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Systemic iron overload: Review of pathophysiology and clinical-radiological diagnostic approach

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Abstract

Systemic iron overload is a condition that carries significant implications for health, making it crucial to understand its pathophysiology and the precise clinical and radiological diagnostic methods. This article comprehensively reviews the pathophysiology of iron metabolism, highlighting its crucial role in multiple cellular processes and the regulatory mechanisms that maintain its balance in the body. Furthermore, the diagnostic approach to iron overload is analyzed in detail, reviewing the role of various imaging techniques; highlighting magnetic resonance imaging as a method to develop an accurate and non-invasive assessment of iron load in various tissues.

Keywords: Systemic iron overload; Iron pathophysiology; Magnetic resonance imaging; Iron deposition patterns; Hemochromatosis; Complications of iron overload; Radiological diagnosis.

1. Introduction

In the human body, the regulation of iron is under strict control, involving various hormones and proteins. When this balance is compromised, whether due to genetic or acquired causes, systemic iron overload can occur, leading to serious consequences for various organs and systems.

The accurate diagnosis of iron overload is essential for guiding therapy and preventing complications. Various clinical and radiological techniques have been developed for this purpose, each with its advantages and limitations. Magnetic resonance imaging has emerged as an invaluable tool for assessing iron burden in a non-invasive and precise manner.

In this review, we will explore the underlying pathophysiology of systemic iron overload and examine in detail the available diagnostic modalities, highlighting the importance of early detection and precise stratification of iron burden severity for effective clinical management.

2. Pathophysiology and Diagnostic approach

2.1. Iron

Iron is recognized as an important cofactor in multiple cellular processes, with the ability to donate and accept electrons rapidly, oscillating between the ferric and ferrous forms. This property makes it a crucial component of cytochromes, enzymes such as catalase and peroxidase, oxygenation molecules and chains, DNA synthesis, replication, metabolism, and cellular growth (1)(2). However, paradoxically, this ability to donate and gain electrons, which confers metabolic

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importance to iron, also makes it participate in highly deleterious free radical-generating reactions (2). Among these reactions, the Fenton reaction stands out, which is catalyzed by iron and converts hydrogen peroxide into hydroxyl free radicals capable of affecting cell membranes, proteins, and DNA (1).

In an adult with adequate nutrition, iron levels of approximately 3-5 grams are expected (1)(3), of which approximately 60% is incorporated into hemoglobin with 10% in muscular myoglobin, and the remainder is stored in hepatocytes and reticuloendothelial macrophages. The exact mechanism of iron excretion is not known; however, about 1-2 mg of iron is lost daily through sweat, blood loss, and losses of intestinal origin (3). To compensate for this loss, the body absorbs at least the same amount of iron daily from the diet (3,4). It is important to note that hemoglobin synthesis requires 20-25 mg of iron daily, so iron must be recycled and tightly regulated. The peptide hormone hepcidin, along with its receptor ferroportin, primarily maintains iron homeostasis, while iron regulatory proteins (IRPs) play an important role in controlling intracellular iron (3).

2.2. Iron Absorption

Iron can physiologically enter the human body through two main mechanisms: during the fetal stage via the placenta and through the wall of the small intestine in the postnatal stage (5). The normal dietary intake of iron is close to 10-20 mg/day, of which 1-2 mg is absorbed in the proximal duodenum through ferroportin transporters that are regulated by the action of hepcidin (4).

Most iron absorption occurs in the upper part of the intestine, more specifically in the duodenum and proximal jejunum, through enterocytes (3,5). Among these, there are enterocytes with high expression of proteins involved in iron absorption such as DMT-1 (Divalent Metal Ion Transporter 1), which is important in multiple pathologies including anemia (5). Additionally, there is a ferrous reductase (Cybrd1/DcytB1) present on the brush border of the enterocyte and duodenal cytochrome (to a lesser extent), which facilitates the reduction of ferric iron to its ferrous form, which is a substrate for DMT-1 (3).

