity, and monitoring therapy with high sensitivity, specificity, and positive and negative predictive values (12,18–20). The accumulation of iron ions in the tissues, because of the superparamagnetic properties of the ions, causes local distortion in the magnetic fields and relaxation of the spins, which results in shortening of the longitudinal relaxation time (T1), the transverse relaxation time (T2), and particularly the transverse relaxation time as affected by magnetic field inhomogeneity (T2*). This effect causes a loss of signal intensity in the affected organs that is proportional to the iron deposition (17,21).

In the general protocol applied to an abdominal study, it is not possible to estimate the hepatic iron concentration, although most of the time, it is possible to diagnose iron overload. This can be done by using “dual-sequence” (gradient in and out of phase) MR imaging, which demonstrates decreased signal intensity in the affected tissues on the in-phase images compared with the out-of-phase images. That effect is the opposite of the effect observed in patients with steatosis (Fig 2). This occurs because the echo time of the in-phase sequence is usually higher than that of the out-of-phase sequence; therefore, the in-phase pulse sequence is more sensitive to iron deposits because of the increased T2* effect (21).
Iron Quantification with MR Imaging

The results of multiple studies have demonstrated that it is possible to estimate the amount of hepatic iron overload at MR imaging, with high correlation to the values found in specimens from biopsy (12,18–20,22,23). In our hospital, the method described by Gandon et al (18,19,24) is used to detect and quantify iron overload. Gradient-echo (GRE) sequences with T2* weighting and progressively longer echo times are acquired. On the Web site of the University of Rennes (http://www.radio.univ-rennes1.fr/Sources/EN/Hemo.html), it is possible to calculate the estimated hepatic iron concentration by filling in the region of interest (ROI) values requested (24).

The results of examination of unaffected subjects show that the hepatic parenchyma demonstrates higher signal intensity than that of the paraspinal musculature with all sequences. Slight to moderate iron overload is better identified and evaluated on the GRE images obtained with longer echo times, which demonstrate a decrease in the signal intensity of the liver parenchyma (Fig 3). When the hepatic iron concentration is high, MR sequences do not have good accuracy because.

Figure 3. GRE T2*-weighted MR imaging performed in a dedicated study to investigate iron overload. (a) On an axial image of a healthy subject, the liver is hyperintense compared with paraspinal musculature. (b) Axial image of a subject with slight iron overload demonstrates a mild decrease in the signal intensity of the liver and spleen (darker than the paraspinal musculature). (c) Axial image of a patient with severe iron overload demonstrates accentuated decrease in the liver signal intensity.
Figure 4. Treatment follow-up of a patient with primary hemochromatosis. (a) Axial GRE T2*-weighted MR image shows the liver hypointensity that is due to iron overload. (b) Axial GRE T2*-weighted MR image obtained 1 year later, after phlebotomy, demonstrates a decrease in the liver hypointensity, which is caused by a decrease in the hepatic iron concentration.

Table 2
Patterns of Iron Deposition in Various Organs

<table>
<thead>
<tr>
<th>Deposition Pattern</th>
<th>Liver</th>
<th>Spleen</th>
<th>Bone Marrow</th>
<th>Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticuloendothelial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Parenchymal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Renal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mixed</td>
<td>Yes</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

*Cannot be seen in a young patient with mild overload or in mild initial disease.

of the complete loss of liver signal (12,18,19). Because of the capacity for quantitative and qualitative evaluation, MR imaging can be used noninvasively in the evolutionary and posttreatment control of hepatic iron overload, thereby avoiding multiple biopsies in these patients (19,23) (Fig 4).

Forms of Iron Deposition
In addition to the primary and secondary forms of hemochromatosis, iron overload can also be classified according to the deposition patterns. These patterns can help to differentiate among the possible causes of hemochromatosis (1,8,25–27) (Table 2).

