HEREDITARY HEMOCHROMATOSIS

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Executive Summary *Hereditary hemochromatosis (HH) is a common genetic disorder of iron metabolism which can affect multiple vital organs. Proper diagnosis, which can be accomplished by laboratory and genetic testing, is important in order to separate HH from other causes of iron overload. If adequate phlebotomy treatment is instituted early in its course, life expectancy is close to normal. Understanding the clinical features and laboratory testing, as well as recognizing possible signs of organ damage, is key to appropriate risk assessment.*

Hemochromatosis is a metabolic disorder in which there is excessive accumulation of iron in multiple organs such as the liver, heart, pituitary, pancreas, joints and skin. This results in damage to the parenchymal cells of the affected organs and may lead to cirrhosis, cardiomyopathy, heart failure, impotence, diabetes mellitus, arthritis and hyperpigmentation of the skin.

Hereditary hemochromatosis (HH) is the most common single-gene disorder in Caucasians, especially those of northern European descent. However, it is also underdiagnosed in the general population and often untreated. It is an autosomal recessive disorder associated with mutations in the HFE gene, one of the genes thought to regulate iron absorption, which is located on the short arm of chromosome 6. The diagnosis is based on a combination of clinical, laboratory and pathologic findings. The estimated mortality is 1.7 cases per 10,000 deaths, but life expectancy is close to normal if the disorder is detected early and treated properly before the onset of diabetes, liver cirrhosis or heart disease.

Iron Metabolism

Iron is essential to life. Its ability to be both an electron donor and an electron acceptor makes it ideal for transporting oxygen, but it is also potentially toxic if excessive amounts are deposited in vital organs. Normal iron metabolism is critical for maintaining health and for producing erythrocytes (red blood cells). Iron is obtained by either intestinal absorption of dietary iron, or by recycling iron from senescent (aging) red blood cells via the reticuloendothelial system (RES). Both of these processes are tightly regulated depending on the body's metabolic needs.

Figure 1 (next page) shows the distribution of iron in adults. Healthy human adults have approximately 3,000-4,000 mg of iron in their bodies, most (around 2,500 mg) of which is found in hemoglobin within erythrocytes. Approximately 1,000 mg are stored in the liver and only 3-4 mg circulate in the plasma pool.

An adult male loses approximately 1 mg of iron per day via intestinal excretion, sweat and skin cell exfoliation, and urine. An adult female loses an average of about 2 mg daily during childbearing years, and an additional 500 mg with each pregnancy. These losses are offset by the absorption of 1-2 mg of dietary iron, most of which takes place in the duodenum (and to a lesser extent in the upper jejunum). Here, iron is absorbed by the villi of the enterocytes when it binds with the protein apoferritin, and is then either stored as the iron compound ferritin or transferred to the plasma via apotransferrin (a transport protein). The transfer to plasma of iron from the enterocytes takes place through specific iron channels (ferroportins), and is assisted by the protein hephaestin, which converts iron from the ferrous to the ferric form.

Another protein, divalent metal transporter 1 (DMT1), facilitates the transfer of iron (as well as other trace metals) across the intestinal epithelial walls. When apotransferrin binds to iron, it forms transferrin, which is the primary means of transfer for iron