Once iron has been taken up by enterocytes, it can be stored within endogenous ferritin or exported into the bloodstream to be transported to other tissues of the body. Ferroportin (a transmembrane protein found in the basolateral membrane of the enterocyte) is the sole iron-exporting protein and is responsible for the movement of iron from the enterocyte into circulation (mutations at this level cause iron accumulation) (5). Iron is also regulated at the intestinal level by cellular iron levels and hypoxia, under the strict control of the Iron Regulatory Protein (IRP) system, which operates by affecting the post-transcriptional regulation of proteins involved in iron metabolism (5).

The overall absorption of iron is controlled by hepcidin (its expression is inversely proportional to the body's demand for iron) (6), which is produced by hepatocytes in the liver (Despite reports of local hepcidin production in other organs such as the heart, alveolar macrophages, and spleen) (7). Hepcidin circulates in the blood and binds to ferroportin (FPN) on the surface of cells (including enterocytes). This binding leads to the degradation and internalization of FPN, resulting in the release of iron into the bloodstream (5).

2.3. Hepcidin Regulation

The expression of hepcidin is regulated by the BMP6/SMAD pathway. BMPs (Bone morphogenic proteins) include BMP 2, 6, and 9, with BMP 2 (8) and BMP 6 (a cytokine from the transforming growth factor beta family produced and secreted by hepatocytes in proportion to their iron load) being the most relevant. BMP 6 binds to the BMP I/II receptor complex on hepatocytes, leading to the phosphorylation of SMADs (Small Mothers Against Decapentaplegic) mediated by receptors 1, 5, and 8. This phosphorylation allows the proteins to interact with SMAD4, and the resulting complex is transported to the nucleus where it stimulates the transcription of the hepcidin encoding gene (HAMP) (5).

2.4. Iron Storage

Erythropoiesis utilizes a significant portion of iron to produce red blood cells and hemoglobin; senescent red blood cells are recycled by macrophages of the reticuloendothelial system (7). Ferrous iron is exported into the plasma by FPN, while unused iron is stored in macrophages and the liver primarily in the form of ferritin (When the blood iron level exceeds the capacity of transferrin binding, the liver becomes the major iron depot) (3), eventually converting into hemosiderin if ferritin deposits are saturated (4).

