Review Article

Hemochromatosis in Heart Failure: Clinical Presentation, Diagnosis, and Treatment

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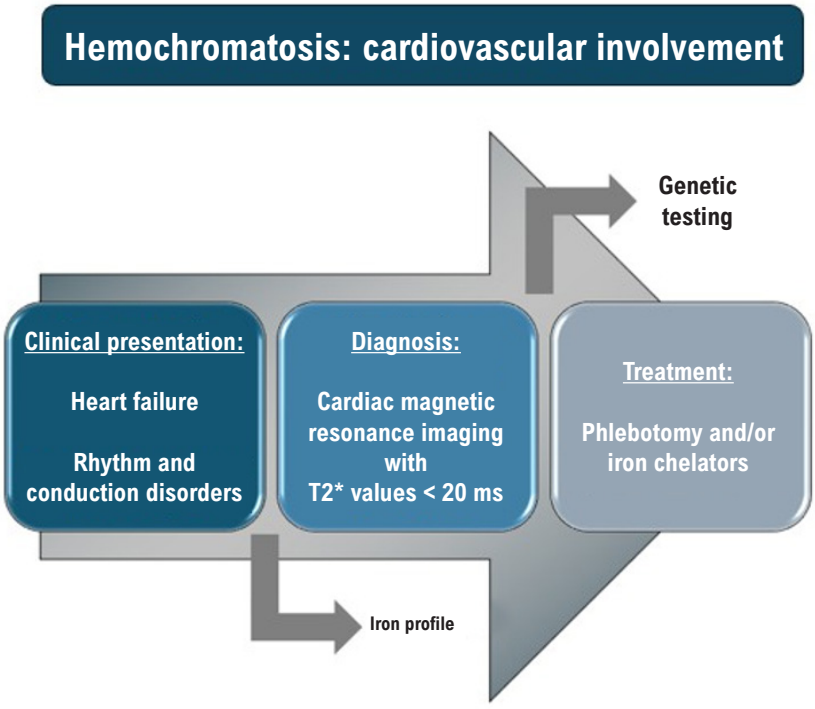
Central Illustration: Hemochromatosis in Heart Failure: Clinical Presentation, Diagnosis, and Treatment



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Introduction

Hemochromatosis is a disease characterized by excessive intestinal absorption of iron and its deposition in various organs, including the heart. There are 2 types of hemochromatosis: primary and secondary. Primary or hereditary hemochromatosis (HH) is a genetic disease, whereas secondary hemochromatosis is a consequence of systemic diseases, such as anemia, thalassemia, liver disease, or excessive blood transfusions.[1]

It was first described in the nineteenth century by the French physician Armand Trousseau, who raised the hypothesis that some excess element in the blood was responsible for causing organ damage and skin pigmentation. In 1935, Joseph Sheldon identified that iron accumulation in tissues was responsible for toxicity and was the first to suggest that this metabolic defect had a genetic origin.[2] In the 1950s, a study of iron kinetics correlated increased intestinal iron absorption in patients with hemochromatosis. It was only in 1996 that the "hemochromatosis gene," HFE ("high Fe"), which is responsible for most cases of the disease, was identified.[3]

In HH, the C282Y genetic variant in the HFE gene has been identified as the most prevalent. Currently, other mutations in

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different genes are also known to be related to the disease, including variants in the genes encoding a second transferrin receptor (TFR2), ferroportin (SLC40A1), hepcidin (HAMP), and hemojuvelin (HJV).[4]

Pathophysiology and classification

Hepcidin, a small hormone produced in the liver, is the main regulator of iron homeostasis. Through its interaction with ferroportin, it inhibits duodenal absorption of dietary iron. Molecular defects that cause hepcidin deficiency lead to uncontrolled intestinal absorption, with progressive accumulation of iron in tissues and organs, especially in the liver, pancreas, and heart.[5]

This is the pathophysiological basis of HH related to mutation of the HFE gene, since abnormally low levels of hepcidin are found in this condition.[5] The iron deposited in the tissues promotes free radical generation, increased oxidative stress, and direct cell damage. The liver and heart are the most affected organs in hemochromatosis. The main causes of death in patients with hemochromatosis are cirrhosis, hepatocellular carcinoma, and heart failure.[6]

Some authors consider that the term "hemochromatosis" should be reserved for the clinical entity caused by genetic alterations that primarily affect the hepcidin-ferroportin system.[5] However, other systemic conditions and excessive blood transfusion can lead to iron overload and consequent clinical manifestations secondary to overload with the same phenotype as HH.[4]

Tables 1 and 2 display the proposed classification for HH or primary hemochromatosis and the main clinical conditions associated with secondary hemochromatosis, respectively.

