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# Recent advances in understanding of Haemochromatosis: A burning issue of life

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**Abstract**

Hemochromatosis is an inherited autosomal recessive iron overload disease that makes normal hepcidin unresponsive to iron storage in the body, leading to increased duodenal absorption of iron from the diet. The central mechanism of iron overload in haemochromatosis is the insufficient response of hepcidin in the liver to the storage of iron in the body, leading to excessive absorption of iron in the duodenum. Type 1 (or HFE haemochromatosis) accounts for the majority of cases of haemochromatosis, most of the published literature. Patients with haemochromatosis should try to abstain from alcohol, especially if there is advanced fibrosis. They should also minimize the use of vitamin C and supplements containing iron tablets. Vitamin C can increase the intestinal absorption of iron and the release of iron reserves.

**Keywords:** Haemochromatosis, Iron, diagnosis, signs and symptoms, treatment

## Introduction

Hemochromatosis is an inherited autosomal recessive iron overload disease that makes normal hepcidin unresponsive to iron storage in the body, leading to increased duodenal absorption of iron from the diet (Simon et al., 1975). The increased iron enters the plasma and can be deposited in various target organs and can cause clinical signs and symptoms (Pietrangelo, 2010).

Since trousseau first described advanced haemochromatosis as "bronze diabetes" in 1865, In 1935 Sheldon discovered the role of iron metabolism in its pathogenesis, and then upon the identification of the C282Y mutation, an understanding of this situation has significantly increased in HFE, which caused the majority of haemochromatosis cases in 1996, hepcidin has recently recognized the central role of hepcidin in regulating iron absorption and the pathogenesis of haemochromatosis. The current classification system for haemochromatosis divides this disease into four types. The most common is type 1 or classic haemochromatosis, which is associated

with a homozygous cysteine to tyrosine nonsense mutation in the HFE gene.

## Epidemiology and pathophysiology of haemochromatosis

Evidence from multiple studies indicates that the prevalence of homozygosity C282Y is approximately one to 250 times that of the population of Nordic descent (Beutler et al., 2002). Feder et al. First reported mutations in most patients with phenotypic haemochromatosis in 1996.

These authors report that mutations C282Y and h63d in the HFE gene (located on the short arm of chromosome 6) are present in the majority of patients (especially those of Nordic descent); the most common pattern is homozygous for the C282Y mutation, of which a small percentage of them carry the heterozygous genotype of the C282Y / h63d compound. These missense mutations are characterized by the substitution of tyrosine for cysteine at position 282 (C282Y) and the substitution of aspartic acid for histidine at position 63 (h63d), respectively. The average prevalence of the C282Y allele varies among multiple screening studies and is approximately 6% (EASL, 2010).

The central mechanism of iron overload in haemochromatosis is the insufficient response of hepcidin in the liver to the storage of iron in the body, leading to excessive absorption of iron in the duodenum (Pietrangelo, 2010). The gene encoding hepcidin is highly expressed in liver cells and is transcriptionally regulated in response to iron storage in the body (Roettotal, 2002). The gene product hepcidin is a 25 amino acid peptide that is cleaved from prohepcidin and released into the circulation, where it controls iron metabolism by binding to the main cellular iron export protein, ferroportin. After internalization of the iron transporter, it is degraded through the lysosomal pathway, reducing the iron output of cells (including hepatocytes and macrophages). The loss of hepcidin-mediated iron transporter in intestinal cells leads to a decrease in the absorption of inorganic iron in the intestine, which leads to a decrease in iron reserves in the body (Gochee *et al.*, 2002)

Since the human body has no major mechanism to mobilize or eliminate excess iron, hepcidin mediates. The reduced iron absorption represents the body's main mechanism for regulating iron storage. Therefore, under iron deficiency conditions, the expression of hepcidin is reduced, leading to an increase in ferroportin activity and an increase in iron output (and subsequent iron input) (Nicolas et al., 2002).

The complete mechanism of haemochromatosis caused by mutated HFE protein in liver cells has not been fully elucidated. However, it is now recognized that hemojuvenile protein (hjv), bone morphogenetic protein (bmp), smad 4, transferrin receptor 1 (tfr1), transferrin receptor 2 (tfr2), and transferrin are affected by the body. 2 (tfr2) and the transmembrane protease serine 6 (tmprss6) appear to be necessary to maintain adequate iron-mediated hepcidin (Maliken et al., 2011).