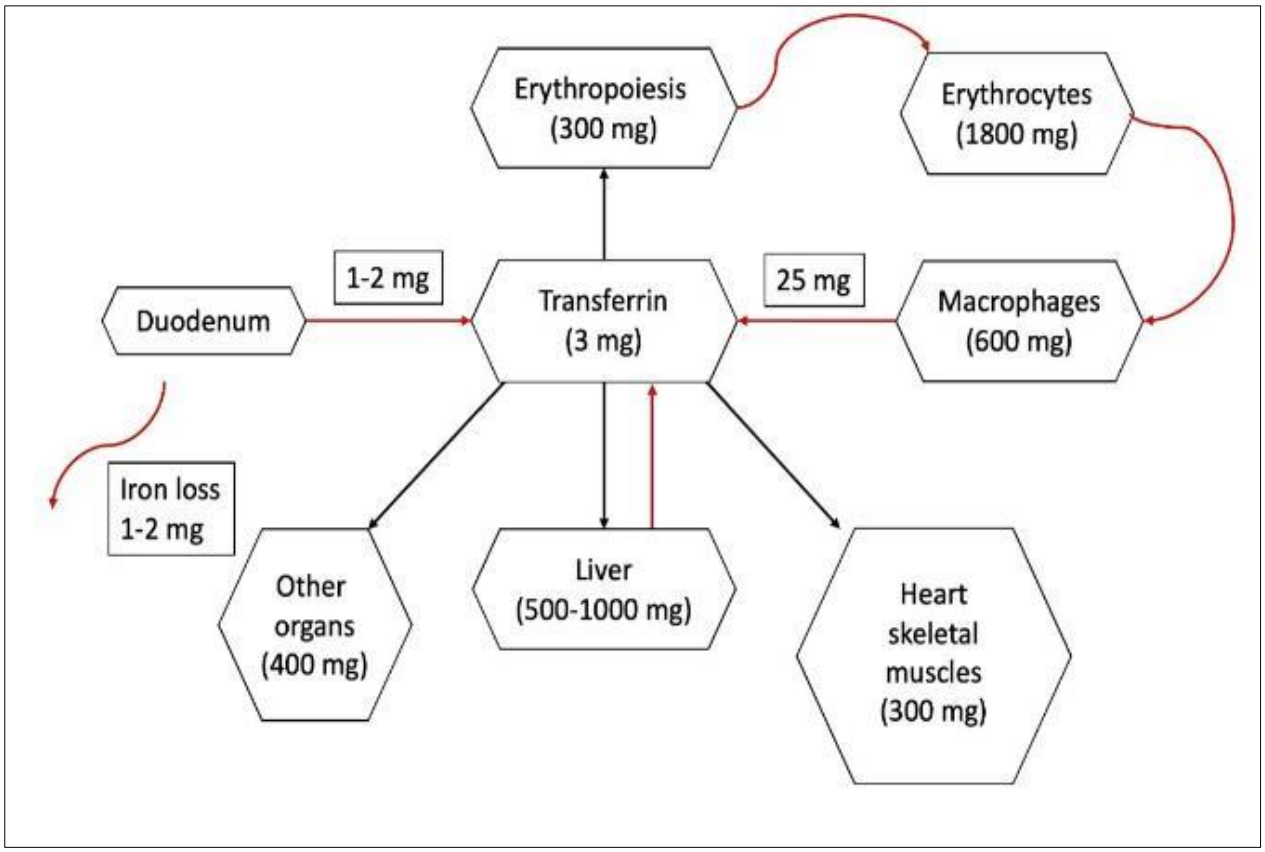

Figure 1 Iron distribution in the body.

2.5. Systemic Iron Overload

Iron overload is a systemic disorder characterized by elevated plasma iron levels and the accumulation of iron in parenchymal cells in the form of ferritin and hemosiderin. As mentioned earlier, the liver is the primary organ of iron storage (hepatocytes and Kupffer cells), and therefore, it is the first to demonstrate iron overload (4).

In iron overload, transferrin saturation can exceed 45%, at which point, non-transferrin-bound iron is created, especially in hepatocytes. Eventually, if transferrin saturation exceeds 75%, a new form of non-transferrin-bound iron is produced, called labile plasma iron, which has the potential to generate toxic reactive radicals (4).

Iron deposition diseases can be classified into two categories: primary and secondary (4).

2.6. Primary Overload

Primary iron overload is caused by genetic disease (4). Primary iron overload is associated with hemochromatosis (systemic iron overload caused by hepcidin deficiency) (9), which is the most common genetic disease in European populations and is basically due to mutations in the HFE gene (High Iron Fe) (4,10). Although multiple mutations can lead to the pathology, the most frequent is the p.Cys282Tyr (C282Y) substitution (9,10), with individuals homozygous for this mutation suffering from the disease and its symptoms (10). Other genetic diseases such as hereditary aceruloplasminemia, diseases affecting ferroportin, and hereditary atransferrinemia, although rare, are also associated with primary iron overload (4).

2.7. Secondary Overload

Secondary iron overload is caused by an increase in exogenous iron, primarily associated with multiple red blood cell transfusions and pathologies requiring them, such as: beta-thalassemia major, sickle cell anemia, myelodysplastic syndromes, aplastic anemia. Similarly, diseases that interfere with hepcidin expression, such as hemoglobinopathies or thalassemias, increase intestinal iron absorption leading to consequent secondary overload. Additionally, although less common, secondary iron overload can be caused by intravenous or oral iron supplementation (4).

