Hereditary hemochromatosis refers to several inherited disorders of the iron metabolism that lead to tissue iron overload. Classical hereditary hemochromatosis is associated with mutations of the HFE gene (C282Y homozygotes or C282Y/H63D compound heterozygotes) and is almost exclusively found in populations of northern European descent. Non-HFE-associated hereditary hemochromatosis is caused by mutations in other recently identified genes involved in the iron metabolism. Hepcidin is an iron regulatory hormone that inhibits ferroportin-mediated iron export from enterocytes and macrophages. Defective hepcidin gene expression or function may underlie most forms of hereditary hemochromatosis. Target organs and tissues affected by hereditary hemochromatosis include the liver, heart, pancreas, joints, and skin, with cirrhosis and diabetes mellitus representing late signs of disease in patients with very high liver iron concentrations. Patients with an established diagnosis of hereditary hemochromatosis and iron overload should be treated with phlebotomy to achieve body iron depletion followed by maintenance phlebotomy. The most frequent causes of death in hereditary hemochromatosis are liver cancer, cirrhosis, cardiomyopathy, and diabetes. However, patients who undergo successful iron depletion before developing cirrhosis or diabetes can have normal life expectancy.

**Keywords:** Iron deficiency/metabolism; Iron overload; Hemochromatosis/genetics; Hemochromatosis/congenital; Phlebotomy

---

**Introduction**

Iron is an essential element in many physiological processes in the human body playing a pivotal role in the cellular energy metabolism. Its total quantity in adults is approximately 3.5 to 4 g; most (from 1.5 to 3.0 g) is bound to the heme in hemoglobin with its main function being the oxygenation of tissues, and some is stored as ferritin or hemosiderin in reticuloendothelial cells, primarily in the liver, bone marrow and spleen.(1)

Physiologically, the body is unable to increase the excretion of iron, even in conditions of overload, so the gradual increase in the amount of iron attained via the gastrointestinal tract or parenterally, leads to the pathological condition of iron overload.(1-4) Table 1 shows the main clinical syndromes that can result in iron overload.

Table 2 describes the genetic and clinical features of major clinical syndromes related to hereditary hemochromatosis.

**Hereditary hemochromatosis**

In the early nineteenth century, Troisier & Trousseau described a clinical syndrome characterized by hepatic
increase in intestinal absorption of iron, with consequent progressive accumulation of these ions in different organs and tissues, in particular the liver, heart, pancreas, skin and joints; it may cause cell damage, tissue fibrosis and functional impairment.\(^{(1,5)}\)

**Epidemiology**

Population studies indicate that HH originated in northern Europe in particular in Nordic or Celtic populations. The HFE C282Y mutation is more common in Caucasians of northwestern Europe, North America, Australia and New Zealand; in Eastern and Southern Europe, North Africa and the Middle East its frequency is intermediate, and among Asians, Africans or African descents from South and Central America, it is rarely found.\(^{(6)}\)

Studies involving populations of the United States, Australia and Europe have shown that the frequencies of homozygotes and heterozygotes for the HFE C282Y mutation vary between 0.2% and 0.7%, and between 7% and 14%, respectively. The HFE H63D mutation is two to three times more common than the HFE C282Y mutation, and the prevalence of heterozygous and homozygous individuals ranges between 15% and 40% and between 2.5% and 3.6%, respectively. The frequency of the genotype C282Y/H63D is approximately 2%.\(^{(6,7)}\)

**Table 1: Major clinical syndromes related to iron overload**\(^{(1-4)}\)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Primary</td>
<td></td>
</tr>
<tr>
<td>a. HH - gene HFE (Type 1)</td>
<td></td>
</tr>
<tr>
<td>b. HH - Juvenile (Type 2)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (Type 2A)</td>
<td></td>
</tr>
<tr>
<td>Hepcidin (Type 2B)</td>
<td></td>
</tr>
<tr>
<td>c. HH - transferrin receptor 2 (Type 3)</td>
<td></td>
</tr>
<tr>
<td>d. HH - ferroportin gene (Type 4)</td>
<td></td>
</tr>
<tr>
<td>e. Other types:</td>
<td></td>
</tr>
<tr>
<td>HH - heavy-chain ferritin gene</td>
<td></td>
</tr>
<tr>
<td>Acruloplasminemia</td>
<td></td>
</tr>
<tr>
<td>DMT1 mutation (neonatal HH)</td>
<td></td>
</tr>
<tr>
<td>Atransferrinemia</td>
<td></td>
</tr>
<tr>
<td>de Friedrich Ataxia</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Genetic and clinical features of major clinical syndromes related to hereditary hemochromatosis**\(^{(1-3)}\)

