Noninvasive assessment of hepatic iron overload in patients with hemochromatosis


Abstract
Our purpose is to analyze the metabolism and pathophysiology of iron deposition, to describe the usefulness of magnetic resonance imaging (MRI) in the estimation of hepatic iron overload using specific sequences, and to review the different pathologies leading to iron overload in the abdominal organs and its characteristic features at MRI. Iron overload in the liver may be due to a genetic disorder (primary hemochromatosis), or to multiple blood transfusions and chronic diseases like increased absorption, myelodysplasia, thalassemia, etc. (secondary hemochromatosis). MRI is a noninvasive method that detects iron overload and allows treatment monitoring after diagnosis, avoiding repeated biopsies. This is due to the paramagnetic properties of iron accumulation in the tissues causing local distortion in the magnetic field. This phenomenon is seen as a reduction of the MRI signal in the affected organs, being directly proportional to the amount of iron deposited.

The conventional in-phase and out-of-phase MRI sequences can show iron deposition in the liver, spleen and pancreas, although milder forms may go undetected if more sensitive sequences, like gradient echo sequence, are not used, according to the technique proposed by Gandon et al., which can quantitatively estimate the severity of iron deposition. Iron deposition can show a reticuloendothelial type pattern (secondary to multiple transfusions with iron deposits in the liver, spleen and bone marrow without tissue damage), a parenchymal pattern (involving the liver and pancreas) and a mixed pattern.

MRI has a fundamental role in the diagnosis of hemochromatosis, especially in the subclinical phase. It helps to stratify the severity of hepatic iron overload and assess response to treatment, avoiding invasive procedures.

Keywords: iron; hemochromatosis; magnetic resonance imaging; gradient echo

Introduction
Iron overload in the liver may be due to a genetic disorder (primary hemochromatosis), or to multiple blood transfusions and chronic diseases like increased absorption, myelodysplasia, thalassemia, etc. (secondary hemochromatosis). Clinical diagnosis is often difficult to establish because patients do not usually develop clinical symptoms until the advanced stages of the disease. Magnetic resonance imaging (MRI) is a noninvasive method that detects iron overload and allows to monitor treatment after diagnosis, avoiding repeated biopsies.

Our purpose is to analyze the metabolism and pathophysiology of iron deposition, to describe the usefulness of MRI in the estimation of hepatic iron overload using specific sequences, and to review the different pathologies leading to iron overload in the abdomen, also describing its appearance at MRI.

Iron metabolism and hemochromatosis
The average adult body contains approximately 4-5 g of iron; 4 g are functional and are present in the hemoglobin of the blood cells, in the myoglobin of muscle and in a variety of enzymes (e.g., cytochromes). The rest is stored in hepatocytes and reticuloendothelial system cells (including the liver, spleen and bone marrow Kupffer cells). Medullary erythropoiesis requires around 20 mg of iron daily.
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Table 1: Features of primary and secondary hemochromatosis 2*

<table>
<thead>
<tr>
<th>Primary hemochromatosis</th>
<th>Secondary hemochromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary autosomal recessive disease</td>
<td>Parenteral administration of iron (repeated blood transfusions)</td>
</tr>
<tr>
<td>Increased intestinal absorption with normal dietary intake of iron</td>
<td>Dietary iron overload</td>
</tr>
<tr>
<td>Iron excess deposits in liver, pancreas, heart, pituitary gland, thyroid and synovium cells</td>
<td>Iron is predominantly deposited in the reticuloendothelial system</td>
</tr>
<tr>
<td>Leads to cellular damage, organ dysfunction, and development of malignant tumors.</td>
<td>Less toxic</td>
</tr>
</tbody>
</table>

* Modified from 2

However, only 1–2 mg of dietary iron is absorbed (i.e. 10% of the total amount ingested)1,2. But an equivalent amount is lost each day because of epithelial desquamation, menstruation, and other forms of blood loss 2. The rest of the daily iron requirement is obtained through an adequate recycling mechanism that includes the reuse of iron found in senescent erythrocytes. Thus, the absorption is physiologically well controlled while excretion has no effective mechanism 3.

The iron absorbed by the small intestine (duodenum and proximal jejunum) binds to transferrin—a transport protein in blood 1,3,4. Once iron is bound to transferrin, it is selectively deposited in hepatocytes, red blood cells (blood tissue-forming precursors and erythron) or, to a lesser extent, in other iron containing tissues, like muscle 3. Instead, the reticuloendothelial system cells store iron derived from the phagocytosis of senescent erythrocytes (a process known as extravascular hemolysis) 1,2. This processed iron may be stored intracellularly as ferritin or released into the circulation bound to transferring 1.