Clinical presentation and complementary tests for hemochromatosis

In the early stages of the disease, the main symptoms are nonspecific, such as fatigue, arthralgia, and abdominal pain.

Table 1 – Classification of hereditary hemochromatosis

Classification	Gene involved	Inheritance	Clinical presentation
Type 1	HFE gene	Autosomal recessive	Onset in adults, more severe in men, predominant liver and joint involvement
Type 2	HJV (subtype A) HAMP (subtype B)	Autosomal recessive	Earlier onset, common cardiac and endocrine involvement
Type 3	Gene TFR2	Autosomal recessive	Rare, similar to type 1, but with early onset
Type 4	Gene SCLC40A1	Autosomal dominant	Rare, similar to type 1, but with early onset and more severe

Adapted from Girelli et al.[5]

Table 2 – Causes of secondary hemochromatosis

Hemoglobinopathies
• Thalassemia
• Sickle cell anemia
• Sideroblastic anemia
Acquired anemias
• Myelodysplastic syndrome
• Myelofibrosis
• Aplastic anemia
• Leukemias
• Chronic kidney disease
Other conditions
• Chronic kidney disease
• Friedreich's ataxia
• High-iron diet

Adapted from Pereira et al.[7]

Findings such as the development of diabetes, hypogonadism, signs or symptoms of heart failure, and changes in skin pigmentation are found in later stages. Therefore, a high level of clinical suspicion is necessary to make the diagnosis in the early stages, which is essential for disease prognosis.[1] The main clinical manifestations of the disease according to the systems involved are displayed in Table 3.

In cases of clinical suspicion, initial tests for disease screening should include serum iron levels, transferrin saturation, and ferritin. The identification of transferrin saturation greater than 55% with ferritin greater than 200 ng/ml for premenopausal women or greater than 300 ng/ml for men and postmenopausal women is indicative of iron overload.[8] Nonetheless, ferritin values should be interpretation cautiously, as they may be above reference values in acute inflammatory processes. Furthermore, in situations such as infection, neoplasia, hemolysis, and liver diseases, these values may be altered regardless of the total amount of iron in the body.[9]

Iron deposits in tissues, especially in the liver and heart, can be detected by means of non-invasive tests, especially magnetic resonance imaging. For this reason, liver and/or endomyocardial biopsies are currently rarely indicated for the diagnosis of hemochromatosis.

Whenever available, genetic testing should be performed, especially to detect the C282Y and H63D mutations in the HFE gene (responsible for most cases of primary hemochromatosis) (Central Illustration). In cases with clinical suspicion, it is recommended to consider performing hemoglobin electrophoresis to detect congenital hemoglobinopathies, such as thalassemia.[7]

Hemochromatosis: cardiovascular involvement

The pathophysiology of cardiomyopathy associated with iron overload is multifactorial. It involves a combination of oxidative stress, iron-mediated toxicity, inflammation, and

Table 3 – Clinical manifestations of hemochromatosis

Affected system	Signs and symptoms
Cutaneous	Skin pigmentation
Hepatic	Persistent increase in transaminases, hepatomegaly, cirrhosis, hepatocellular carcinoma
Osteoarticular	Arthralgia, arthritis, chondrocalcinosis, reduced bone mineral density
Endocrine	Diabetes mellitus, hypopituitarism, hypoparathyroidism, hypogonadotropic hypogonadism
Cardiovascular	Cardiomyopathy, heart failure, arrhythmias

Adapted from Girelli et al.[5]

fibrosis.[1] It is a storage disease that progressively affects cardiac tissue, starting in the epicardial region and reaching the endomyocardial layer.[10]

The increased free iron in circulation generates greater influx and iron deposition in cardiomyocytes, which leads to greater susceptibility to oxidative stress, inhibition of the Ca^{2+}-ATPase pump in the endoplasmic reticulum, and dysfunction of the sodium-calcium cotransporter. As a consequence, there is an increase in the concentration of intracellular calcium with impaired contractile force and cardiac relaxation.[1]

In the initial stages, symptoms result from diastolic dysfunction, with characteristics of restrictive cardiomyopathy. In the absence of treatment, it can progress to a dilated cardiomyopathy phenotype with systolic dysfunction and possible biventricular involvement.[3]

The clinical manifestation consists of signs and symptoms of heart failure, such as dyspnea on exertion, orthopnea, peripheral edema, and paroxysmal nocturnal dyspnea. It is progressive in nature, and symptoms usually begin during the second and third decades of life.[7]