<table>
<thead>
<tr>
<th>Genetic disease</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Transmission</th>
<th>Start of clinical symptoms (decade)</th>
<th>Principal clinical alteration (Clinical course)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE (HH type 1)</td>
<td>HFE</td>
<td>6</td>
<td>AR</td>
<td>3(^{rd}), 5(^{th})</td>
<td>Hepatic &amp; articular (mild to severe)</td>
</tr>
<tr>
<td>Hemojuvelin (HH type 2A)</td>
<td>HJV</td>
<td>1</td>
<td>AR</td>
<td>2(^{nd}), 3(^{rd})</td>
<td>Cardiac &amp; endocrine (severe)</td>
</tr>
<tr>
<td>Hepcidin (HH type 2B)</td>
<td>HAMP</td>
<td>19</td>
<td>AR</td>
<td>3(^{rd}), 5(^{th})</td>
<td>Hepatica (mild to severe)</td>
</tr>
<tr>
<td>Receptor of transferrin (HH type 3)</td>
<td>TIR2</td>
<td>7</td>
<td>AR</td>
<td>4(^{th}), 5(^{th})</td>
<td>Rare (mild)</td>
</tr>
<tr>
<td>Ferroportin disease (HH type 4A)</td>
<td>SLC40A1</td>
<td>2</td>
<td>AD</td>
<td>2(^{nd}), 3(^{rd})</td>
<td>Hepatica &amp; articular (mild)</td>
</tr>
<tr>
<td>Ferroportin disease (HH type 4B)</td>
<td>SLC40A1</td>
<td>2</td>
<td>AD</td>
<td>3(^{rd}), 5(^{th})</td>
<td>Neurological, hematological &amp; endocrine (severe)</td>
</tr>
<tr>
<td>Acruloplasminemia</td>
<td>Ceruloplasmin</td>
<td>3</td>
<td>AR</td>
<td>1(^{st}), 2(^{nd})</td>
<td>Hematological (severe)</td>
</tr>
<tr>
<td>Hypoceruloplasminemia</td>
<td>Transferrin</td>
<td>3</td>
<td>AR</td>
<td>3(^{rd}), 5(^{th})</td>
<td>Hematological &amp; hepatic (mild to severe)</td>
</tr>
<tr>
<td>DMT1 (divalent metal transporter)</td>
<td>DMT1</td>
<td>12</td>
<td>AR</td>
<td>3(^{rd}), 5(^{th})</td>
<td>Hematological &amp; hepatic (mild to severe)</td>
</tr>
</tbody>
</table>

HH - hereditary hemochromatosis; AR - autosomal recessive, AD - autosomal dominant; Hepatic - hepatomegaly, elevated aminotransferase levels; Articular - arthralgia, arthritis, Cardiac - cardiomyopathy, arrhythmia; Endocrine - diabetes, hypogonadism; Neurologic - retinal degeneration, extrapyramidal syndrome, cerebellar ataxia and dementia; Hematologic - microcytic anemia with low serum iron and transferrin saturation.
The frequency of the HFE C282Y mutation is three to eight times lower in Brazilian individuals than the rate observed in Whites of northern Europe with this difference probably being due to the ethnic diversity of the population. The allele frequency of the HFE H63D mutation appears to be similar in both populations. Table 3 lists the allele frequencies of the HFE C282Y, H63D and S65C mutations in five Brazilian studies.

### Correlation between genotype and phenotype

The greatest risk of iron overload is associated with homozygosity for the HFE C282Y mutation; patients with the C282Y/H63D or H63D/H63D genotypes have an intermediate risk and patients with the C282Y/wild-type and H63D/wild-type genotype are at low risk.\(^{13-18}\)

C282Y/wild-type Individuals usually do not develop the clinical disease, however, approximately 1% to 15% of patients with this genotype develop the hemochromatosis phenotype similar to that observed in C282Y/C282Y patients suggesting the coexistence of additional genetic or clinical factors which may influence the development of hemochromatosis.\(^{13-18}\)

