Patient education: Hemochromatosis (hereditary iron overload) (Beyond the Basics)

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HEMOCHROMATOSIS OVERVIEW — Hemochromatosis is a condition that causes excess absorption of iron from the digestive tract. Over time, the excess iron accumulates in tissues throughout the body, leading to iron overload. Signs of iron overload may include sexual dysfunction, joint pains, weakness, changes in skin coloration, liver damage (cirrhosis), heart failure, diabetes mellitus, and rarely, thyroid disease or liver cancer.

Early identification and treatment of hemochromatosis can prevent complications. Treatment typically involves regular phlebotomy (removal of blood) since blood cells contain an abundance of iron.

HEMOCHROMATOSIS CAUSES — Hemochromatosis is caused by the excessive absorption of iron. The exact process is still being studied. As a general rule, a number of chemical events take place that regulate how much iron is absorbed. Central to this process is a gene called HFE. Mutations in this gene cause excessive amounts of iron to be absorbed. The most common mutation is referred to as C282Y.

Hemochromatosis is most often seen in people who have two copies of this mutation (one inherited from their mother and the other from their father). However, other mutations causing hemochromatosis continue to be discovered. Furthermore, for unclear reasons, a majority of people with two copies of the C282Y mutation do not develop iron overload.

Risk factors — Hemochromatosis is usually inherited and most often affects people who are white. In the United States, about 5 in every 1,000 people who are white have the condition, although some are unaware of its presence. Family members of people with hemochromatosis should undergo testing since they may be unaware of the diagnosis. (See ‘Implications for the family’ below.)

About 10 percent of people who are white carry one of the gene defects associated with hemochromatosis, although most of these people have no symptoms.

HEMOCHROMATOSIS SYMPTOMS — Symptoms of hemochromatosis usually occur in people who have inherited two copies of the gene defects (the most common of which are called C282Y mutations) associated with the condition. However, the relationship between the gene defects and iron accumulation is still being explored; some people who have two copies of the gene defect do not have iron overload.

In the past, hemochromatosis was often advanced by the time a person noticed symptoms and sought medical care. Today, most people with hemochromatosis are identified at a young age because of abnormalities on
routine blood tests or because they undergo testing after a family member is diagnosed. As a result, about 75 percent of people with hemochromatosis are diagnosed before they have symptoms, and most people do not have complications at the time of diagnosis.

Symptoms typically do not occur until after the age of 40. The symptoms tend to occur later in women than in men because women lose iron throughout their lives through menstrual periods, pregnancy, and breastfeeding.

**Liver disease** — Accumulation of iron in the liver can cause liver enlargement, fibrosis (increase in scar tissue), and cirrhosis (extensive scarring) ([figure 1](#)). About 75 percent of people who have symptoms at the time of diagnosis have abnormal liver function.

Cirrhosis can cause a number of complications and can ultimately lead to liver failure or death. People with cirrhosis are also at increased risk for developing liver cancer. Liver disease is often worse in people with hereditary hemochromatosis who also have chronic hepatitis (such as hepatitis B or C) or are alcoholics, so it is important to simultaneously identify and treat these conditions. (See "[Patient education: Hepatitis B (Beyond the Basics)](https://www.uptodate.com/contents/hepatitis-b-beyond-the-basics)" and "[Patient education: Hepatitis C (Beyond the Basics)](https://www.uptodate.com/contents/hepatitis-c-beyond-the-basics)" and "[Patient education: Cirrhosis (Beyond the Basics)](https://www.uptodate.com/contents/cirrhosis-beyond-the-basics)".)

**Weakness and lethargy** — About 75 percent of people who have symptoms at the time of diagnosis have weakness and lethargy (a feeling of mental and physical sluggishness).

**Infections** — Hemochromatosis can increase the risk of infections with specific types of bacteria. Accumulation of iron in immune cells interferes with their ability to fight off certain bacteria, and other bacteria grow well in an iron-rich environment.