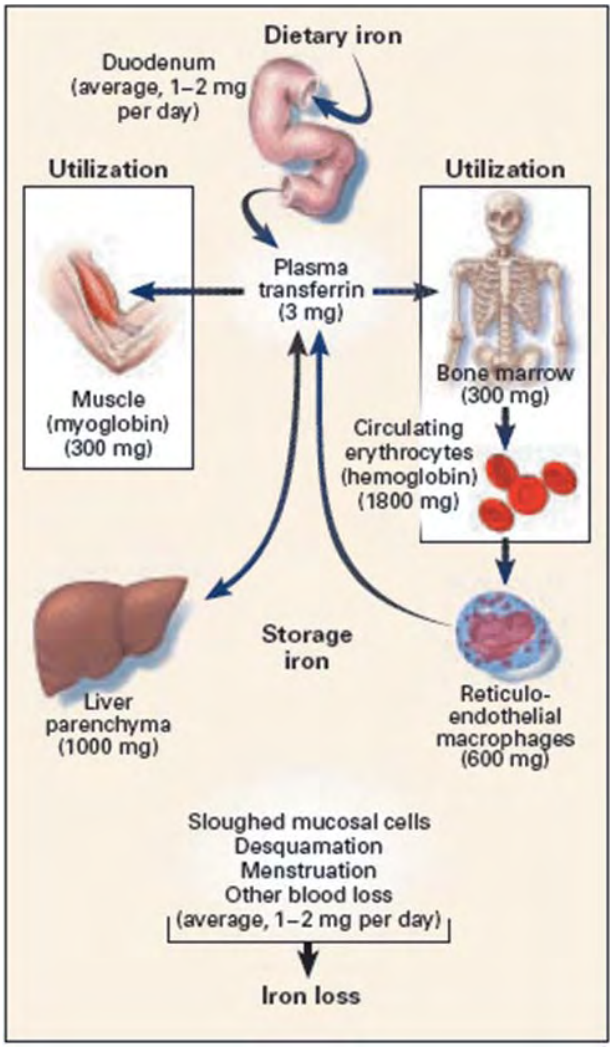


Figure 1. Distribution of Iron in Adults
In the balanced state, 1 to 2 mg of iron enters and leaves the body each day. Dietary iron is absorbed by duodenal enterocytes. It circulates in plasma bound to transferrin. Most of the iron in the body is incorporated into hemoglobin in erythroid precursors and mature red cells. Approximately 10 to 15% is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes). Iron is stored in parenchymal cells of the liver and reticuloendothelial macrophages. These macrophages provide most of the usable iron by degrading hemoglobin in senescent erythrocytes and reloading ferric iron onto transferrin for delivery to cells.

throughout the body. Transferrin helps maintain iron in the human body in a non-toxic state. It has two binding sites and is about 30% saturated under normal conditions, allowing additional room to transport excess iron if required.

Cells have transferrin receptors on their plasma membranes, which enable iron to be imported into cells in response to intracellular iron concentrations. Some iron ions are transported to the bone marrow, while others are transported to the liver, where they are stored in the hepatocytes. Erythrocyte precursors obtain iron for hemoglobin synthesis from plasma transferrin or from recycled senescent red cells by macrophages in the bone marrow, spleen and liver. Excess iron not required for hemoglobin production is stored in macrophages.

Iron is stored in the human body as either ferritin or hemosiderin, an insoluble protein that is a product of hemolysis.

Iron stores can be released from macrophages when needed for erythropoeisis (the production of red blood cells). Ferritin levels are, therefore, a good indicator of iron stores, and transferrin saturation a good indicator of recycled iron. Erythrocytes transport oxygen from the lungs to cells throughout the body, but in order to carry out this function they require ferritin, which is stored in hemoglobin, where it helps in binding oxygen molecules.

[See Figure 2, next page]