H63D and S65C mutations alone are not a high risk for iron overload even when homozygous, however, when associated with the C282Y mutation or pathological conditions that can alter the iron metabolism, such as alpha or beta thalassemia and hereditary spherocytosis, they may play a role in predisposition to a pathologic accumulation of iron in the body.\(^{1,5,13-18}\)

Cançado et al., Studying the major HFE gene mutations in patients with iron overload (most patients with serum ferritin (SF) > 1000 ng/mL and with symptoms and signs secondary to excess iron), observed an allele frequency of 76% (38/50), with 30% being homozygous for the C282Y mutation (Table 1). Furthermore, they demonstrated that the rate of transferrin saturation (ST) and SF were significantly higher in patients homozygous for the C282Y mutation, thereby confirming both the correlation between the C282Y/C282Y genotype with higher risk of iron overload and that chronic hemolytic anemia, hepatitis C and excessive alcohol consumption contribute to higher levels of iron in the body and constitute additional risk factors for the condition of iron overload in patients with HFE gene mutations.\(^{19}\)

Led by Professor Pierre Brissot, the French group that studies HH proposed the classification of C282Y/C282Y individuals in five stages according to laboratory and clinical data: stage 0, only the C282Y/C282Y genotype; Stage 1: C282Y/C282Y genotype and ST > 45%; Stage 2: C282Y/C282Y genotype, ST > 45% and SF ≥ 300 ng/mL (men) or ≤ 200 ng/mL (women); Stage 3: the alterations included in Stage 2 plus clinical manifestations such as ashen skin, fatigue and impotence; Stage 4: changes stated in Stage 3 associated with systemic complications such as cirrhosis, cardiomyopathy or insulin-dependent diabetes mellitus. Stages 0-2 correspond to the preclinical stage, and stages 3 and 4, the clinical phase. It is estimated that 50% of C282Y/C282Y individuals are in stage 2, 25% in stage 3 and less than 10% in stage 4.\(^{13}\)

### Physiopathology

HH patients have an increased rate of intestinal iron absorption that may reach up to 10 mg/day or more. Currently
hepcidin is considered the main protein responsible for body iron regulation; it is synthesized in the liver and its production is stimulated by the increase in iron deposits, lipopolysaccharide and by interleukin-6, but it is inhibited due to anemia, tissue hypoxia, ineffective erythropoiesis (due to the synthesis of the GDF-15 protein) and alcoholism. Hepcidin, by binding to ferroportin located in the basolateral membrane of enterocytes, macrophages and erythrocytes and the main protein that exports iron, causes its internalization and degradation, inhibiting intestinal iron absorption and decreasing the release of iron present in macrophages to the plasma.\(^{(1,2)}\)

In Type-1, -2 and -3 HH patients, there is reduced synthesis of hepcidin, which causes an increase of intestinal iron absorption and iron release from macrophages, leading to a gradual and pathological accumulation in the body.\(^{(1,2)}\)

The toxicity of iron is related to free iron, that is, iron that is not bound to transferrin. From the moment the amount of plasma iron exceeds the capacity of transferrin saturation, the concentration of free iron not bound to transferrin (NTBI, non-transferrin-bound iron), or more specifically, the redox-active fraction called labile plasma iron (LPI) increases, causing cell damage, as its ability to penetrate cells is easier and faster than the iron bound to transferrin.\(^{(1,3)}\)

Free iron acts as a catalyst of oxidative reactions and the consequent synthesis of superoxide radicals and free hydroxyl radicals; the conversion of superoxide into H2O2 by superoxide dismutase causes peroxidation of lipids in the membrane of various organelles such as the mitochondria and microsomes with resulting cell damage, reactive fibrosis, multiple sclerosis and functional impairment.\(^{(1,3)}\)

In HH patients, there is an increase in the collagen gene expression, with consequential increase in its production within the hepatic lipocytes, which are progressively replaced by fibrosis. The coexistence of factors such as excessive alcohol consumption and chronic liver disease due to hepatitis C virus infection aggravates and accelerates the process even further.\(^{(1-5)}\)

**Clinical manifestations**

Clinically, HH is quite variable and dependent on the insidious accumulation of iron, which occurs slowly and steadily over several decades. Most patients become symptomatic between the third and fifth decades of life, with the clinical manifestations being observed in women five to ten years after men due to lactation and the physiological blood losses that occur during menstruation and pregnancy.\(^{(1,13-18)}\)

