

Clinical Update for
General Practitioners and Physicians

Haemochromatosis

Updated 2021



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1. Definition

Hereditary haemochromatosis (HFE) is a common inherited disorder in which excessive iron absorption may lead to increased body iron stores with deposition of iron in parenchymal cells of the liver, heart, pancreas and other organs. A number of genes have been implicated in HFE and at present mutations in five different genes are known to cause iron overload. HFE1 is an autosomal recessive condition caused by mutations in the *HFE* gene and is by far the most prevalent form in Australia¹.

Disorders, other than hereditary haemochromatosis, which give rise to iron overload are classified under the broad heading of **secondary iron overload** syndromes (usually iron-loading anaemias such as thalassemia major).

2. Iron studies

Serum iron studies usually reflect body iron stores and are often increased in HFE. These tests are based on measurement of serum ferritin, iron and transferrin. Ferritin is the storage protein for iron and its serum concentration provides an indirect guide to body iron stores. Serum ferritin concentration is influenced by age and gender in healthy individuals.

Laboratory reference ranges are expressed accordingly: up to 200 µg/L in pre-menopausal women and 300 µg/L in men and post-menopausal women. However, serum ferritin concentration is also increased in inflammatory conditions, systemic infections and as a consequence of hepatocyte injury. Metabolic (dysfunction) associated fatty liver disease (MAFLD) is frequently associated with mild to moderate elevation of serum ferritin (<1000 µg/L). Serum ferritin may be increased by hazardous alcohol consumption, but usually returns to normal with abstinence. In patients with significant iron overload,

particularly if the ferritin level is >1000 µg/L, secondary iron overload should be excluded by examination of the blood film, particularly for evidence of thalassemia, hereditary spherocytosis and other iron loading anaemias.

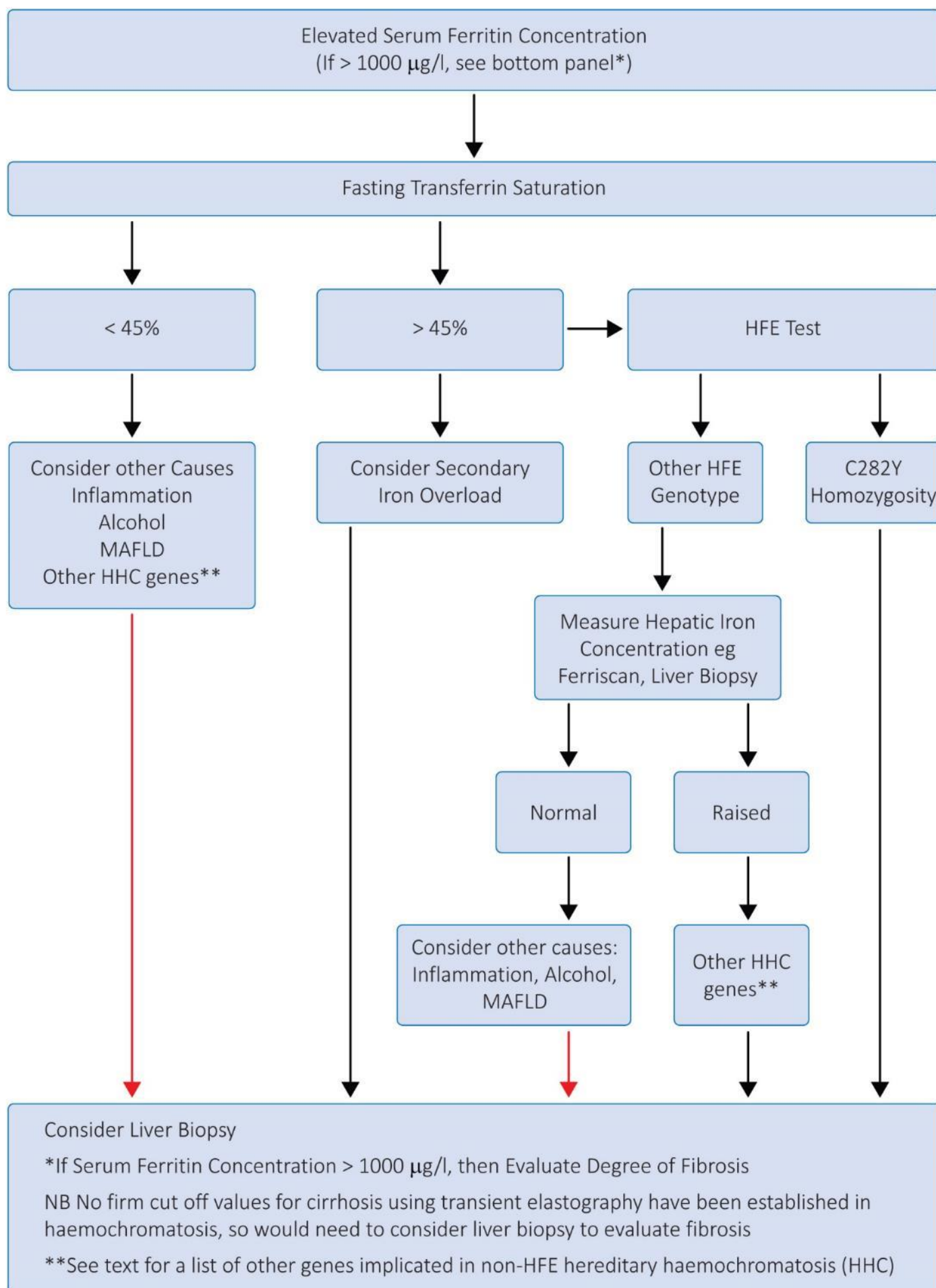
Other types of HFE should also be considered.

