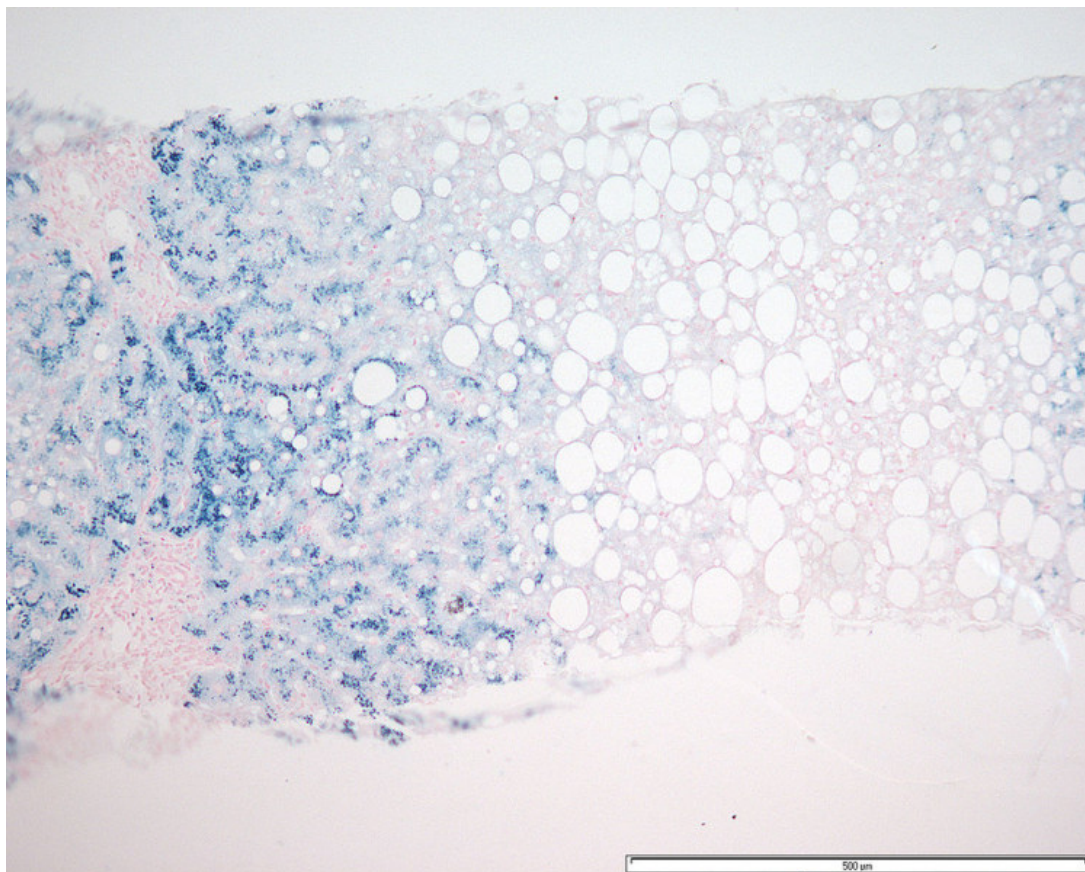


Hereditary Hemochromatosis: Risk Factors, Classifications, Diagnosis

[See online here](#)

Hereditary hemochromatosis (HH), also termed 'genetic hemochromatosis', is a genetic autosomal recessive disorder that occurs as a result of genetic mutations of certain genes (HFE gene) involved in the metabolism of iron, resulting in increased intestinal iron absorption. Common initial symptoms comprise abdominal pain, paleness, lethargy, and weight loss. The start of symptoms is between 30 to 50 years in males and afterward menopause in females. If left untreated, hemochromatosis could cause serious disease and early death. The keystone of screening is the level of serum transferrin saturation as well as the serum ferritin level. Definition, risk factors, pathophysiology, clinical features, investigations and treatment of hemochromatosis will be discussed in this article.



Definition

Hereditary hemochromatosis (HH) is an **inherited disorder caused by high accumulation of iron in the body usually because of excessive absorption of**

iron by the colonic tract. The areas most commonly affected are the [liver](#), [skin](#), [pancreas](#), [heart](#), joints, and testes.

The additional iron gives the skin a bronze color and harms the liver. [Diabetes](#) similarly occurs because of harm to the pancreas. Congestive heart failure & arrhythmias, [arthritis](#), and hypogonadism also may occur.

Risk Factors of Hereditary Hemochromatosis

Populations affected by hereditary hemochromatosis

Haemochromatosis is **one of the most common congenital (genetic) disorders in the United States**. Haemochromatosis is most common in Caucasians of north European ancestry. It is rare in African Americans and more common in men than in females.

Clinical manifestations do not typically appear in men until the ages 40 to 60. In females, they do not typically appear until after the age of 50 (after menopause).