**Physical changes**

- Darkening of the skin — Accumulation of iron in the skin, along with accumulation of the pigment melanin, can darken the skin and give a person a tanned appearance. About 70 percent of people who have symptoms at the time of diagnosis have darkening of their skin.

- Joint pain — The cause of joint pain in people with hemochromatosis is incompletely understood. One hypothesis is that the excess iron leads to the collection of calcium crystals in the joint spaces. These crystals can cause joint pain and, over time, joint deformity. About 44 percent of people who have symptoms at the time of diagnosis have joint pain. The joints of the hands, especially the knuckles of the second and third fingers, are most commonly affected.

**Other conditions**

- Diabetes mellitus — Accumulation of iron in the pancreas can interfere with insulin production and cause diabetes mellitus. About one-half of people who have symptoms at the time of diagnosis have diabetes. (See "[Patient education: Diabetes mellitus type 2: Overview (Beyond the Basics)](https://www.uptodate.com/contents/diabetes-mellitus-type-2-overview-beyond-the-basics)".)

- Reproductive problems — Accumulation of iron in the pituitary gland can interfere with the pituitary's control of sex hormones. In men, pituitary damage can lead to impotence, loss of libido (sex drive), and even osteoporosis (bone weakening) leading to fractures. About 45 percent of men who have symptoms at the time of diagnosis have impotence.

In women, pituitary damage can lead to amenorrhea (absence of menstrual periods), although women with hemochromatosis seldom experience loss of libido or premature menopause. (See "[Patient education: Sexual problems in men (Beyond the Basics)](https://www.uptodate.com/contents/sexual-problems-in-men-beyond-the-basics)" and "[Patient education: Absent or irregular periods (Beyond the Basics)](https://www.uptodate.com/contents/absent-or-irregular-periods-beyond-the-basics)".)
Heart disease — Accumulation of iron in the heart can cause enlargement of the heart, abnormal electrical conduction in the heart, and even heart failure. About 30 percent of people who have symptoms at the time of diagnosis have conduction problems, which may cause symptoms of rapid or irregular heart beat. Rarely, heart disease is the first sign of hemochromatosis.

Thyroid disease — Accumulation of iron in the thyroid gland can cause hypothyroidism (poor thyroid function) in about 10 percent of people with hemochromatosis. (See "Patient education: Hypothyroidism (underactive thyroid) (Beyond the Basics)".)

HEMOCHROMATOSIS DIAGNOSIS — It is important to diagnose hereditary hemochromatosis early in the course of the disease because early treatment can help prevent complications. Diagnostic tests can help differentiate hemochromatosis from other conditions that mimic hemochromatosis, such as alcoholic liver disease. Tests can also determine the severity of hemochromatosis and the presence of complications.

Blood tests — Three blood tests are usually recommended to determine iron levels in the body.

- Iron levels — Most people with hemochromatosis have elevated levels of iron in the blood.

- Transferrin saturation — Transferrin is a protein that binds iron and transports it between the tissues. Transferrin saturation is calculated from iron levels in the blood. The transferrin saturation increases as the body's iron stores increase. This test is one of the most sensitive tests for detecting early hemochromatosis. A transferrin saturation greater than 45 percent should be investigated further.

- Ferritin levels — Ferritin is a protein that reflects the body's stores of iron. Blood ferritin levels increase when the body's iron stores increase; however, levels of ferritin usually do not rise until iron stores are high. Therefore, the results of this test may be normal early in the course of hemochromatosis.

  Ferritin levels greater than 300 ng/mL in men and 200 ng/mL in women support a diagnosis of hemochromatosis. However, ferritin levels can also be increased by many common disorders other than hemochromatosis.

Genetic tests — Genetic testing can reveal the presence of gene defects associated with hemochromatosis.