Serum iron is affected by dietary intake, shows diurnal variation, and is not a reliable indicator of body iron stores.

Transferrin is the major iron transport protein in the body. Transferrin saturation is calculated from serum iron and transferrin concentrations and reflects altered iron metabolism. In HFE the transferrin saturation is likely to be elevated (>45%) before serum ferritin increases.

Measuring transferrin saturation after an overnight fast decreases the effect of diurnal variation of serum iron, and a value of >45% is suggestive of iron overload².

Figure 1: Elevated-Serum-Ferritin



Genetics of hereditary haemochromatosis

The majority of cases of HFE1 are due to a mutation of both copies of the *HFE* gene resulting in a cysteine to tyrosine substitution at amino acid 282 in the protein product (the C282Y mutation).

Homozygosity for C282Y is present in 60-90% of patients with HFE1. A minority of cases will have one gene with the C282Y mutation, and the other with a histidine to aspartate mutation at amino acid 63 (H63D mutation) – this pattern is described as compound heterozygosity. Only a very small proportion of compound heterozygotes develop clinically significant iron overload, in which the level of iron loading is usually less than seen in C282Y homozygotes.

Most C282Y heterozygotes (one mutation only) express minor or no abnormalities of serum iron indices but a few develop progressive iron-overload and overt disease. H63D homozygotes and heterozygotes usually do not develop clinically significant iron overload. Other *HFE* mutations (S65C) do not cause clinically significant iron overload. If a patient with these mutations develops raised serum ferritin, another cause such as MAFLD or hazardous alcohol use should be sought.

Key point:

Significant iron loading occurs principally in C282Y homozygotes and occasionally in C282Y/H63D compound heterozygotes. Other HFE genotypes, including heterozygosity for C282Y, usually do not develop significant iron overload.

The prevalence of patients homozygous for the C282Y mutation of HFE in Australia, the United Kingdom and Europe is 3.6 per 1000 individuals³. The prevalence of clinical disease is much lower. The prevalence of C282Y heterozygous subjects (carriers) has been estimated as 12%.

The male: female ratio for C282Y homozygosity is 1:1, although the male: female ratio for clinical disease is about 5:1, due primarily to physiological blood and iron loss in women secondary to menstruation and pregnancy.

Genes that are implicated in other rare forms of HFE⁴ include hemojuvelin (HFE2A), hepcidin (HFE2B), transferrin receptor 2 (HFE3), ferroportin 1 (HFE4), and ferritin heavy chain (HFE5). Genetic testing for mutations of these genes is not routinely available.

3. Clinical manifestations

In the majority of patients with overt haemochromatosis, the first symptoms develop between the ages of 30 and 60 years. Iron loss related to menstruation and pregnancy contribute to later presentation of the disorder in women.

Many patients have no symptoms. When present, the most common symptoms are:

- Lethargy and weakness
- Arthralgia
- Loss of libido
- Upper abdominal discomfort.

Physical examination may be normal, but if present, the most common physical signs are:

- Hepatomegaly and/or signs of chronic liver disease
- Grey skin pigmentation
- Testicular atrophy
- Joint swelling and tenderness.