Excess iron may result from increased intestinal absorption or parenteral administration (blood transfusion) (table 1) 1-3. Thus, iron storage diseases can be classified into 2 groups: primary, including genetic hemochromatosis, and secondary, which comprises chronic diseases or diseases related to multiple transfusions (secondary hemochromatosis) (table 2).

Primary hemochromatosis is a recessive autosomal disorder that alters a protein involved in the regulation of iron absorption3,5. 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. Primary hemochromatosis is considered the most common genetic disease in the white population, with a rate of disease of 0.2%–0.5% for homozygous and as much as 10% for heterozygous 2.

Absorbed iron is transported to the liver, where it accumulates initially in the periportal hepatocytes. Reticuloendothelial system cells absorb normal amounts of iron from erythrocytes, but rapidly release intracellular ferritin, being unable to store excess iron (the same as intestinal mucosal cells) 1. Making a clinical diagnosis is often difficult for two reasons: firstly, patients usually remain asymptomatic during the first decade of their disease; but in addition, the first signs and symptoms of liver dysfunction, diabetes mellitus, cardiomy-
Figure 1. Conventional non-contrast enhanced magnetic resonance imaging in a healthy patient: (a) T2-weighted sequence, (b) in-phase sequence, (c) fat-suppressed T1-weighted sequence and (d) out-of-phase sequence.

Figure 2. Conventional magnetic resonance imaging in a young patient with hemochromatosis secondary to thalassemia and multiple transfusions who was splenectomized: (a) T2-weighted sequence, (b) in-phase sequence, (c) fat-suppressed T1-weighted sequence and (d) out-of-phase sequence. MR image shows a decrease in the signal intensity of the liver, which is even more evident on the in-phase image (b). Also note the decrease in signal intensity of the pancreatic parenchyma in this sequence (star) in relation to the out-of-phase sequence (d). There is also a decrease in the signal intensity of the bone marrow vertebrae in all sequences, flagged with a circle in (a).
opathy and/or arthropathy are nonspecific. In fact, they are often attributed to other causes. Laboratory values used in the diagnosis of hemochromatosis include the ferritin level and the transferrin saturation index, which are generally increased in these cases. 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.

Even if liver hepatic biopsy is considered the reference standard method for diagnosis, it is an invasive procedure with potential risks, susceptible to sampling error because of the tiny amount of tissue obtained.

MR imaging is a noninvasive method that is useful for detecting the presence of iron overload and for monitoring therapy once diagnosis has been established, thus avoiding repeated biopsies. This is due to the paramagnetic properties of iron ions, whose accumulation in the tissues causes local distortion in the magnetic fields, with a consequent loss of signal intensity in the affected organs that is proportional to the amount of iron deposition.

### Hepatic iron overload: detection and characterization by specific gradient-echo sequences

Conventional MRI study of the liver includes a T2-weighted sequence, a fat-suppressed T1-weighted sequence, an in-phase and out-of-phase sequence and eventually a T1-weighted sequence with fat suppression after the administration of intravenous contrast (fig. 1). As previously mentioned, because of the paramagnetic properties of the iron ions accumulated in tissues, a local distortion occurs in the magnetic fields with a consequent loss of signal intensity in the affected organs that is proportional to the iron deposition (fig. 2).

In-phase and out-of-phase sequences can demonstrate the presence of hepatic iron overload in tissues. The in-phase sequence shows a decrease in the signal intensity of tissues, as compared to the out-of-phase sequence. This effect, which is the opposite of the effect observed in patients with steatosis (fig. 4), 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.

Even if with conventional in-phase and out-of-phase imaging we can infer the presence of iron deposition in the liver, spleen and pancreas, slight iron overloads might go unnoticed if we do not use more sensitive sequences, such as the gradient-echo sequences (fig. 5). The latter, according to the technique proposed by Gandon et al., can quantitatively estimate the severity of iron deposition (fig. 6). When GRE sequences are obtained with increasingly longer echo times, iron deposition becomes evident, even in slight overloads, and the approximate value can be estimated from a worksheet.

Hepatic iron overload estimation may be performed using scanners of 0.5T, 1.5T, 3T and 5T, by choosing the appropriate protocol depending on the equipment.

In addition to being classified as primary or secondary, iron storage diseases may be divided into 3 types according to the iron deposition pattern (table 3).