Figure 5. Secondary hemochromatosis and reticuloendothelial pattern of iron overload. Axial GRE T2*-weighted MR image shows that the liver, spleen, and bone marrow demonstrate decreased signal intensity. The pancreas (arrow) has normal signal intensity.
Figure 6. Sickle cell disease. (a) Axial GRE T1-weighted in-phase MR image shows a decrease in the signal intensity of the spleen (arrow). Comparison with the GRE T1-weighted out-of-phase MR image (not shown) did not demonstrate the T2* effect, a finding consistent with calcium. (b) Axial nonenhanced CT image helps confirm that the MR appearance of the spleen is due to diffuse calcification (arrow) secondary to autosplenectomy.

Figure 7. Primary hemochromatosis and parenchymal pattern of iron overload. Axial GRE T2*-weighted MR image demonstrates that the liver and pancreas (arrow) show decreased signal intensity. The spleen and bone marrow have normal signal intensity.

Reticuloendothelial Deposition Pattern
In iron overload secondary to multiple transfusions, deposition generally occurs in the cells of the reticuloendothelial system of the liver, spleen, and bone marrow. This type of accumulation is not associated with tissue damage (8,25).

The signal intensity of the spleen and bone marrow can be used to evaluate the type of deposition pattern because in two of the other forms of iron deposition (parenchymal and renal), we normally do not observe any effect on these structures (8,25,27) (Fig 5). One of the diagnoses that is differentiated by the low signal intensity of the spleen is diffuse calcification secondary to autosplenectomy, which can be observed in cases of sickle cell anemia (Fig 6).

In the reticuloendothelial deposition pattern, the signal intensity of the pancreas is generally preserved, except when the volume of blood infused goes beyond the storage capacity of the reticuloendothelial system, leading to parenchymal deposition (1,25,28).

Parenchymal Deposition Pattern
This pattern occurs secondary to increased iron absorption. The pattern is observed mainly in patients with primary hemochromatosis or in cases of chronic anemia with inefficient erythropoiesis (thalassemia syndromes, congenital dyserythropoietic anemias, and sideroblastic anemias).

The excess iron accumulates initially in the periportal hepatocytes and then spreads to the rest of the liver, the pancreas, and the thyroid and leads to tissue damage (1,24–26). In this pattern of deposition, decreased signal intensity is observed in the liver and the pancreas, while in the spleen and the bone marrow, signal intensity is preserved (Fig 7).

In advanced forms of the disease, the myocardium and the hypophysis are affected. In young patients with mild overload, the signal intensity of the pancreas can be preserved (8,25).
Figures 8, 9.  (8) Iron overload and cirrhosis. Axial fat-saturated fast spin-echo (SE) T2-weighted MR image shows nodularity of the liver outline, morphologic changes suggestive of cirrhosis, and a low signal intensity of the liver that is due to iron overload. (9) Iron overload and hepatocellular carcinoma. (a) Axial fast SE T2-weighted MR image demonstrates low signal intensity of the liver that is due to iron overload and also shows a slightly hyperintense nodule (arrow). (b, c) On axial dynamic fat-saturated GRE T1-weighted MR images obtained after administration of a gadolinium-based contrast agent, the nodule shows enhancement in the arterial phase (arrow in b) and washout in the portal venous phase (arrow in c). The findings from histologic analysis disclosed that the nodule was a hepatocellular carcinoma.

In addition to the decreased signal intensity of the liver, hepatomegaly, fibrosis, and cirrhosis are observed in advanced cases (1,8,25) (Fig 8). Investigators have also shown a considerable increase in the rate of occurrence of hepatocellular carcinoma in these patients (1,29,30) (Fig 9).

Iron deposition in the heart may cause cardiomyopathy, pericarditis, and arrhythmias. Accumulation of iron in the endocrine system may lead to diabetes mellitus, hypopituitarism, hypogonadism, and hypoparathyroidism (1,28).
Renal Deposition Pattern
Iron deposition in the kidneys is only seen in cases of intravascular hemolysis caused by mechanical stress in patients with heart valves, in patients with paroxysmal nocturnal hemoglobinuria, or in hemolytic crises of sickle cell disease (8,31–34). In these cases, hemosiderin is deposited in the proximal convoluted tubules, promoting inversion of the signal intensity of the renal cortex, which is hypointense in relation to the medulla on the T1-weighted images and demonstrates an accentuated decrease in the cortical signal intensity on the T2-weighted images (32–34). Despite the dramatic appearance of this type of accumulation, it is not believed that this accumulation affects renal function (8,31,35) (Fig 10).