2.8. Diagnosis of Systemic Iron Overload

Iron overload in the liver leads to the release of reactive oxygen species, causing toxic effects on the cell membrane and nucleus of hepatocytes (4,11). Therefore, early detection and gradation are important to prevent organ dysfunction through oxidative cytotoxicity at the hepatic level (leading to cirrhosis, end-stage liver failure, hepatocellular carcinoma), cardiac level (resulting in cardiomyopathy, arrhythmias, and congestive systolic dysfunction), endocrine system (with growth failure of pituitary origin and type 2 diabetes at the pancreatic level) (4), and some additional types of cancer (2).

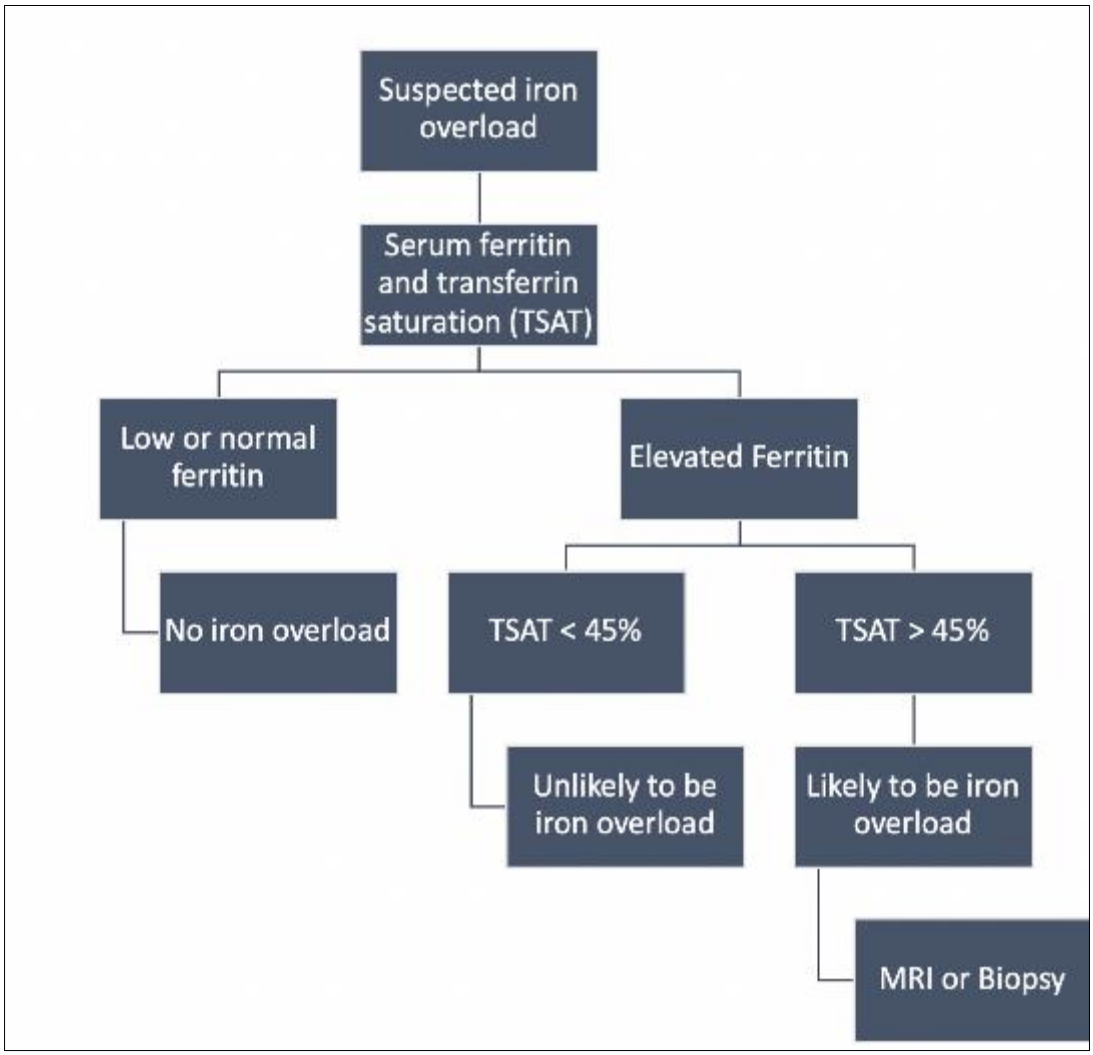

Figure 2 Diagnostic algorithm for suspected iron overload.