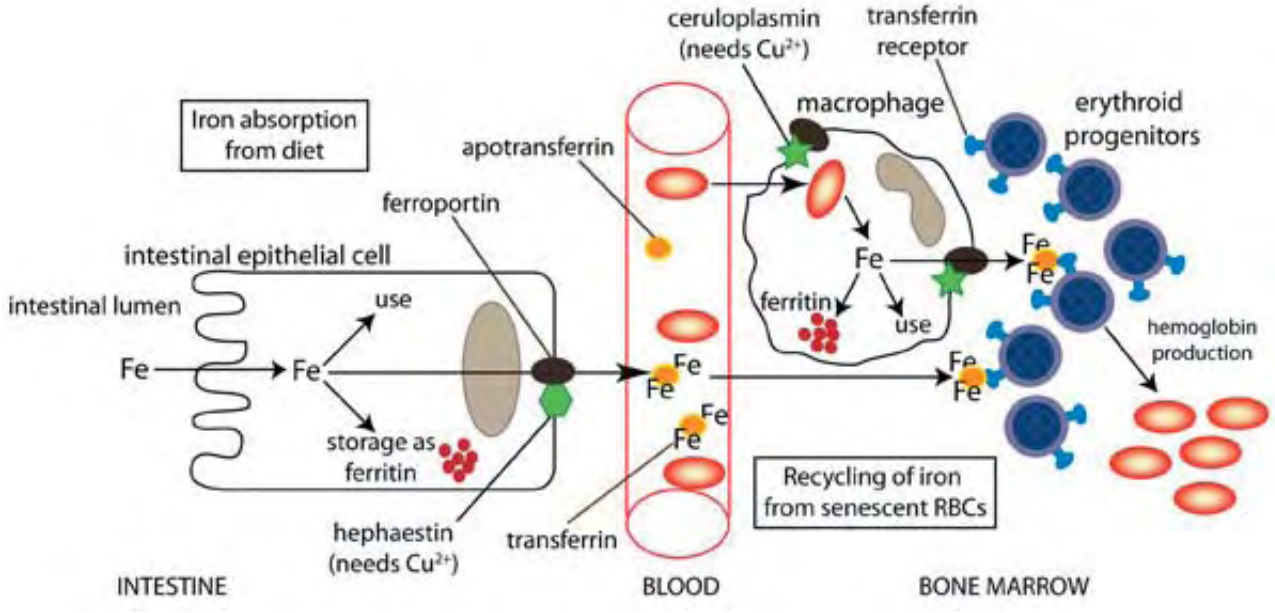
Although the amount of iron absorbed by the enterocytes is small, efficient regulation of iron absorption is vital for maintaining the body's homeostasis. Hepcidin, a protein synthesized in the liver, plays a key role in iron regulation. It inhibits ferroportin release and signals enterocytes to retain any absorbed iron (to be eliminated in a few days), thereby reducing the flow of iron into plasma. A decrease in hepcidin results in increased iron absorption.

Most individuals with hereditary hemochromatosis have mutations in the HFE gene which result in hepcidin deficiency. Iron toxicity occurs when there is free (or unbound) iron in cells, which generally occurs when iron levels exceed the capacity of transferrin to bind the iron. Iron overload is harmful, as it promotes the formation of free radicals such as the hydroxyl radical and the superoxide radical. These result in oxidative stress and can ultimately lead to cell injury and fibrosis.

Clinical Features

Hereditary hemochromatosis (also referred to as primary hemochromatosis) is a primary iron-overload condition which affects approximately 1 in 300 people. HH affects men more than women (1.8:1), and iron overload develops less frequently in women, likely due to blood loss through menstruation and therefore slower accumulation of iron. Over 70% of individuals with hereditary hemochromatosis are

Figure 2. Intestinal Absorption of Iron and Recycling of Iron



(from http://ahdc.vet.cornell.edu/clinpath/modules/chem/femetb.htm)

homozygous for the missense mutation C282Y, the substitution of tyrosine for cysteine at amino acid position 282 of the HFE gene. The highest prevalence seen for C282Y homozygosity is 1 in 83 people in Ireland, which is why hemochromatosis has also been called "the Celtic curse." Another missense mutation, H63D, is also associated with hereditary hemochromatosis, but its clinical effects appear to be much milder.

Individuals who are heterozygous for the C282Y mutation are not considered to have hereditary hemochromatosis. Those with compound heterozygosity for C282Y/H63D, however, seem to be more at risk for iron overload. An additional mutation associated with iron overload is in the gene encoding transferrin receptor 2 (TfR2), but few cases have been reported. Another form of hemochromatosis is juvenile hemochromatosis, in which iron accumulation begins much earlier (generally between the ages of 15 and 30). This form, however, is not associated with mutations in the HFE gene, but with the HJV gene and in some cases with the HAMP gene. The HFE, TfR2 and HJV genes all encode for proteins that affect hepcidin.

As people with hereditary hemochromatosis absorb only a few milligrams of excessive iron per day, clinical manifestations are usually not apparent until after many years, once the iron stores are 15 mg-50 mg. Disease expression usually occurs after age 40 in men and after age 50 in women, but it may occur much earlier.