<table>
<thead>
<tr>
<th>Deposition pattern</th>
<th>Liver</th>
<th>Spleen</th>
<th>Pancreas</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reticuloendothelial</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mixed</td>
<td>Yes</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
</tbody>
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* Modified from 2

### Parenchymal deposition pattern

This pattern occurs as a result of increased iron absorption. The pattern is observed mainly in patients with primary hemochromatosis or in cases of chronic anemia with ineffective erythropoiesis (thalassemia syndromes, congenital dyserythropoietic anemias, and sideroblastic anemias). Initially, the iron in excess accumulates in the perportal hepatocytes and then spreads to the rest of the liver, the pancreas, and the thyroid, causing tissue damage.

In this pattern, signal intensity decreases in the liver and the pancreas, while in the spleen and the bone marrow, signal

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**Table 3: Patterns of iron deposition in the body**

<table>
<thead>
<tr>
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</tr>
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* Modified from 2
Figure 3. Comparative in-phase and out-of-phase sequences in 2 patients: one healthy (a and b) and the other with secondary hemochromatosis (c and d). Note the diffuse hypointensity of the hepatic parenchyma (star) and, to a lesser extent, of the spleen (c).

Figure 4. MRI in two different patients with in-phase and out-of-phase sequences. (a and b) Secondary hemochromatosis with accentuated diffuse hypointensity of the hepatic parenchyma in the in-phase sequence (a). (c and d). Hepatic steatosis: MRI shows a decrease in the signal intensity of the hepatic parenchyma in the out-of-phase sequence (d).
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Figure 5. Specific gradient-echo sequences in a patient with hepatic iron overload: (a) T1-weighted GRE 120/4/90; (b) DP-weighted GRE 120/4/20; (c) T2-weighted GRE 120/9/20; (d) T2+-weighted GRE 120/14/20; (e) T2++-weighted GRE 120/21/20. Note the decrease in the signal intensity as compared with the paraspinal muscles. The in-phase sequence (f) does not show alterations in the signal intensity of the liver.

Figure 6. Signal intensity measurements done by means of regions of interest (ROIs) of approximately 1 cm². Three ROIs must be placed on the right part of the liver to avoid artifacts and 2 ROIs must be placed on the paraspinal muscles (right and left). These ROIs must be placed on the same image in all sequences in order to avoid global signal intensity variations. At the time of placing the ROI on the image, try to avoid liver vessels, heterogeneous areas, artifacts and particularly the decrease in signal intensity of the paraspinal muscle, adjacent to the lung bases.
intensity is preserved. Nevertheless, in young patients with slight iron overload, the signal intensity in the pancreas may be preserved.

**Reticuloendothelial deposition pattern**

In iron overload secondary to multiple transfusions, iron deposition generally occurs in the reticuloendothelial system cell of the liver, spleen, and bone marrow. Unlike the parenchymal deposition pattern, this type of accumulation is not associated with tissue damage. The signal intensity of the spleen and bone marrow can be used to evaluate the type of deposition pattern because in the parenchymal form, no effect is normally observed on these structures. In addition, the signal intensity of the pancreas is generally preserved, except when the amount of iron administered (by multiple transfusions) exceeds the storage capacity of the reticuloendothelial system.

Figure 7. Classification of iron overload diseases according to the iron deposition pattern. MRI in 3 different patients with in-phase and out-of-phase sequences: (a and b) parenchymal pattern; note the decrease in signal intensity in the in-phase sequence, both in the liver and in the pancreas (stars), indicating the presence of iron deposition; (c and d) reticuloendothelial pattern, iron deposition in the liver, spleen and bone marrow (stars); (e and f) mixed pattern: patient with iron deposition in the liver, spleen and pancreas, as well as in the bone marrow (stars).
Mixed deposition pattern

Patients with chronic anemias caused by ineffective erythropoiesis (such as thalassemia) often require multiple transfusions, which can result in atypical distribution patterns (parenchymal and reticuloendothelial deposition).

Conclusion

Hemochromatosis is a disease with little clinical impact, which sometimes makes diagnosis difficult in the early stages of the disease. However, knowledge of the imaging findings, the patterns of iron distribution and associated diseases can facilitate diagnosis. MR imaging has a fundamental role, especially in the subclinical stage, because it can contribute to stratify the severity of hepatic iron overload and assess the response to treatment, avoiding invasive procedures.

References


Conflicts of interest

The authors declare no conflicts of interest