Mixed Deposition Patterns
In patients with advanced forms of the disease, an atypical distribution pattern of iron overload is observed (8,25,36,37). Patients with chronic anemias caused by ineffective erythropoiesis may require multiple transfusions, which can result in parenchymal and reticuloendothelial deposition patterns (25,28). Similarly, it is possible to observe patients with paroxysmal nocturnal hemoglobinuria or patients with anemias that are accompanied by intravascular hemolysis receiving multiple transfusions, resulting in renal and reticuloendothelial deposition (8,31,32).

Iron Overload and Other Storage Diseases
The association between deposition of fat and deposition of iron in the hepatic parenchyma is not infrequent. This association can make diagnosis challenging if the correct concepts and sequences are not used. The decrease in signal intensity occurs on the out-of-phase images in steatosis, while the decrease occurs on the in-phase images in hemochromatosis (21,38).

With CT, the diagnosis of combined steatosis and hemochromatosis can be difficult. Unlike CT, the MR imaging sequences used for quantification of hepatic iron are not influenced by steatosis because with the selected echo times, the water and fat spins are in phase.
Because of the decrease in the hepatic parenchymal signal intensity that is due to iron overload, some lesions may appear with relatively high signal intensity on the T2-weighted images, a finding that is generally seen in benign lesions (cysts and hemangiomas) (39). Thus, particularly in this situation, the use of intravenous contrast agent injection is crucial for lesion characterization (Fig 13).

The diffuse forms of hemochromatosis and steatosis generally do not cause greater difficulties for diagnosis (Fig 11). However, the nodular form can simulate true lesions. These pseudonodules result from areas of focal steatosis or from areas of hepatic parenchyma that are spared from steatosis or iron overload. To differentiate these pseudonodules from true nodules, we need to observe the variations in signal intensity on the in-phase and out-of-phase images, together with the enhancement pattern, which should be similar to that of the normal liver, and the lack of expansive effect and the absence of vascular distortion (Fig 12).

**Iron Overload and Hepatic Focal Lesions**

Great care should be taken when evaluating the signal of focal lesions in relation to the hepatic parenchyma. Because of the decrease in the hepatic parenchymal signal intensity that is due to iron overload, some lesions may appear with relatively high signal intensity on the T2-weighted images, a finding that is generally seen in benign lesions (cysts and hemangiomas) (39). Thus, particularly in this situation, the use of intravenous contrast agent injection is crucial for lesion characterization (Fig 13).
Figure 12. Pseudonodules (arrows) and iron overload. (a) Axial GRE T2-weighted MR image demonstrates the low signal intensity of the liver that is due to iron overload and also shows nodules without expansive effect or vascular distortion. (b, c) Axial GRE T1-weighted out-of-phase MR image (b) demonstrates a decrease in the signal intensity of the nodules compared with the signal intensity of the nodules on the axial GRE T1-weighted in-phase MR image (c), a finding suggestive of focal steatosis and spared areas of hemochromatosis. (d) Axial gadolinium-enhanced fat-saturated GRE T1-weighted MR image shows no different enhancement. (e) Ultrasonographic image demonstrates that this area is hyperechoic.
**Figure 13.** Focal hepatic lesion in iron overload. (a) Axial fat-saturated fast SE T2-weighted MR image shows low signal intensity of the liver that is due to iron overload and also shows relatively high signal intensity of the lesion (arrow), simulating a benign lesion. (b) Axial gadolinium-enhanced fat-saturated GRE T1-weighted MR image shows peripheral enhancement of the lesion (arrow). The findings from histologic analysis showed that the lesion was a colon cancer metastasis.