Most inherited iron overload diseases (especially haemochromatosis type 1-3) are caused by decreased hepcidin production, which can lead to excessive iron absorption, eventually leading to excessive iron deposition in certain tissues, leading to injury and disease in the organs internal Type 4 haemochromatosis or "ferroportin disease" can be caused by mutations in the transporter (fpn) that prevent it from binding or resisting interaction with hepcidin (Letocart et al., 2009).
Alcohol, obesity, and viral hepatitis have been shown to accelerate the progression from liver fibrosis to cirrhosis in patients with type 1 haemochromatosis. In vitro studies have shown that both hepatitis C virus and alcohol reduce the expression of hepcidin and lead to increased iron storage in the liver (Flanagan et al., 2007). There is also more and more literature showing that liver iron load may be related to advanced fibrosis. Excessive iron in the reticuloendothelial system

## Diagnosis

Type 1 (or HFE haemochromatosis) accounts for the majority of cases of haemochromatosis, most of the published literature. Regarding the clinical

features, diagnosis and examination are all related to the disease. Routine clinical genotyping is currently only applicable to type 1 haemochromatosis. In addition, because of the large case series and natural history studies, it is mainly based on the cohort of patients with type 1 or HFE haemochromatosis (Beutler et al., 2002).

## Clinical characteristics

The clinical characteristics of haemochromatosis vary widely, from the presence of homozygous C282Y mutations with normal and elevated serum levels (Adams et al., 2000). Haemochromatosis is related to the iron load of the liver, pancreas, heart, pituitary gland, skin and joints, leading to fibrosis, liver cirrhosis and hepatocellular carcinoma, diabetes, cardiomyopathy, impotence, hypogonadism, abnormal increase in skin pigmentation and affectation of the first. Arthritic joints of the second and third metacarpal phalanx (mcp) (Bacon et al., 1997).

On physical examination, signs of haemochromatosis include hepatomegaly, tanned skin, cardiac abnormalities, and signs of liver cirrhosis, testicular atrophy, and swelling and thickening of the second and third mcps (Bacon et al., 1997). The most common sign at the time of the visit to the doctor is hepatomegaly.

Diabetes is often associated with haemochromatosis, especially in advanced disease (Hramiak et al., 1997). This association may be due to iron deposition in pancreatic beta cells or possibly insulin resistance (Mendler et al., 1999). The presence of diabetes before the onset of iron overload in the liver can increase the progression of liver fibrosis. Although age and the presence of cirrhosis are confounding factors, the signs of hypogonadism in patients with haemochromatosis have been fully documented. The underlying pathophysiology can be multifactorial, because hypogonadism can be caused by dysfunction of the hypothalamus, pituitary, or gonads (Siminoski et al., 1990).

## Assessment of iron overload in the liver (liver biopsy)

Liver biopsy has always been the cornerstone of the diagnosis of haemochromatosis. The characteristic pattern of increased staining iron in hepatocytes is a decrease in the "iron gradient" from around the portal vein to the center and a lack of iron in cells of the reticuloendothelial system (res) are characteristic of haemochromatosis type. 1; observed in type 3 haemochromatosis. Similar pattern (Wrede et al., 2006). Type 2 haemochromatosis is characterized by strong iron staining, which may be filled with leaflets and does not retain res cells (Deugnier et al., 2011). Type 4 haemochromatosis has a significantly different iron staining pattern. As the disease progresses, red blood cells are predominantly iron and liver cells are affected (Bassett et al., 1986).