2.8.1. Ferritin and Transferrin Levels

Blood levels of ferritin and transferrin are widely used to detect iron overload; however, these can be affected by various mechanisms such as proinflammatory states, infections, tumors, alcoholism, cellular necrosis, and chronic iron deficiency (4)(12).

2.8.2. Hepatic Biopsy

Hepatic biopsy serves three main purposes: for diagnosis, for disease staging (prognosis), and to assist in therapeutic decision-making (13). Due to the close relationship between iron and the liver (related to total iron levels), the liver is the organ of choice for biopsies in the context of iron overload studies, where the appearance of iron staining granules in periportal hepatocytes is the first evidence of overload (11). The histological staging of hepatic iron concentration is done by two main methods:

1. Biochemical (Reference Method), where techniques such as colorimetric or atomic absorption are employed (14), and 2. semi-quantitative histological staging using Prussian blue staining and different levels of microscopic magnification where a value ranging from 0 to 4 is assigned, where 0 indicates absence of granules at x400 magnification and 4 indicates iron visualization at x10 magnification or by naked eye (4)(14). It is important to recognize that this technique offers advantages such as evaluating the parenchyma for the gradation of iron found, as well as other potentially present findings in the sample such as fatty infiltration, fibrosis, inflammation, and biliary pathology. However, it has limitations when studying the entire organ due to sample size and zone, observer dependence, and inherent characteristics of the procedure itself (4).

2.9. Diagnostic Imaging

Ultrasound does not allow for the detection or quantification of iron overload. Computed tomography enables the detection of iron overload by demonstrating increased attenuation of the hepatic parenchyma, but it is not sensitive or specific for staging. However, there is sufficient validity when comparing the image obtained by magnetic resonance imaging (MRI) with pathological methods, which supports its use as it is more accurate than liver biopsy for the evaluation of total body iron and non-invasive staging of iron overload (15). Therefore, MRI is considered the standard for the non-invasive diagnosis and monitoring of diseases or conditions potentially triggering systemic iron overload, such as chronically transfused patients (16)(4).

2.9.1. Ultrasound (US)

As mentioned, ultrasound lacks utility in diagnosing iron overload. However, it is used in diagnosing pathologies secondary to iron overload, such as fibrosis, cirrhosis, portal hypertension, or hepatocellular carcinoma (4)(17).

2.9.2. Computed Tomography (CT)

CT demonstrates a homogeneous increase in hepatic parenchymal attenuation at 72 HU or more, with low sensitivity (63%) and high specificity (96%) in diagnosing iron overload (18)(19). Additionally, conditions that decrease liver attenuation, such as hepatic steatosis, Wilson's disease, and chronic amiodarone therapy, further decrease the study's sensitivity (18). Due to exposure to ionizing radiation, it is not a useful monitoring and follow-up method (20).

2.9.3. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is the best non-invasive method for measuring the total level of iron in the liver for the purpose of confirming diagnosis, determining severity, and monitoring therapy (18)(21). It has high sensitivity, specificity, positive and negative predictive values (18). Additionally, the percentage of iron overload diagnosed by MRI has a high correlation with values found in liver biopsies (18).

At a technical level, the diagnosis by MRI is evident because the accumulation of iron in tissues due to the superparamagnetic properties of ions causes local distortion in the magnetic field and spin relaxation, resulting in shortening of both longitudinal relaxation time (T1) and transverse relaxation time (T2), especially T2*. This effect leads to a loss of signal intensity in the affected organ, which is proportional to the iron deposition on in-phase images compared to out-of-phase images (18)(22). This effect is opposite to the characteristic in patients with hepatic steatosis; therefore, the in-phase sequence has higher sensitivity to detect iron deposits due to the increased T2* effect (18).