Main risk factors

1. **Having a pair of irregular HFE genetic factors** (one from each parent) is the main risk factor for haemochromatosis. Though, numerous people with two copies of the irregular gene do not have the disease
2. **Alcoholism**
3. A **family history** hemochromatosis symptoms such as heart disease, diabetes, arthritis, liver disease, and erectile dysfunction

Classifications of Hereditary Hemochromatosis

There are two kinds of hemochromatosis:

Primary hemochromatosis

Primary hemochromatosis is a **genetic disorder** causing increased accumulation of iron within the body.

Secondary (acquired) hemochromatosis

Secondary hemochromatosis is increased iron accumulation as a **result of other blood-related complaints** (such as thalassemia or certain anemias) or **excess blood transfusions**. It can also occur in patients with long-term alcoholism.

Pathophysiology of Hereditary Hemochromatosis

In most patients (> 85 %) with hemochromatosis, **mutations in the iron-controlling gene HFE** can be found. Excess iron in the body can induce oxidative stress and suppresses mitochondrial processes. Patients with hemochromatosis can also have evidence of colonic irritation. Additionally, patients with gene mutations associated with hemochromatosis have also been found to have an increased risk for colon cancer.

Normally, the entire body iron content is around 2.5 g in women and 3.5 g in men.

Because symptoms may not occur until iron buildup is extreme (eg, > 10 to 20 g), **hemochromatosis usually manifests later in life**. In women, symptoms do not usually appear until after menopause because menses helps to alleviate excess iron.

Hepcidin, a liver-derived peptide, is the body's main regulator for iron absorption. Hepcidin is usually up-regulated when the body has high levels of iron. It has an inhibitory effect on **ferroportin** (which participates in iron absorption), and therefore stops iron absorption and storage.

Clinical Features of Hereditary Hemochromatosis

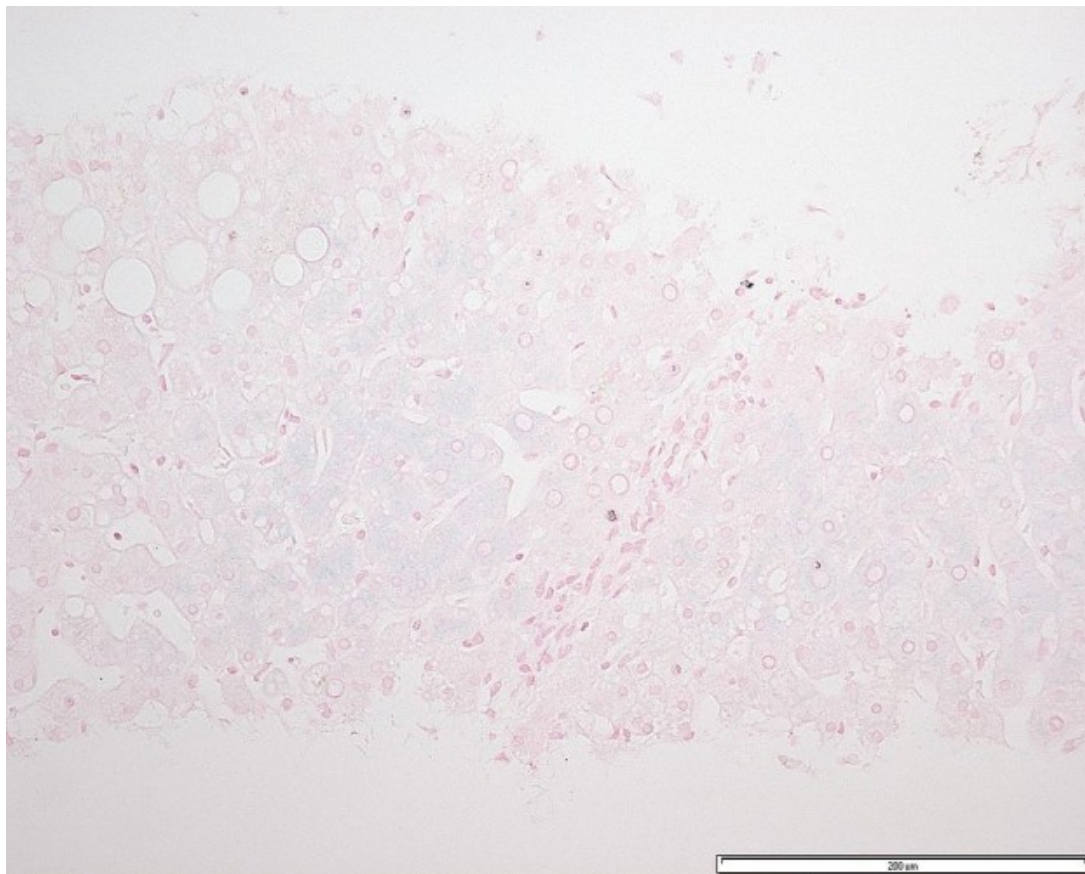


Image: "Perl's Prussian Blue stain for iron shows a typical pattern of iron accumulation seen in heterozygous genetic Hemochromatosis" by Mathew, J et al.. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

The clinical manifestations of hereditary hemochromatosis include:

- Liver function abnormalities
- Lethargy and weakness
- Skin hyperpigmentation
- Diabetes mellitus
- Arthralgia
- Impotence in males
- Electrocardiographic abnormalities

Women usually present with non-specific symptoms first, such as **fatigue**. In men, problems such as **diabetes** or else **cirrhosis** (damaging of the liver) are often the first symptoms.