Rhythm disorders are another cardiovascular manifestation present in hemochromatosis. Iron deposition in the cardiac conduction system causes direct cell damage due to iron toxicity and increased oxidative stress. Furthermore, replacement of the myocardium by fibrotic tissue leads to abnormalities in the generation and propagation of electrical stimuli, which ultimately promotes an arrhythmogenic substrate. Supraventricular arrhythmias are common, atrial fibrillation being the most commonly associated with the disease, conferring a greater thromboembolic risk due to the formation of thrombi in the left atrium.[1] Involvement of the conduction system predisposes to the development of node disease and advanced atrioventricular blocks requiring pacemaker implantation.[11] Finally, ventricular arrhythmias are less common, with a higher incidence in later stages of the disease, associated with the presence of greater fibrotic burden and a dilated cardiomyopathy phenotype.[12]

Other mechanisms may contribute to increased risk of cardiovascular events in hemochromatosis. Oxidative stress increases the oxidation of low-density lipoproteins and stimulates the formation of atherosclerotic plaques. Additionally, the inflammatory process leads to a prothrombotic state and endothelial dysfunction, contributing to increased risk.[1]

There is also the possibility of valve involvement due to the disease, with thickening of the leaflets and fibrosis of the valve tissue impairing its function, manifesting mainly as valve regurgitation.[1]

Complementary tests for assessment of cardiac involvement (Figure 1)

Echocardiography is the initial tool for identifying structural and functional changes in the heart.[13] Left ventricular ejection fraction is normally preserved, with normal ventricular wall thickness in the early stages of iron overload cardiomyopathy.[7] At this phase, the commonly present functional change is diastolic dysfunction, ranging from grade 1 to a restrictive physiology pattern with increased filling pressures in the left ventricle, with early identification of a reduction in the lateral and medial diastolic velocity of the mitral annulus on tissue Doppler imaging.[14] In the absence of adequate treatment, chamber dilation may occur associated with left ventricular systolic dysfunction, or even biventricular involvement.[7,15]

The only test capable of noninvasively identifying and quantifying iron deposition in cardiomyocytes is cardiac magnetic resonance imaging, which is currently the gold standard for diagnosing cardiomyopathy secondary to hemochromatosis.[16] The values found in the images obtained through quantification on T1, T2, and T2* maps are inversely correlated with the amount of iron in the tissue; in other words, the higher the iron concentration, the lower the signal intensity of the image. Analysis of the T2* map sequence has the highest sensitivity for detecting iron in cardiac tissue and is considered the best sequence for diagnosis. Preferably, analysis of the middle segment of the intraventricular septum should be performed, as it has a high representation of the global distribution of iron in the myocardium.[17]

Iron overload is diagnosed by T2* values < 20 ms. Values < 10 ms are indicative of severe overload, and they have a better ability to predict the risk of developing heart failure and arrhythmias, with a sensitivity of 97.5% and specificity of 83%.[7,15] A prospective study in patients with cardiomyopathy due to iron overload secondary to thalassemia demonstrated that 98% of patients who developed heart failure within the first year of follow-up had T2* < 10 ms.[18]

Another finding that may be present, especially in patients in more advanced stages of the disease, is the presence of late enhancement after gadolinium infusion, identifying areas of myocardial fibrosis.

Finally, magnetic resonance imaging is also used to assess response to treatment, which, if initiated in early stages, is expected to reduce the iron deposited in the tissue, with improved cardiac function and reduced risk of developing heart failure.[19]

Treatment

After the diagnosis of hemachromatosis, whether primary or secondary, treatment should be proposed early, as it is possible to prevent the development of organ dysfunctions secondary to excess iron in tissues, particularly hepatic and heart failure,[11]