## The main treatment for haemochromatosis

Haemochromatosis is removal through therapeutic phlebotomy Surgery (also called phlebotomy) to remove iron. Bloodletting increases red blood cell production, which causes iron to be excreted from the liver (the main iron storage site) until the iron reserves are exhausted. The amount of blood drawn to deplete excess iron reserves in the body varies greatly, although an average reduction of 30 µg/L per blood collection (Harrison et al., 2003). Most patients with type 1 haemochromatosis expressing this phenotype have a total iron storage> 4 g, which would require approximately 15 therapeutic phlebotomy operations with 500 cc of blood (each unit of blood contains approximately 250 mg of elemental iron) (Pietrangelo Et al., 2010). ). If a hemoglobin reduction of less than 12 g/dl is observed, the frequency of bleeding can be reduced to once every 2 weeks. Therefore, excessive iron consumption at iron-deficient levels can be counterproductive and significantly increase iron absorption, so the need to maintain phlebotomy may further increase

## The next treatment option

The use of agents Iron chelators have been reserved for disabled patients reluctant to tolerate bloodshed (Nelson et al., 2003). Deferasirox is a recently approved oral iron chelator. It is safe and effective. It is usually used to treat iron overload caused by erythropoiesis anemia.

Hepcidin, as a peptide hormone, may have potential as a therapeutic agent for the treatment of haemochromatosis. However, large-scale production of synthetic hepcidin is currently not feasible and clinical use is limited by the potential risks of a short half-life, low oral absorption, and overdose.

## Dietary recommendations

Patients with haemochromatosis should try to abstain from alcohol, especially if there is advanced fibrosis. They should also minimize the use of vitamin C and supplements containing iron tablets. Vitamin C can increase the intestinal absorption of iron and the release of iron reserves. When necessary, the concomitant risk factors for liver disease should be evaluated and treated. Therefore, patients with metabolic syndrome should be advised to lose weight through proper diet and exercise. Non-citrus fruits may be beneficial (Milward et al., 2008)

Similarly, proton pump inhibitors (such as omeprazole) are also helpful because they reduce the acidity of the duodenal content, thus reducing iron absorption ( Milward et al., 2008). ). The increased absorption of iron from the diet, especially in patients with haemochromatosis, is related to the higher concentration of sf in some patients (Leggett et al., 1990).

Iron-fortified inorganic foods may aggravate the severity of iron overload in patients with haemochromatosis. Although it is not clear whether the use of supplemental iron will cause clinical symptoms in patients with undiagnosed haemochromatosis, the use of supplemental iron is prohibited because reports of excessive iron intake have been described in the literature (Adams et al., 2010). Similarly, there are reports that ingestion of raw shellfish or undercooked oysters can become infected with Vibrio vulnificus (Ashrafian, 2003), and patients with haemochromatosis should receive appropriate education. Iron steady state is also related to other metals such as copper.

## Orthotopic liver transplantation

Orthotopic liver transplantation (OTT) is considered a curative treatment for patients with end-stage liver disease. It can also be used for patients with haemochromatosis and decompensated cirrhosis or hcc. However, compared with other indications of olt, the survival rate of patients with haemochromatosis after hospitalization has been poor. This is due to multiple perioperative infections, especially within one year after transplantation, and cardiomyopathy after the first year (Kowdley et al., 1995). A recent study showed that the postpartum outcome of haemochromatosis may be improved and is comparable to other indications of olt, although the latest study did not use objective criteria to confirm the diagnosis of haemochromatosis, but used the diagnostic code transplant center report Data (Yu and Ioannou, 2007). ).

## Cancer risk

The risk of hepatocellular carcinoma (HCC) is increased due to cirrhosis caused by haemochromatosis and other causes of cirrhosis, and HCC monitoring should be performed every 6 months. Although many studies believe that the average risk of HCC in patients with haemochromatosis, especially in patients with cirrhosis of the liver, is approximately 8 to 10 seconds (Hsing et al., 1995), recent studies report that the risk may be lower. These studies indicate that approximately 5-6% of men with haemochromatosis and 1.5% of women will develop HCC (Haddow et al., 2003).

# Conclusion

Hemochromatosis is an inherited autosomal recessive iron overload disease that makes normal hepcidin unresponsive to iron storage in the body,

leading to increased duodenal absorption of iron from the diet. The central mechanism of iron overload in haemochromatosis is the insufficient response of hepcidin in the liver to the storage of iron in the body, leading to excessive absorption of iron in the duodenum. Patients with haemochromatosis should try to abstain from alcohol, especially if there is advanced fibrosis. Vitamin C can increase the intestinal absorption of iron and the release of iron reserves.

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