**Figure 14.** Colon cancer, liver metastases, and iron overload in a young male patient. (a) Axial fast SE fat-saturated T2-weighted MR image demonstrates low signal intensity of the liver and secondary hyperintense liver nodules. (b) Axial GRE T1-weighted in-phase MR image demonstrates hypointense secondary liver nodules and slight iron overload. (c) Coronal single-shot fast SE T2-weighted MR image shows a tumor (arrow) of the descending colon.
Hemochromatosis and Neoplasias

Although no consensus exists in the literature, some investigators have demonstrated links among iron overload, the genes of hemochromatosis, and neoplasias other than hepatocellular carcinoma, particularly those of the colon (adenoma and adenocarcinoma). Also, an increased rate of occurrence of these tumors is seen in a younger age group (Fig 14) (40–42).

Other Findings Associated with Iron Overload

Patients with anemias that are accompanied by inefficient erythropoiesis, as well as iron overload signal intensity, can also show other evidence of long-term anemia, such as foci of extramedullary erythropoiesis in the paravertebral regions and, less frequently, in the hepatic parenchyma, leading to a differential diagnosis with neoplastic lesions (Fig 15).

Some types of anemia, such as Fanconi anemia, benefit from treatment with steroids (oxymetholone, methyltestosterone, or danazol) to stimulate erythropoietin production. However, these drugs can induce the development of hepatic tumors, including hepatocellular carcinoma and adenoma (43), as well as peliosis hepatis (44–46).
Figure 16. Fanconi anemia treated with oxymetholone. Axial fat-saturated fast SE T2-weighted MR image (a) and gadolinium-enhanced fat-saturated GRE T1-weighted MR image (b) show low signal intensity of the liver and spleen that is due to secondary hemochromatosis. Multiple small (1–3-mm) blood-filled lacunar spaces seen in a are suggestive of peliosis hepatis. Multiple enhancing nodules (arrows) seen in b were confirmed as adenomas at percutaneous biopsy.

(Fig 16). Suspension of administration of those drugs can lead to regression of the lesions.

Conclusions
Iron overload is a relatively common disease with various causes. Making a clinical diagnosis is often difficult. Knowledge of the imaging findings, the patterns of distribution, and associated diseases can facilitate diagnosis. MR imaging has a fundamental role because it can contribute, in a noninvasive way, to the diagnosis, the estimation of liver iron concentration, and the follow-up of these patients.

References


MR Imaging Findings of Iron Overload  
Marcony Queiroz-Andrade, MD, et al

MR imaging is the best noninvasive method for measuring the level of iron in the liver for the purposes of confirming the diagnosis, determining the severity, and monitoring therapy with high sensitivity, specificity, and positive and negative predictive values (12,18–20). The accumulation of iron ions in the tissues, because of the superparamagnetic properties of the ions, causes local distortion in the magnetic fields and relaxation of the spins, which results in shortening of the longitudinal relaxation time (T1), the transverse relaxation time (T2), and particularly the transverse relaxation time as affected by magnetic field inhomogeneity (T2*). This effect causes a loss of signal intensity in the affected organs that is proportional to the iron deposit (17,21).

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The results of examination of unaffected subjects show that the hepatic parenchyma demonstrates higher signal intensity than that of the paraspinal musculature with all sequences. Slight to moderate iron overload is better identified and evaluated on the GRE images obtained with longer echo times, which demonstrate a decrease in the signal intensity of the liver parenchyma (Fig 3).

In addition to the primary and secondary forms of hemochromatosis, iron overload can also be classified according to the deposition patterns. These patterns can help to differentiate among the possible causes of hemochromatosis (1,8,25–27) (Table 2).

Patients with anemias that are accompanied by inefficient erythropoiesis, as well as iron overload signal intensity, can also show other evidence of long-term anemia, such as foci of extramedullary erythropoiesis in the paravertebral regions and, less frequently, in the hepatic parenchyma, leading to a differential diagnosis with neoplastic lesions (Fig 15). Some types of anemia, such as Fanconi anemia, benefit from treatment with steroids (oxymetholone, methyltestosterone, or danazol) to stimulate erythropoietin production. However, these drugs can induce the development of hepatic tumors, including hepatocellular carcinoma and adenoma (43), as well as peliosis hepatis (44–46).