The following are clinical manifestations of HH:

- Arthropathy
- Hypogonadism or impotence in males
- Skin pigmentation
- Liver disease
- Diabetes mellitus
- Cardiac enlargement

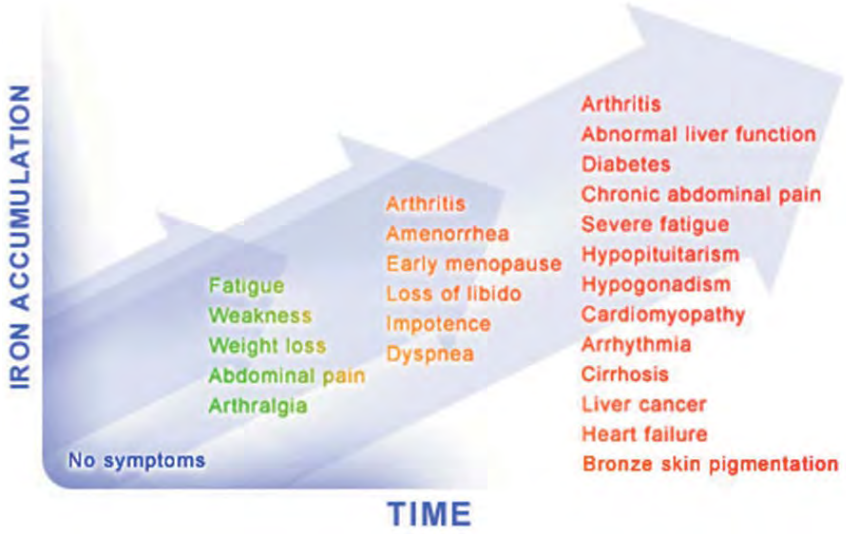
Some individuals never have any clinical manifestations, and many (between 50% and 70% of patients) are asymptomatic. In the past, hemochromatosis was diagnosed at older ages, with cardiac disease frequently a presenting manifestation (in up to 15% of cases). Today, a diagnosis most often occurs after routine lab testing shows elevated serum iron levels in asymptomatic people. Other patients might be diagnosed after being tested due to a family history of hemochromatosis.

Many cases are not suspected due to the patients' vague symptoms. Figure 3 (next page) shows the symptoms and manifestations of hemochromatosis over time. Today, due to genetic testing and early detection, full clinical expression of hemochromatosis is observed in only a minority of cases.

The most common early symptoms are fatigue and arthralgia. Males may also have hypogonadism (causing decreased libido and impotence) as a result of iron accumulation in the pituitary gland. Later in the course of the disease, patients may present with skin bronzing (hemochromatosis is sometimes referred to as bronze diabetes) or skin hyperpigmentation

(from iron deposition and melanin), diabetes or cirrhosis. Patients with cirrhosis (which occurs in approximately 13% of cases) may eventually progress to hepatocellular carcinoma, which is the most common cause of death in hereditary hemochromatosis. Cardiomyopathy is sometimes seen in hemochromatosis (especially in younger individuals), often accompanied by arrhythmias or conduction disturbances, such as sick sinus syndrome. Diabetes mellitus in individuals with hemochromatosis is caused by iron accumulation in the beta cells of the pancreas. These patients usually already have other signs of hemochromatosis such as liver disease or skin hyperpigmentation. There is also evidence that HH (and iron overload disease in general) also results in an increased susceptibility to infectious diseases, as it affects the ability of phagocytes to kill microorganisms.

Figure 3. Clinical Expression of Hemochromatosis Over Time



(from the CDC) http://www.cdc.gov/ncbddd/hemochromatosis/training/clinical_features/clinical_expression.html

Other Causes of Iron Overload

Other problems to be considered include:

- *Alcoholic liver disease* – iron can accumulate in the liver (especially with ingestion of iron-fortified wines); Kupffer cells in the liver may release free radicals.
- *Non alcoholic steatohepatitis (NASH)* – characterized by fatty infiltration and inflammation in the liver.
- *Transfusional iron overload* (which occurs with severe, chronic anemias such as thalassemia major, sideroblastic anemia, myelodysplastic syndrome and moderate aplastic anemia) – senescent RBCs are destroyed by reticuloendothelial cells, iron is deposited onto transferrin and is then distributed to tissues in the body. Large deposits of iron in the reticuloendothelial cells are typically seen.
- *Porphyria cutanea tarda* – the deficiency of a liver enzyme (URO-D) involved in heme (the deep red, ferrous component of hemoglobin) production, which leads to the accumulation of porphyrins and excess iron in the liver; affects skin pigmentation and can cause recurring blisters on sun-exposed areas.
- *Viral hepatitis* – serum iron, ferritin and hepatic iron content (HIC) are frequently elevated. Chronic hepatitis C, in particular, may lead to increased hepatocyte or reticuloendothelial iron stores.
- *African iron overload* (Bantu siderosis) – iron overload seen in parts of sub-Saharan Africa, initially thought to be caused by the preparation of home-brewed beer in iron pots or drums, but recent evidence suggests it is caused by a genetic mutation.
- *Chronic iron supplementation* – individuals who take iron as a dietary supplement.

The above causes are characterized by initial iron deposition in the reticuloendothelial system, the presence of an underlying cause, iron accumulation not controlled by a genetic factor, and the absence of excessive intestinal iron absorption. A detailed description of the aforementioned disorders is beyond the scope of this article.

Diagnosis and Tests

Serum iron concentrations vary throughout the day and are influenced by food ingestion. Testing for transferrin saturation, that is, for the ratio of serum iron to total iron binding capacity, is the screening test of choice. It does have its limitations, however, as it can be affected by liver disease and inflammation. The upper limit for fasting transferrin saturation is 45% to 50%.

A diagnosis of hemochromatosis is suggested by persistently elevated transferrin saturation in the absence of other causes of iron overload. It should be noted, however, that many with hereditary hemochromatosis (including approximately 30% of women younger than 30 with HH) have normal transferrin saturation levels early in the course of the

disease. Serum ferritin, which indicates the amount of iron stored in the body, is highly sensitive for iron overload, but can also be elevated in the setting of infections and other inflammatory conditions even in the absence of iron overload.

The normal range of serum ferritin concentration in adult men is 20-300 mcg/L, and the normal range for adult women is 20-200 mcg/L. A ferritin level above 1,000 mcg is highly suggestive of liver fibrosis or cirrhosis. Patients with hemochromatosis commonly have high transferrin saturation levels, a high serum iron level and a low total iron binding capacity (TIBC).

In addition to genetic testing, important laboratory test results in diagnosing and following hemochromatosis are:

- Transferrin saturation
- Serum iron
- Ferritin
- Total iron binding capacity (TIBC)

Other laboratory tests to consider are those that pertain to the target organs.

In the past, liver biopsy and histologic evaluation with iron staining were recommended in order to diagnose hemochromatosis, but it is no longer essential for diagnosis in many cases, particularly with the availability of testing for the C282Y mutation. However, a liver biopsy is still considered the gold standard for determining the degree of fibrosis, and may be indicated either for individuals with ferritin levels in excess of 1,000 mcg/L or for those with hereditary hemochromatosis and elevated liver enzymes. Iron accumulation in the hepatocytes and biliary epithelial cells (staining shows a brownish pigment in the hepatocytes and Perl's Prussian blue staining confirms iron), and relative sparing of Kupffer cells are common findings in those with hemochromatosis. However, iron tends to accumulate in Kupffer cells of individuals with transfusional iron overload or from parenteral iron. Hemosiderotic liver damage does not typically result in significant inflammation; liver enzymes may be mildly elevated or normal even when there is significant fibrosis.

Genetic testing for the HFE mutation is indicated in first-degree relatives of people with hereditary hemochromatosis and also in patients with evidence of possible iron overload once other causes have been excluded. Although population screening for hereditary hemochromatosis has been considered and discussed for years, no consensus has been reached regarding recommendations for screening.

Organ Damage

As mentioned, iron overload in hereditary hemochromatosis can cause significant organ damage.