Key point:

Many patients will have no symptoms or signs suggestive of the disorder.

Liver function tests are frequently normal but may be abnormal in symptomatic patients. Diabetes mellitus usually is present only in patients with advanced disease due to iron deposition in the pancreas. Many patients are now detected in the course of family screening or routine health checks and have no symptoms or signs suggestive of the disorder.

The complications of untreated haemochromatosis include the following:

- Liver disease with fibrosis or cirrhosis, with hepatocellular carcinoma occurring in up to a third of cirrhotic patients
- Arthritis
- Gonadal failure
- Diabetes mellitus
- Cardiac failure and arrhythmias.

4. Diagnosis

Haemochromatosis should be suspected in:

- Patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease
- Family members of haemochromatosis patients. Such subjects are frequently asymptomatic with no clinical signs
- Other increased risk groups such as patients with diabetes mellitus, typical arthritis, cardiomyopathy, or chronic fatigue

The approach to testing for haemochromatosis may be summarised as follows²:

1. In people without a family history of HFE, fasting transferrin saturation and serum ferritin concentration are the most useful screening tests. The transferrin saturation is more sensitive in detecting early iron overload. These tests should be performed in the morning after an overnight fast. If the transferrin saturation **or** serum ferritin is increased on more than one occasion, haemochromatosis should be suspected - even if there are no clinical symptoms or abnormal liver tests. The HFE gene test should be performed in this situation.

Key point:

The transferrin saturation and serum ferritin concentration are the most useful initial tests for haemochromatosis in people without a family history.

2. All first-degree relatives (siblings, offspring, and parents) of the index case should be screened. The risk of HFE1 is greatest in siblings of the index case or siblings of other affected family members. These relatives should be tested for the C282Y mutations of HFE, as well as serum iron indices. Those found to be C282Y homozygotes are at risk of iron overload, whilst those found to be heterozygous are at low risk. Those found to have no HFE mutations do not develop iron overload.

Key point:

All first-degree relatives of an index case of HFE1 should be evaluated for haemochromatosis by testing for mutations of the HFE gene.

3. It has been recommended that genetic testing for HFE within families occur during adolescence. However, screening of the children of a patient with haemochromatosis can be foregone if the child's other parent is tested and does not have any copies of the C282Y mutation.
4. People found to be homozygous for the C282Y mutation but with normal ferritin and transferrin saturation should have their iron studies checked every 2-3 years.
5. Certain groups of patients at increased risk of HFE should also be tested for haemochromatosis: patients with liver disease, diabetes, the typical arthritis associated with HFE1, cardiomyopathy or testicular failure. Serum iron and ferritin studies may be difficult to interpret in these conditions because of non-specific increases in the serum levels related to systemic or hepatic inflammation but testing for HFE mutations may be helpful.
6. Although haemochromatosis is prevalent, screening of the general population has not been shown to be cost-effective.
7. Liver biopsy was previously the gold standard in the diagnosis of haemochromatosis. This allows histological staining of iron and measurement of hepatic iron concentration. Importantly, it remains the only reliable way to determine the presence of cirrhosis. This is relevant because patients with cirrhosis are at risk of hepatocellular carcinoma (HCC) and other life-threatening complications of cirrhosis such as oesophageal variceal haemorrhage. The risk of HCC persists in cirrhotic patients even after adequate treatment of iron overload.
8. Since the discovery of the HFE gene, the diagnosis of HFE1 can be made confidently with blood testing alone. Liver biopsy is required to establish or exclude the presence of cirrhosis and should be considered when there is a history of significant alcohol; hepatomegaly on clinical exam; the liver enzymes are raised; or the serum ferritin is >1000 µg/L⁵

Key point:

Haemochromatosis can usually be confidently diagnosed without liver biopsy. However, biopsy is recommended if there is suspicion of cirrhosis.

5. Treatment

The treatment of haemochromatosis consists of life-long venesection therapy, which depletes the body of iron by removal of iron in haemoglobin. 500ml of blood contains approximately 250mg of iron.

An initial course of one or two venesections per week, each of 500ml, is performed until the excess iron stores are removed (see below). It may take 1-2 years to remove 10-20g of excess body iron in severely affected patients. Once this is achieved, patients usually require one venesection every 3-4 months to keep iron stores at low normal levels, without rendering the patient iron deficient. It is rare for patients not to tolerate venesection therapy, but this may occur in patients with severe cardiac disease, anaemia or hypoproteinemia. These patients may be given chelation therapy for removal of iron, but this is costly and in practice is rarely needed.