The most commonly reported symptoms are: fatigue (70% to 80%), arthralgia/arthritis (40% to 50%), abdominal pain (20% to 60%), decreased libido or impotence (20% to 50%) and weight loss (10% to 50%); the most frequent clinical symptoms for diagnosis are hepatomegaly (50% to 90%), skin hyperpigmentation (30% to 80%), hypogonadism (20% to 50%), arthropathy, splenomegaly, diabetes mellitus, cirrhosis, cardiomyopathy and arrhythmia.\(^{(1,13-18)}\)

The risk of hepatocellular carcinoma is approximately twenty times higher in patients with HH and is even more common in patients with liver cirrhosis.\(^{(1,20)}\)

**Diagnosis**

The diagnosis of HH includes both a physical examination and laboratory diagnosis of iron overload with the investigation of HFE gene mutations (C282Y, H63D and S65C). Two consecutive measurements of ST with values above 45% for both genders and SF above 200 ng/mL in women and 300 ng/mL in men with the presence of the homozygous C282Y mutation - and in some cases, C282Y/H63D - determines the diagnosis.\(^{(1,4,21)}\)

Persistently high ST is the most important and the first identified laboratory parameter in the diagnosis of HH; usually it occurs before the onset of the signs and symptoms related to iron overload.\(^{(1,4)}\)

When SF is consistently high, it is associated with clinical signs and symptoms related to iron overload. Thus, clinical history and physical examination are essential to assess the presence and intensity of possible signs and symptoms, for example, chronic asthenia, impotence, joint pain, skin hyperpigmentation, hepatomegaly, diabetes, osteopenia and cardiomyopathy; gender, age and type of involvement (hepatic or extrahepatic) should also be considered.\(^{(1,4)}\)

The diagnosis of iron overload may be confirmed by liver biopsy when the histochemical method for qualitative analysis (staining non-heme iron with Prussian blue - Perls reaction) detects the presence of grade III/IV hepatic siderosis. Diagnosis can also be by the quantitative analysis of hepatic iron content by atomic absorption spectroscopy or mass spectrometry with levels being higher than 3 mg/g dry liver tissue.\(^{(1,4,20,22)}\)

More recently, nuclear magnetic resonance (NMR) became an important instrument in the diagnosis of iron overload, because it is a noninvasive method that allows indirect measurement of iron content in different organs; the method has been validated both the U.S. and in Europe and is currently the preferred test to diagnose and monitor patients with transfusional iron overload.\(^{(4,20-24)}\)

Although invasive, liver biopsy is needed both to evaluate the intensity and extent of liver inflammation and to detect the presence of cirrhosis, so this procedure is indicated for patients with positive serology for the hepatitis B or C viruses, those homozygous for the C282Y mutation and over 40 years old or with elevated alanine aminotransferase or SF > 1000 ng/mL. In the absence of these three factors, the
risk of liver fibrosis is minimal, while in the presence of two or three, the risk is high with this situation having an impact on prognosis.\(^\text{20,23}\)

The identification of iron overload in subjects with no HFE gene mutation is rare; in these cases if the patient is under 30 years old, it is most likely related to the existence of hemjuvelin or hepcidin gene mutations, thus an investigation of these genes is necessary. If the patient is older than 30 years old, it is quite likely related to ferroportin or transferrin receptor 2 mutations.\(^\text{20-24}\)

Importantly, regardless of whether the genotypic diagnosis is confirmed or not, the presence of iron overload indicates the need to start treatment to remove the excess.\(^\text{4}\)

**Differential diagnosis**

In obese individuals, or those who have an inflammatory condition, the ST may appear normal or decreased so in these cases a high C-reactive protein concentration confirms inflammation.\(^\text{4,23-24}\)

SF can also be elevated without any correlation to increases in iron deposits, and in this case, the ST is usually normal; this can be observed when there is inflammation or an infectious disease, hepatocellular necrosis, viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis, metabolic syndrome and cancer.\(^\text{4,23-26}\)

Metabolic syndrome, one of the most frequent causes today of hyperferritinemia, is characterized by obesity, hypertension, non-insulin-dependent diabetes, hyperlipidemia, and hyperuricemia, so it is essential to investigate and rule out other causes not related to HH hyperferritinemia, particularly liver disease and alcoholism, which are much more frequent than HH itself.\(^\text{23-26}\)

There are less frequent causes of hyperferritinemia not related to iron overload such as hyperferritinemia-cataract syndrome, Gaucher's disease and macrophage activation syndrome.\(^\text{25,26}\)