- *Skin* – Hyperpigmentation results from the effects of iron deposition and melanin; tends to be more pronounced in sun-exposed areas such as the face. Patients typically have a bronze coloration, although it can also frequently be gray.
- *Joints (arthropathy)* – The hips, the metacarpal phalangeal (MCP) joints, proximal interphalangeal joints, knees, wrists, ankles, back and neck are frequently involved. Chondrocalcinosis may occur; individuals may experience severe cramps and/or disabling myalgias. Muscle biopsies may show iron deposits in the myocytes.
- *Pituitary* – Pituitary dysfunction with the most common hormonal deficit involving the gonadotrophins (FSH and LH), producing secondary hypogonadism (loss of libido, impotence). Can less frequently cause TSH and ACTH deficiency, resulting in secondary hypothyroidism and adrenal insufficiency. The latter is extremely important, as a cortisol deficiency can lead to an adrenal crisis, necessitating replacement therapy with glucocorticoids.
- *Pancreas (diabetes mellitus)* – Approximately 30-50% of those diagnosed with hemochromatosis will have diabetes. The development of diabetes in HH is probably multifactorial. Secondary diabetes due to long-term iron accumulation in the beta cells of the pancreas (exocrine pancreatic function is usually unaffected) results in impaired insulin synthesis and release. It can also occur due to insulin resistance and hemochromatosis, as liver fibrosis can lead to insulin resistance. One study, which followed female patients for 10 years, concluded that higher iron stores are associated with an increased risk of Type 2 diabetes in healthy women independent of known diabetes risk factors. Many patients require insulin therapy, often in larger amounts in order to achieve optimal glucose control. It is rare to find an individual with both hemochromatosis and diabetes who does not also have liver disease. The more favorable cases are those well-controlled diabetics (also without diabetic complications) who have no evidence of liver fibrosis, have normal liver enzymes and serum ferritin levels under 500 ng/mL.
- *Heart* – Cardiac involvement in hereditary hemochromatosis is usually manifested by cardiomyopathy (dilated or restrictive), which can progress to congestive heart failure (CHF). In restrictive cardiomyopathy, the myocardium becomes rigid and noncompliant. Restrictive filling and reduced diastolic volume of either or both ventricles can be seen, usually with normal or near-normal systolic function. Low voltage on electrocardiograms is

another common finding. Dilated cardiomyopathy can also result from hereditary hemochromatosis. These cases are characterized by a dilated left ventricle (or both ventricles) and impaired contraction, with a low ejection fraction. Patients may have significant arrhythmias such as sick sinus syndrome. Iron deposition in the bundle of His and in Purkinje fibers can result in conduction defects. Sudden death can also occur. Cardiac MRIs can also be useful for the diagnosis of cardiac involvement. In any event, HH with cardiac involvement carries a poor prognosis.

- *Liver* – This is the major site of iron storage, and progressive iron deposition can result in tissue damage. Hepatomegaly develops early in the course of the disease, followed by fibrosis and then can progress to cirrhosis, which is one of the most common manifestations of HH. This can then progress to hepatocellular carcinoma, which is one of the main causes of death in hemochromatosis. Liver function abnormalities occur in a high percentage of individuals with hemochromatosis. Those with hereditary hemochromatosis and cirrhosis have a significant risk of developing hepatocellular carcinoma (over 200-fold). One study, which followed 95 patients with HH and cirrhosis, showed that 20% of the patients developed hepatocellular carcinoma. The cumulative survival for all patients was 88% at 1 year, 69% at 5 years and 56% at 20 years.

Treatment

Treatment is usually initiated for those with presumed iron overload, suggested by elevated serum ferritin concentration. Phlebotomy is the treatment of choice as it is simple, effective and inexpensive. The goal of this treatment is to remove iron from the body so as to avoid iron overload before it causes irreversible parenchymal damage in the organs. Patients are encouraged to have weekly phlebotomies of 500 mL of whole blood (approximately 200-250 mg of iron) until iron-limited erythropoietin develops (with a significant depletion of iron stores in the bone marrow), signaled by a hemoglobin concentration lower than the reference range (usually 12-13 g/dL), a serum ferritin level no greater than 50 mcg/L, and a transferrin saturation of less than 50%. After that, maintenance therapy is advised, in which one unit of blood is removed every 2-3 months.