Similarly, at a clinical level, patients with elevated ferritin levels without evidence of iron overload (T2* >18 ms) should be evaluated for hyperferritinemia cataract syndrome, which has a genetic origin (12). Those with high transferrin saturation and evidence of hepatic (T2* <18 ms) and splenic (T2* <20 ms) iron overload should be genetically evaluated for classical ferroportin disease (SLC40A1 gene) (12). Patients with elevated ferritin saturation without evidence of hepatic iron deposition (T2* relaxation >20 ms) usually have non-alcoholic liver disease and metabolic syndrome (12).

The staging of iron overload severity at the time of diagnosis is important for establishing the timeliest treatment to prevent complications. This staging can be done as mild, moderate, or severe (4). Similarly, it can be performed subjectively or quantitatively. In the subjective approach, the intensity signal of the liver is compared with adjacent structures less prone to iron effects, such as spinal muscles. In the quantitative approach, quantitative imaging techniques of magnetic resonance imaging are utilized (4).

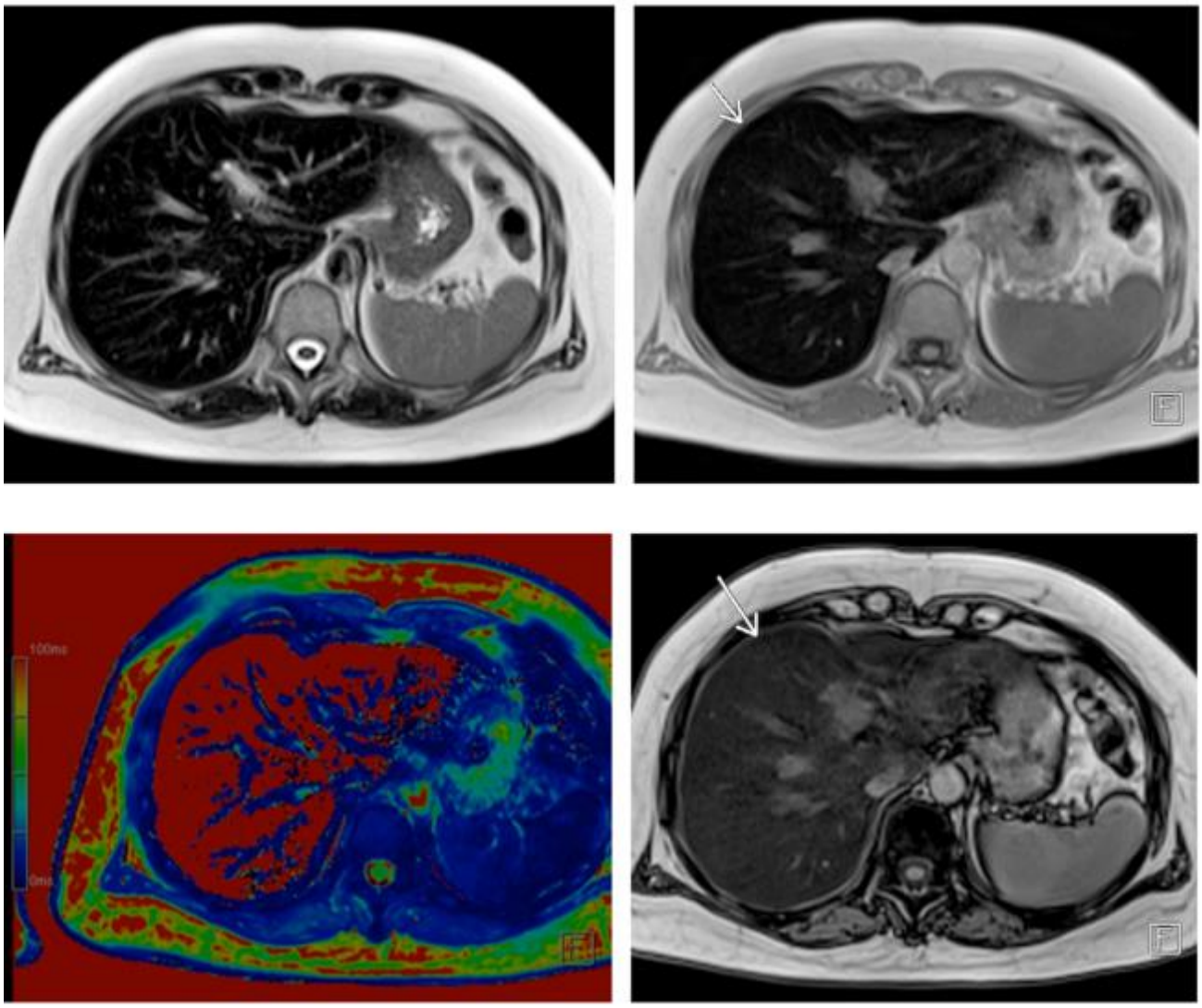

Figure 3 Contrast-Enhanced Liver Elastorresonance with Quantification of Lipids and Iron. Images in axial slices in T2, T1 in-phase, T2* and T1 out-of-phase sequences. Liver parenchyma is markedly and diffusely hypointense in the in-phase T1 sequence, and in T2, compared to the spleen, consistent with increased hepatic iron concentration. The R2* measurement was 305.0 s-1, corresponding to an intrahepatic iron concentration (LIC) of 9.6 mg/g, indicating moderate iron overload.

2.10. Quantification of Iron Overload by Magnetic Resonance Imaging

There are several methods to quantify iron overload using MRI: Liver-to-muscle signal intensity ratio (GRE), T2 and R2 relaxometry, T2* and R2* relaxometry, and quantitative susceptibility mapping (4)(20)(23)(17). Among these, the most sensitive, available, and commonly used method is GRE (Gradient-Recalled-Echo) with T2 weighted (21)(4)(18)(24)(25)(22). In healthy subjects, the liver parenchyma shows higher signal intensity than spinal muscles throughout the sequence. Conversely, in patients with iron overload, a decreased signal intensity in liver parenchyma is observed (in mild/moderate cases, better identified in GRE sequences obtained with longer echo times). However, although precision decreases due to possible complete loss of liver signal in severe overload cases (18), liver signal intensity is still lower than spinal muscle even in sequences with limited sensitivity for iron overload diagnosis (4).

Using this method, in patients affected at the cardiac level, a decrease in signal intensity in the myocardium compared to skeletal striated muscle is demonstrated, which may or may not be accompanied by myocardial hypertrophy (19). MRI remains a better option for the diagnosis of hemochromatosis compared to Doppler echocardiography (which, according to studies, has a sensitivity of 56%, specificity of 74%, positive predictive value of 68%, and negative predictive value of 57%) (26).

2.10.1. Measurement Technique

At 1.5 T, five GRE sequences are performed during separate breath-holds with a constant repetition time of 120 msec and a constant flip angle of 20 degrees, and variable TE to achieve different weightings: a T1-weighted sequence with TE of 2 msec, a proton density-weighted sequence with TE of 4 msec, a T2*-weighted sequence with progressively longer TEs of 9 msec, 14 msec, and 19 msec (4).

2.10.2. Measurement Method

This technique requires measurements of intensity signal in five regions of interest (ROIs) of approximately 1 cm^2 each. Three ROIs are taken from the hepatic parenchyma excluding vascular areas, and one is taken from each erector spinae muscle; the process is repeated with the five necessary MRI sequences for the technique (4). The values obtained from the ROI measurements are used to compute five liver-to-muscle intensity ratios, which are then analyzed using the algorithm designed by Gandon (21)(4).