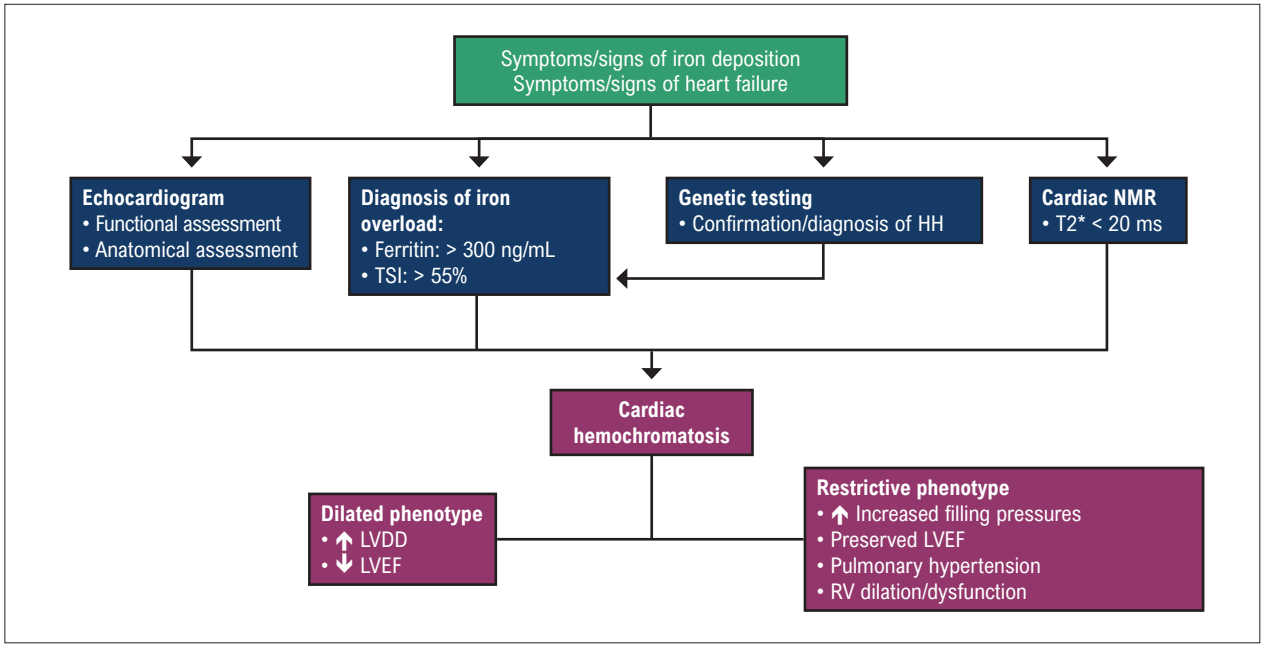

Figure 1 – *Diagnosis of cardiac hemochromatosis. Adapted from Kremastinos et al.15 HH: hereditary hemochromatosis; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; NMR: nuclear magnetic resonance; RV: right ventricle; TSI: transferrin saturation index.*

in the initial phases of the disease. Generally, appropriate therapy is associated with increased survival.[20] To date, phlebotomy and iron chelators are the two main therapies linked to better outcomes.[15] Figure 2 outlines an accepted strategy for managing phlebotomy and iron chelators.

From a cardiovascular perspective, the treatment of iron overload can improve cardiac function, resulting in an increased ejection fraction, reduced systolic and diastolic diameters of the left ventricle, decreased diameter of the left atrium, and reduced left ventricular mass, as well as a decrease in long-term mortality.[21]

Phlebotomy remains one of the primary and most effective therapeutic options for removing excess iron deposited in tissues in hemachromatosis. Its goal is to promote the depletion of this ion, which leads to the utilization of iron stored in tissues.[1] Initially, the procedure involves the removal of 400 to 500 ml of blood during each phlebotomy session, facilitating the removal of 200 to 250 mg of iron. It should be performed weekly until ferritin levels are < 50 mg/ml and transferrin saturation is < 30%. After this initial phase, maintenance phlebotomies should be conducted with the necessary frequency to keep ferritin levels < 100 mg/ml and transferrin saturation < 50%, while maintaining hemoglobin levels above 11 g/dl (Figure 2).[9,15]

Some clinical situations impede phlebotomy. In hemochromatosis secondary to hemolytic anemia or hemoglobinopathies, with iron overload resulting from repeated blood transfusions, iron chelators are safe and effective alternatives for treatment. The currently available options are oral deferasirox, oral deferiprone, and parenteral deferoxamine mesylate (Table 4).

These drugs have a high affinity for iron, binding to the free ion in the bloodstream and tissues, promoting excretion through urine or bile.[11] Like phlebotomy, chelation therapy has shown benefits in prognosis and increased survival, with the potential to prevent the development of heart failure or other cardiovascular complications.[22] Previous studies means using serial cardiac resonance imaging have shown the efficacy of these medications in reducing iron deposited in cardiac tissue, in addition to demonstrating an ability to improve diastolic and systolic function and prevent arrhythmias.[23]

Heart transplantation is an option for patients who develop cardiomyopathy with advanced heart failure criteria and who are refractory to optimized treatment, regardless of the phenotype presented. Nevertheless, patients with the restrictive cardiomyopathy phenotype, regardless of the etiology, have higher mortality while awaiting transplantation when compared to other phenotypes.[25]

Data from patients with hemochromatosis undergoing heart transplantation, although limited, suggest that, after transplantation, the outcomes are similar to those of patients transplanted for other etiologies.[26] Finally, these patients, after transplantation, should continue phlebotomy and/or iron-chelating therapies in order to prevent the development of cardiomyopathy secondary to iron overload in the cardiac graft.[27]

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for content: Sguario RMR, Biselli B, Seguro LFBC.