TESTS TO DIAGNOSE TISSUE IRON OVERLOAD

Liver biopsy — A liver biopsy is one of the useful tests to determine if and how much of the liver is affected by hemochromatosis. In some cases, a liver biopsy is not necessary because other tests are able to confirm the diagnosis. (See "Patient education: Liver biopsy (Beyond the Basics)".)

Response to phlebotomy (blood removal) — The body's response to phlebotomy (the removal of blood) can confirm the presence of hemochromatosis. During quantitative phlebotomy, a fixed amount of blood (which contains large amounts of iron) is withdrawn once or twice per week while iron levels are monitored.

In people without hemochromatosis, four to five weekly phlebotomy sessions will cause iron deficiency and, ultimately, iron deficiency anemia. In people with hemochromatosis, 20 or more weekly phlebotomy sessions may be needed to cause iron deficiency.

Quantitative phlebotomy is an option to diagnose hemochromatosis if a person cannot undergo or does not need a liver biopsy; it is also an option for people under the age of 40 who have evidence of hemochromatosis but normal results on liver function tests. Some young people with hemochromatosis, who have not had time to accumulate much iron, may only require four to six phlebotomy sessions to deplete their iron stores.
**MRI methods** — Radiologic/MRI methods called T2* have been developed to provide useful information about the level of accumulation of iron in the liver and heart.

**HEMOCHROMATOSIS TREATMENT** — Treatment of hemochromatosis requires removal of excessive iron from the body, usually by periodically removing blood (phlebotomy). Treatment can help prevent complications and even reverse some complications after they occur. Treatment is usually continued throughout a person's life, although it may be temporarily discontinued in some cases, such as during pregnancy.

**Therapeutic phlebotomy (blood removal)** — Therapeutic phlebotomy entails periodic removal of fixed amounts of blood. Over time, phlebotomy returns iron stores back to normal levels. Phlebotomy is appropriate and beneficial for most people with evidence of iron overload, including older adults and people who have no symptoms.

The decision to begin phlebotomy in a person with hemochromatosis is usually based on a person's age, sex, and level of ferritin in the blood; when ferritin levels are significantly elevated for a person's age and sex, phlebotomy should be started as soon as possible. Some physicians do not recommend starting phlebotomy until tissue iron overload is documented by one of the three methods listed above.

- **Phlebotomy procedure** — Phlebotomy is generally safe and can be performed in a clinician's office, blood bank, hospital, or even a person's home. People undergoing phlebotomy should drink an adequate amount of fluids and avoid exercise within 24 hours of the procedure.

  Typically, 1 unit of blood (about 473 mL or 1 pint) is removed per week; however, 1.5 to 2 units of blood can often be removed from men, whereas it may be possible to remove only 0.5 units of blood from women or frail or elderly patients with other medical problems.

  Iron levels are usually monitored every four to eight weeks during treatment. These values help to determine when the excess iron stores have been depleted; they also help determine if phlebotomy has caused anemia by depleting iron too rapidly. If anemia occurs, phlebotomy may be temporarily stopped.

  In people with hemochromatosis who do not have symptoms at the time of diagnosis, the excess iron stores are depleted to normal after about 30 or fewer phlebotomy sessions. In people who have symptoms at the time of diagnosis, 50 or more phlebotomy sessions may be needed to deplete excess iron stores. Each unit of blood drops the ferritin by about 30 ng/mL.

- **Maintenance phlebotomy** — After iron stores have been reduced to normal levels (eg, ferritin levels in the range of 50 to 100 ng/mL), maintenance phlebotomy is essential to prevent iron from accumulating again. Maintenance phlebotomy entails removing 1 unit of blood every two to four months.

- **Effectiveness of phlebotomy** — Phlebotomy can effectively prevent or resolve some, but not all, complications of hemochromatosis.

  - Phlebotomy can prevent complications of iron overload in people who do not yet have complications. It can also help to ensure a normal life expectancy. For example, phlebotomy can help prevent the potentially life-threatening complications of cirrhosis and liver cancer.