Key point:

The treatment of haemochromatosis consists of life-long venesection therapy.

Venesection therapy is performed using a standard blood collection bag. Immediately prior to venesection, the patient should rest for 15 minutes and drink 500ml of water. Firm pressure is applied to the venepuncture site for 5 minutes following removal of the needle, and the patient should rest for 15 minutes following the procedure. Fainting may sometimes occur when the patient stands. The patient may feel tired for 24 hours following venesection and strenuous exercise should be avoided.

To monitor the first phase of venesection treatment, the haemoglobin concentration is measured approximately second weekly and the serum ferritin each month. The endpoint of this initial course of treatment is either a sustained fall in the haemoglobin concentration (to under 11.0 g/dL) or a serum ferritin concentration in the low normal range (50 – 100 µg/L). There is no need to make the patient iron deficient. The patient then enters the maintenance phase of treatment with measurement of the serum ferritin concentration approximately 6 monthly, maintaining it below 100 µg/L. A liver biopsy is repeated only if there was initial uncertainty with respect to the presence or absence of cirrhosis. Cirrhosis rarely regresses to normal after venesection therapy, nor does it develop if the patient is non-cirrhotic at diagnosis and is adequately treated.

There is no requirement for a low iron diet in the management of HFE as venesection is so effective in removing excess iron stores. However, it is reasonable for patients to choose to reduce red meat intake if they wish to do so (e.g., to approximately 90-120 g/day), as this may reduce the frequency of venesections. Vitamin C (ascorbic acid) supplements should be avoided since vitamin C can increase iron absorption and iron toxicity. As with any liver disease, alcohol consumption should be kept to a minimum (less than 20 g/day), but abstinence is not required unless there are other indications such as established cirrhosis.

6. Prognosis

The prognosis of haemochromatosis has been significantly improved by venesection therapy. Overall cumulative survival is 76% at 10 years and 49% at 20 years⁶. Non-cirrhotic patients diagnosed and treated early have a normal life expectancy compared to age and sex-matched controls, provided they continue treatment.

Life expectancy is reduced in those who present with cirrhosis or diabetes mellitus. Patients with cirrhosis have a risk of death due to hepatocellular carcinoma even when complete iron depletion is achieved. Almost all cases of HCC in HFE occur in patients with established cirrhosis, with males at greater risk than females. The usual practice is that cirrhotic patients should undergo HCC surveillance every six months with hepatic ultrasound and serum alpha-fetoprotein measurement. In cirrhotic patients, endoscopy should be considered to determine if varices or other evidence of portal hypertension that might require therapy are present.

Key point:

Non-cirrhotic patients diagnosed and treated early have a normal life expectancy.

Skin pigmentation usually decreases with venesection. The response of hypogonadism to venesection is variable.

Insulin-dependent diabetic patients usually need to continue insulin therapy after venesection, although their dose requirements may be reduced.

Arthropathy has a variable response to venesection treatment. The arthropathy may antedate the onset of liver disease or may occur for the first time after venesection therapy. Venesection therapy usually leads to some improvement in cardiac symptoms, cardiomegaly, and haemodynamic abnormalities.

7. Key points

- Type 1 hereditary haemochromatosis (HFE1) is a common genetic disease in Australia (the most prevalent genetic disease in people of Northern European descent).
- Haemochromatosis should be suspected in patients with raised iron studies, particularly an increased fasting transferrin saturation; a family history of HFE1; and in patients with liver disease, diabetes, arthritis, skin pigmentation, impotence, or cardiomyopathy.
- The best screening tests for detection of hereditary haemochromatosis are a fasting serum transferrin saturation and serum ferritin concentration.
- Many patients with early-stage disease are asymptomatic.
- The diagnosis can be confirmed by identifying homozygosity for the C282Y mutations of the *HFE* gene.
- Family members of an affected individual should be screened by testing for *HFE* gene mutations and measuring serum iron indices.
- Early diagnosis and treatment of the disease prevents organ damage and results in normal life expectancy.
- Liver biopsy is required to establish or exclude the presence of cirrhosis when there is a history of significant alcohol; hepatomegaly on clinical exam; or the serum ferritin is >1000 µg/l.

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