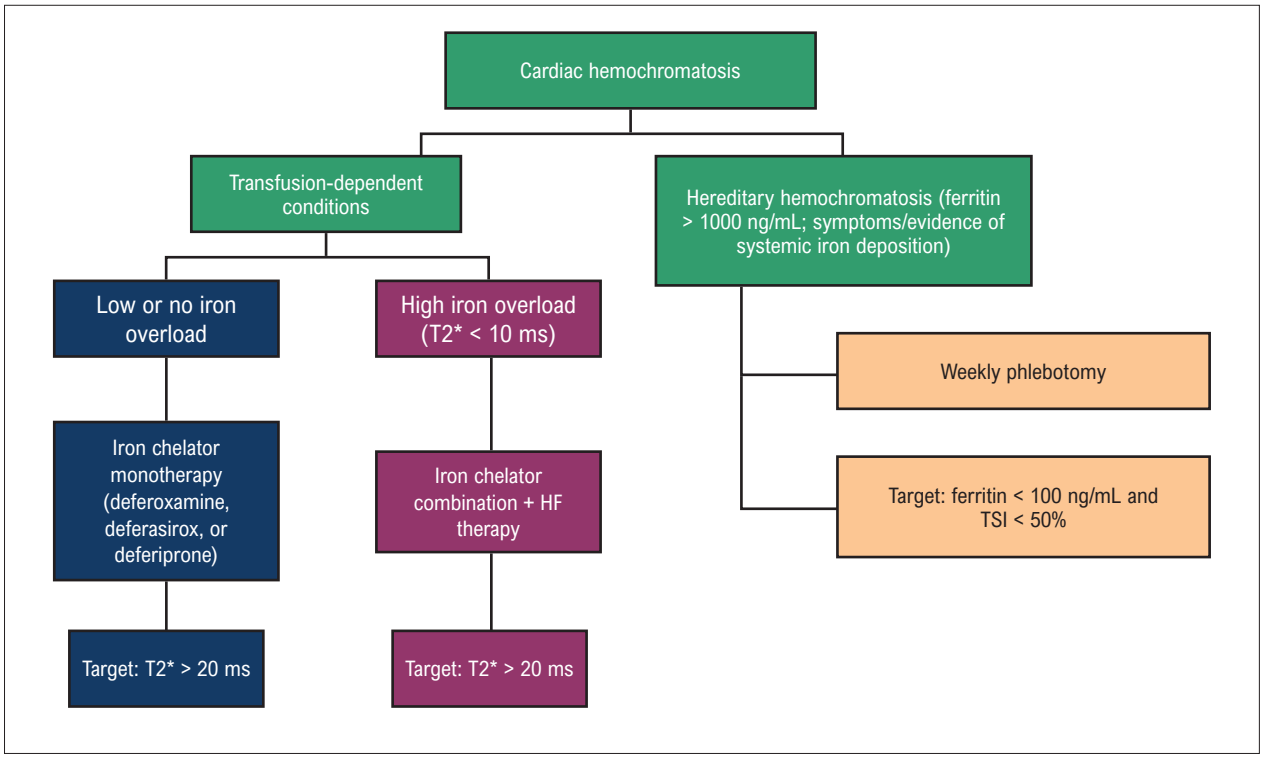

Figure 2 – *Management of iron chelation in cardiac hemochromatosis. Adapted from Kremastinos DT, et al.[15] HF: heart failure; TSI: transferrin saturation index.*

Table 4 – Iron chelator options

	Deferoxamine mesylate	Deferiprone	Deferasirox
Routine dose	20 to 60 mg/kg/day	75 mg/kg/day	20 to 30 mg/kg/day
Administration route	Intravenous (in 4 to 6 hours); subcutaneous (in 8 to 12 hours) or intramuscular	Oral	Oral
Frequency	Once daily 5 to 7 days a week	3 times a day	Once daily
Adjustment for renal insufficiency (creatinine clearance)	10 to 50 ml/min/1.73: 20% to 25% of the dose < 10 ml/min/1.73: avoid use	No specific recommendations	< 40 ml/kg/1.73: contraindicated

Adapted from Cançado.[24]

Potential conflict of interest

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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