  - Phlebotomy can resolve or markedly improve weakness, fatigue, and lethargy; darkening of the skin; and high blood ferritin levels. It can also resolve or greatly improve poor liver function, liver enlargement, and liver pain. Phlebotomy is most likely to reverse liver disease when it is in an early stage, but phlebotomy can still improve liver function in people who have developed cirrhosis.
- Phlebotomy may resolve joint pain and heart disease. Studies suggest that phlebotomy improves joint symptoms in about 20 percent of people with hemochromatosis. Phlebotomy is most likely to reverse heart disease when it is in an early stage.

- Phlebotomy only rarely improves joint deformity, pituitary disease, elevated blood iron levels, susceptibility to certain infections, diabetes, and thyroid disease. Phlebotomy is most likely to restore normal levels of sex hormones in men who are less than 40 years.

- Phlebotomy may not reverse cirrhosis or lessen the risk of liver cancer that is associated with cirrhosis.

**Can I be a blood donor?** — A recurrent question is whether a patient with HH can serve as a blood donor. The scientific and clinical answer is yes. HH is not a blood disease; the red blood cells and other blood components are not affected, and HH cannot be transmitted by blood. However, some hospitals will, and others will not, accept blood from donors with HH.

**Dietary considerations** — People who are receiving treatment for hemochromatosis do not have to follow a special diet. There is no evidence that the condition is worsened by consuming moderate amounts of iron-rich foods such as red meat and organ meats (eg, liver).

However, people with hemochromatosis should avoid iron supplements, and they may also be advised to avoid vitamin C supplements, which promote iron absorption. Alcoholic beverages may be consumed in moderation. However, drinking more than two alcoholic beverages per day increases the risk of cirrhosis. People with hemochromatosis and liver disease should avoid alcohol completely.

People with hemochromatosis should avoid eating uncooked seafood because it may contain bacteria that grow well in an iron-rich environment.

**Chelation therapy (deferoxamine or deferasirox treatment)** — Chelation therapy refers to treatment with the drug deferoxamine or deferasirox. This drug tightly binds iron and removes it from the body, lowering iron stores. However, chelation therapy is seldom used because phlebotomy is a simpler and equally effective treatment.

**Treatment of complications** — Although phlebotomy can alleviate or even completely resolve some complications of hemochromatosis, other measures may be necessary to treat complications that persist.

For example, liver disease may eventually require liver transplantation; diabetes may require insulin therapy. (See "Patient education: Cirrhosis (Beyond the Basics)" and "Patient education: Diabetes mellitus type 2: Insulin treatment (Beyond the Basics)".)

**IMPLICATIONS FOR THE FAMILY** — Hereditary hemochromatosis is almost always caused by a genetic mutation that is passed from both parents to a child. Therefore, clinicians usually recommend that first-degree relatives (parents, siblings, and children) of people with hemochromatosis undergo screening. There is a 25 percent chance that a full brother or sister of a person with hereditary hemochromatosis (with two copies of the C282Y mutation) will have hemochromatosis.

The primary goal of screening is to detect hemochromatosis before there are symptoms or complications. The optimal age for screening is between 18 and 30 years; during this time, the condition can be detected, but serious tissue damage has not yet occurred. The optimal strategy for screening is still being determined, so it is important to discuss the advantages and disadvantages of family screening with a healthcare provider.

**Iron levels** — The first phase of screening for hemochromatosis may entail blood tests to determine a person’s transferrin saturation and ferritin levels.
Genetic tests — The second phase of screening for hemochromatosis usually involves genetic testing. This testing may not be necessary for all first-degree relatives; the genetic profile of the affected family member may indicate which relatives should be tested.

For couples who have or plan to have children, testing of the spouse may be recommended to determine if he or she carries mutations associated with hemochromatosis.