Other symptoms include **joint pain, fatigue, general faintness, weight loss, in**

addition to stomach pain.

Liver disease

Excess iron deposition in the liver may result in **hepatomegaly** with increased liver enzymes and progressive fibrosis, which can eventually lead to cirrhosis. Excessive iron deposition and damage in the liver is also associated with increased risk for hepatocellular carcinoma.

Diabetes mellitus

Diabetes mellitus occurs in about 50% of cases with hereditary hemochromatosis due to excess iron deposition and damage to the pancreas. The triad of diabetes mellitus, liver cirrhosis, and skin pigmentation is termed '**bronze diabetes**' which occurs in the advanced disease when the total iron content increases 5 times its normal level.

Arthropathy

Hereditary hemochromatosis can be associated with pseudogout, chondrocalcinosis, and chronic arthropathy.

Heart disease

Excess iron deposition in the myocardium can lead to **dilated cardiomyopathy** with subsequent heart failure and/or conduction disturbances, such as sick sinus syndrome.

Hypogonadism

Excess iron deposition in the pituitary cells may reduce the levels of the trophic hormones causing **decreased libido & impotence** in men. **Amenorrhea** may also occur in women.

Excessive skin pigmentation

The characteristic metallic '**bronzing**' color of the skin occurs in the advanced disease due to increased iron and melanin in the skin.

Investigations and Diagnosis of Hereditary Hemochromatosis

Blood tests

Haemochromatosis is typically identified using blood tests, which might include:

Transferrin saturation

Measures how much iron is willingly accessible for use in the body. It is elevated early in the course of the disease but has significant false positive and negative rates.

Serum ferritin concentration

Measures the quantity of iron stored in the body. Although serum ferritin level >1000 mg/L is a strong indicator of hemochromatosis, it can also be elevated in patients with

any type of hepatocellular necrosis/insult. Therefore, it is important to repeat the ferritin level after resolving any acute hepatic damage (e.g. alcoholic liver disease).

Genetic testing

Would usually confirm the diagnosis and help screen for the disease in family members.

Liver biopsy

A liver biopsy may be helpful but is not required for the diagnosis of hemochromatosis. A biopsy will show excess accumulation of iron within hepatocytes.

MRI of the liver

Excessive iron deposition in the liver can be revealed as an increased density of the liver by the MRI. MRI can be very accurate in determining the concentration of the iron in the liver.

Screening

If a diagnosis of hereditary hemochromatosis is established in a patient, it is important to screen other family members. Both symptomatic and asymptomatic patients with hemochromatosis have:

- High transferrin saturation
- High serum-ferritin concentration

Patient's first-degree relatives should be tested for C282Y and H63D mutations.

Treatment of Hereditary Hemochromatosis

Treatments for hemochromatosis are iron chelation therapy and therapeutic phlebotomy. Patients with hemochromatosis are not required to follow a distinct diet. However, iron and vitamin C supplements must be avoided. Patients should also avoid alcohol consumption.

Therapeutic phlebotomy

Therapeutic phlebotomy **eliminates excess iron from the body**. Removal of the iron from the body is best done by **removal of 500 mL of blood once or else twice a week**. After normal levels are achieved, phlebotomy may be needed less frequently — usually every 2–4 months, to maintain serum ferritin levels around 50 and 100 mg/L.

Iron chelation therapy

Chelating agents such as **deferoxamine** can remove 10–20 mg of iron from the body per day. This is less than what can be removed by phlebotomy. Although phlebotomy is less expensive and safer for most patients with hemochromatosis, iron chelating therapy is indicated:

1. When there is severe anemia or hypoproteinemia.
2. In persons who cannot have routine blood elimination.

Treatment for complications

People with hemochromatosis have increased risk for heart diseases, diabetes, and hepatic failure.

In cases of hemochromatosis-induced hypogonadism, patients should receive **testosterone replacement or gonadotropin therapy**.

The end-stage liver disease should be treated with **liver transplantation**.

Review Questions

The correct answers can be found below the references.

1. What is the type of genetic inheritance of hereditary hemochromatosis?

- A. Autosomal recessive
- B. Autosomal dominant
- C. X-linked
- D. Non-inheritance disease

2. Iron-chelating therapy is used in the treatment of hereditary hemochromatosis if there is...

- A. ...severe anemia.
- B. ...hypoproteinemia.
- C. ...heart failure.
- D. A & B.

3. The characteristic blood tests abnormality in hereditary hemochromatosis are what?

- A. High transferrin saturation and low ferritin level
- B. High transferrin saturation and high ferritin level
- C. Low transferrin saturation and high ferritin level
- D. Low transferrin saturation and low ferritin level

References

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Correct answers: 1A, 2D, 3B

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Notes