Phlebotomy therapy has been shown to improve or even cure some of the manifestations and complications of the disease, and slow the progression of liver disease in patients with biopsy-proven fibrosis. The most significant improvement occurred in those with the least degree of liver fibrosis.

For those unable to undergo phlebotomy, oral chelation is another option. Deferoxamine, deferasirox and deferipone have been used. Chelating agents are chemical compounds that bind to metal ions, forming complexes that are then safely excreted. Oral iron chelators can be effective at decreasing serum ferritin levels, but there are reports of poor compliance by patients and limited acceptability of this therapy (some are also very expensive).

It is also recommended that individuals with hemochromatosis or other iron overload disorders avoid iron supplements, limit alcohol consumption (especially red wine, which contains high concentrations of iron), avoid raw or undercooked shellfish, limit ingestion of vitamin C supplements to 500 mg a day (as vitamin C increases the absorption of inorganic iron), and avoid eating red meats and organ meats. Some substances such as tannates (in tea) can be helpful, as they can bind to iron and inhibit its absorption. Surgical treatment for hemochromatosis is indicated for end-stage liver disease and severe arthropathy (liver transplantation and arthroplasty).

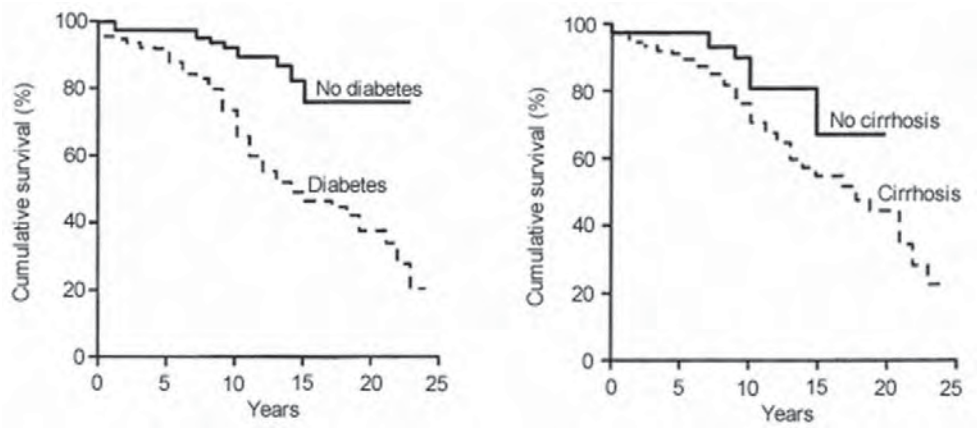
Underwriting Perspective

The main causes of death in patients with hemchromatosis are cirrhosis, hepatoma, diabetes and cardiac disease. When underwriting individuals with hemochromatosis, several crucial questions should be answered.

- Is the person being treated?
- Is the person compliant with phlebotomy treatment?
- Are there any signs of liver disease or parenchymal disease in other target organs and, if so, what is the degree of organ damage?
- What are the serum ferritin levels?
- Are liver enzymes elevated (as this suggests liver damage)?

Serum ferritin results give a good indication of the total body iron stores as well as the effectiveness of treatment. Serum ferritin levels should be below 1,000 ng/mL and ideally between 25-300 ng/mL. If treatment is too aggressive, however, red blood cell production might not be sufficient and anemia can result. This is another reason why compliance and good follow-up are important.

Figure 4. Survival in Hereditary Hemochromatosis



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Early detection and treatment of hereditary hemochromatosis are important. The prognosis of untreated hemochromatosis is poor while those who are treated, well followed and have no evidence of any end-organ damage have a very favorable prognosis.

One study conducted in Denmark, which followed 179 patients with overt hemochromatosis from 1948 to 1985, showed that the survival rates for individuals without cirrhosis or diabetes were similar to survival rates expected in the general population. Moreover, patients with adequate phlebotomy treatment experienced a higher survival rate than those treated inadequately. Regular phlebotomies can slow or stop disease progression and prevent all complications of hemochromatosis.

Today, hemochromatosis is usually diagnosed before there is damage to the liver, pancreas or heart. However, such damage does happen, and so it is important to be aware of the signs of end-organ damage when assessing the risk.

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