HOW WILL HEMOCHROMATOSIS AFFECT MY LIFE? — Most people with hemochromatosis have a normal life expectancy. Survival may be shortened in people who develop cirrhosis or diabetes mellitus.

SUMMARY

- Hemochromatosis causes the body to absorb and store too much iron. The extra iron builds up in organs and can damage them. Without treatment, the iron overload causes these organs to stop working, which can lead to death.

- The condition is carried in the genes, and can be passed to a child when both parents carry one or two abnormal genes (the genetic material in the sperm and egg).

- Symptoms of hemochromatosis usually appear after age 40, and may include liver enlargement (figure 1), weakness, infections, darkened skin and joint pain. People with hemochromatosis are more likely to develop heart disease, type 2 diabetes, thyroid problems, and hormonal changes (eg, bone thinning, irregular or missed menstrual periods, sexual problems in men).

- Tests are available to diagnose hemochromatosis. Family members (siblings, children) of people with hemochromatosis should also be tested. Early testing and treatment can help to prevent complications.

- The most common treatment of hemochromatosis is removal of a small amount of blood, which lowers the iron level. Blood removal is similar to the process of donating blood. It is usually done once per week until the iron levels are normal. This may require 9 to 12 months of weekly blood removal.

- Iron levels are measured with a blood test every month or two. Blood removal is done every two to four months to manage the iron level. Treatment is usually needed for a lifetime.

- People with hemochromatosis do not need to follow a special diet. Iron supplements and vitamin C supplements should be avoided. Drinking alcohol occasionally (one or two drinks per week) is probably safe unless the person has liver disease (cirrhosis or hepatitis).

WHERE TO GET MORE INFORMATION — Your healthcare provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed on our web site (www.uptodate.com/patients). Related topics for patients, as well as selected articles written for healthcare professionals, are also available. Some of the most relevant are listed below.

Patient level information — UpToDate offers two types of patient education materials.

The Basics — The Basics patient education pieces answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials.

Patient education: Hemochromatosis (The Basics)
Beyond the Basics — Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are best for patients who want in-depth information and are comfortable with some medical jargon.

Patient education: Hepatitis B (Beyond the Basics)
Patient education: Hepatitis C (Beyond the Basics)
Patient education: Cirrhosis (Beyond the Basics)
Patient education: Diabetes mellitus type 2: Overview (Beyond the Basics)
Patient education: Sexual problems in men (Beyond the Basics)
Patient education: Absent or irregular periods (Beyond the Basics)
Patient education: Hypothyroidism (underactive thyroid) (Beyond the Basics)
Patient education: Liver biopsy (Beyond the Basics)
Patient education: Diabetes mellitus type 2: Insulin treatment (Beyond the Basics)

Professional level information — Professional level articles are designed to keep doctors and other health professionals up-to-date on the latest medical findings. These articles are thorough, long, and complex, and they contain multiple references to the research on which they are based. Professional level articles are best for people who are comfortable with a lot of medical terminology and who want to read the same materials their doctors are reading.

Chelation therapy for thalassemia and other iron overload states
Clinical manifestations and diagnosis of hereditary hemochromatosis
Genetics of hereditary hemochromatosis
Methods to determine hepatic iron content
Approach to the patient with suspected iron overload
Screening for hereditary hemochromatosis
Management of patients with hereditary hemochromatosis

The following organizations also provide reliable health information.

- National Library of Medicine
  (www.nlm.nih.gov/medlineplus/healthtopics.html)
- National Institute of Diabetes and Digestive and Kidney Diseases
  (www.niddk.nih.gov/)
- The Centers for Disease Control and Prevention
  (www.cdc.gov)
- American Liver Foundation
  (www.liverfoundation.org)
- Hemochromatosis Foundation
  (www.hemochromatosis.org)
- American Hemochromatosis Society
  (www.americanhs.org)
Organs inside the abdomen (belly)

Graphic 64960 Version 6.0