**Treatment**

Treatment of patients with HH includes the removal of iron excess from the body by phlebotomy or bloodletting therapy; this is a safe, economical and effective procedure.\(^\text{1,3,4,23,25}\)

Treatment should be started as soon as iron overload is observed, preferably still in the asymptomatic phase of the disease (stage \(\leq 2\)), especially before the development of fibrosis or cirrhosis.\(^\text{4,25}\)

Despite of the accumulation of iron, patients with aceruloplasminemia and those with ferroportin disease (HH type 4A) usually have anemia and do not respond satisfactorily, or even do not tolerate the repetition of phlebotomy.\(^\text{4,25}\)

**Treatment with phlebotomy therapy**

This procedure involves removing 450 to 500 mL of blood, that is, the removal of 200 to 250 mg of iron. It is recommended to perform phlebotomy weekly, although the time interval varies according to the patient's tolerability of the procedure. The duration of treatment can vary from weeks to months, depending on the amount of excess iron and the patient's tolerance to treatment.\(^\text{4,25}\)

The bleeding must be maintained until iron depletion is achieved, which usually occurs when there is microcytic anemia (Hb \(\leq \text{11 g/dL}\) and mean corpuscular volume of less than 75 fl), SF is less than 25 ng/mL and ST is less than 40%.\(^\text{4,25}\)

From then on, the concentration of circulating Hb must be maintained within the normal range, and phlebotomy should be performed at appropriate intervals in order to maintain the values of SF between 100 and 200 ng/mL, and ST between 20% and 30%. For this, it is recommended that, on average, four to six bleeds annually are performed in men, and two to four in women, although some individuals may require a larger number.\(^\text{4,25}\)

The control of patients submitted to phlebotomy should be by blood test prior to each procedure with the determination of SF and ST after three or four bleeds.\(^\text{4,25}\)

**Erythrocytapheresis associated with erythropoietin**

Although little studied, the efficacy of the combination of erythrocytapheresis and erythropoietin (150 U/kg/week) to rapidly remove excess iron has been proven and therefore, although more complex and more expensive, can be considered an option for patients with serious complications that require more intensive treatment.\(^\text{27}\)

**Nutritional guidance**

In the dietary management of patients with HH, it is recommended to avoid the intake of compounds based on iron and vitamin C, abstain from alcohol and refrain from handling or eating seafood or raw marine fish due to risk of infection by Vibrio vulnificus and Salmonella enteritidis which can sometimes be fatal.\(^\text{1,4}\)

**Expected results after phlebotomy**

The results observed in most patients submitted to repeat phlebotomy are: improvement in asthenia, hyperpigmentation of the skin and liver and heart function; worsening of arthralgia can occur in the first phlebotomies but with subsequent improvement; and easier control of diabetes mellitus with, in some cases, a reduction in the required dose of insulin. Patients who already have cirrhosis
usually do not show any improvement of symptoms and the risk of hepatocellular carcinoma persists high despite treatment.(4,24)

An iron chelator, such as subcutaneous deferoxamine, can be used for patients with anemia and those who do not tolerate or refuse to remove excess iron by phlebotomy. More recently, a new oral iron chelator called deferasirox at a single daily dose was approved for patients with transfusional iron overload; this possibly will be a new therapeutic option for this specific group of patients with HH.(26)

**Prognosis and mortality**

HH patients have shorter survival compared to the general population for the same gender however and age (Table 2), when the diagnosis precedes the onset of diabetes mellitus and treatment is instituted before the development of liver cirrhosis, life expectancy of patients is similar. The leading causes of death in patients with untreated HH are: heart failure, arrhythmia, hepatocellular failure and carcinoma.(4,5,15,17,22)

**Conclusions**

The HFE gene mutation indicates the existence of a genetic change related to HH and higher susceptibility to develop the disease phenotype, but this is not enough, on its own, to diagnose HH.

HH is not the most common cause of hyperferritinemia.

In the diagnosis of HH the phenotype, in particular, iron overload and its clinical and laboratory effects on the body should prevail rather than just the genotypic expression.

Early diagnosis of HH and prompt commencement of treatment are able to prevent the onset of severe organic complications and even in individuals with some degree of dysfunction, progression can be reversed or prevented.

Treatment with phlebotomy, if initiated before the development of liver cirrhosis, gives HH patient survival rates similar to those of the general population.

**References**