2.10.3. Technique Limitation

The main limitations of the technique lie in referencing normal tissue that may be affected by pathologies such as muscle atrophy, fat infiltration, which can cause confusion (4); possible interference in the presence of comorbidities such as hepatic steatosis and iron overload (22). Additionally, as mentioned, it may not be accurate for detecting severe overload (4).

2.11. Forms (Patterns) of Iron Deposition

In addition to primary and secondary iron overload, there are different deposition patterns that can help identify its origin (18)(25). The intensity signal of the spleen and bone marrow can be used to assess the type of deposition pattern because no impairment is observed in 2 out of the 4 typical overload patterns (18).

2.11.1. Reticuloendothelial Deposition Pattern

Characteristic of iron overload secondary to multiple transfusions, where deposition generally occurs in reticuloendothelial system cells of the liver, spleen, and bone marrow (18) (25), not being associated with tissue damage, while the intensity signal of the pancreas is generally preserved, except when the volume of infused blood exceeds the reticuloendothelial system's storage capacity, leading to parenchymal deposition (18). In cases of sickle cell anemia, there is low intensity signal of the spleen with diffuse calcification secondary to autosplenectomy, which is a differential diagnosis (18).

2.11.2. Parenchymal Deposition Pattern

This pattern occurs secondary to increased iron absorption, mainly observed in patients with primary hemochromatosis or in cases of chronic anemia with ineffective erythropoiesis (such as thalassemias, dyserythropoietic anemias, sideroblastic anemias) (18). In this case, excess iron initially accumulates in periportal hepatocytes and then disseminates to the rest of the liver, pancreas, and thyroid, potentially causing tissue damage. In this deposition pattern, decreased signal intensity is observed in the liver and pancreas, while the intensity signal of the spleen and bone marrow is preserved (18).

In advanced cases, although with appropriate treatment and timely diagnosis, some complications could be reversible (24). Hepatic involvement is considered a risk factor for hepatocellular carcinoma, potentially leading to fibrosis and cirrhosis (18). Similarly, other organs and systems may be affected, such as the heart (24), where it can cause restrictive and dilated cardiomyopathy, sterile pericarditis, and arrhythmias (18)(19); the pituitary gland (causing hypopituitarism); the endocrine system (causing diabetes mellitus, hypogonadism, and hypoparathyroidism) (18). Meanwhile, in milder cases, especially in young individuals, the intensity signal of the pancreas may be preserved (18).

2.11.3. Renal Deposition Pattern

Renal iron deposition is not considered a direct cause of renal dysfunction (18). It is only observed in cases of intravascular hemolysis secondary to mechanical stress in patients with cardiac valve prostheses, paroxysmal nocturnal hemoglobinuria, or in patients with sickle cell anemia crises, extramedullary hematopoiesis (18) (27). In this type of deposition, hemosiderin is deposited in the proximal convoluted tubules, causing a reversal of signal intensity in the renal cortex, which is hypointense relative to the medulla on T1-weighted images and shows a marked decrease in cortical signal intensity on T2-weighted images (18) (27).

2.11.4. Mixed Deposition Pattern

In patients with advanced forms of the disease, an atypical distribution of patterns can be observed (18). Chronic anemic patients, whose anemia is due to ineffective erythropoiesis, β-thalassemia, require multiple transfusions, which can produce mixed deposition patterns (parenchymal and reticuloendothelial) (18) (25). Likewise, renal/reticuloendothelial deposition can occur in patients with anemias accompanied by intravascular hemolysis undergoing multiple transfusions and those with paroxysmal nocturnal hemoglobinuria (18).

3. Conclusion

Systemic iron overload represents a significant clinical challenge that requires a deep understanding of its pathophysiology and a correct approach to its clinical and radiological diagnosis. Early identification of this condition and appropriate severity stratification are essential to guide treatment and prevent serious complications in vital organs such as the liver, heart, and pancreas. With the ongoing development of more advanced imaging techniques, such as magnetic resonance imaging, and a greater understanding of the underlying mechanisms, the outcome of affected patients can be significantly improved.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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