

Hemochromatosis

Hemochromatosis occurs when too much iron accumulates in the body. Although iron is essential for life, excessive iron can be very dangerous because iron is easily oxidized (think of rust). Iron reacts easily with organic molecules to create highly reactive oxygen species that contribute to high levels of oxidative stress in the body. The result can be free radical damage to the liver, pancreas, heart, joints, and skin.

Hemochromatosis is known to cause cirrhosis of the liver, diabetes, arthritis, cardiomyopathy, and hormone problems, including hypothyroidism and hypogonadism (Kasper DL et al 2005). Iron has also been implicated in oxidative diseases such as Alzheimer's, in which high levels of iron contribute to neuron damage.

Conventional medicine generally relies on a one-dimension approach to iron overload: the removal of excess iron-containing red blood cells. Life Extension, however, goes two steps further: we advocate that people with abnormally high iron levels guard themselves with antioxidants to reduce oxidative stress and also reduce the amount of iron that is absorbed into the body.

The most common form of iron overload is known as hereditary hemochromatosis (HH). It is a relatively common genetic disorder, especially among people of northern European descent. Although many people carry the genes for hemochromatosis, it is expressed in only about half of these people. The first symptoms usually become apparent between the ages of 40 and 60. HH is an iron storage problem in which the body stores too much iron.

The following conditions and circumstances can also cause iron overload:

- Iron overload anemias, such as thalassemia major
- Chronic liver disease, including hepatitis and alcoholic liver disease
- Excess supplemental iron
- Transfusions

The most common complications of hemochromatosis are cirrhosis and liver cancer. Up to 30 percent of patients who develop cirrhosis will go on to develop liver cancer, which is the leading cause of death among people with hemochromatosis (Kasper DL et al 2005). Alcohol plays a significant role in contributing to the development of cirrhosis. Some 44 percent of HH patients who consumed more than four drinks of alcohol daily developed cirrhosis, compared with only 10 percent of those who were not heavy drinkers (Borgaonkar MR 2003).

Iron-induced cardiac complications are also an important cause of death among patients with HH. The exact mechanism that causes cardiac complications is not known, but elevated levels of iron may increase risk of heart disease by creating high levels of free radicals that damage the inner lining of arteries (endothelium) (Crowe S 2002). Endothelial dysfunction is central to the development and progression of coronary artery disease.

THE DIAGNOSIS OF IRON OVERLOAD

Hereditary hemochromatosis causes the intestinal mucosa to absorb excess iron. Under normal circumstances, the human body maintains between 2 g and 6 g iron, such that iron absorption from dietary sources is equal to iron loss. In HH, however, the total iron stores in the body may be dramatically increased. At advanced stages of the disease, iron stores may increase to 20 g or more, with most of this excess iron being deposited in the liver, pancreas, and heart. At these levels, iron is acutely toxic because it freely interacts with organic cells, causing oxidation and excess collagen synthesis, which leads to scar tissue. Secondary iron overload, caused by anemia or liver disease, has similar results: the inappropriate accumulation of iron in these target organs.

The first symptoms of iron overload usually include fatigue, weakness, change in skin color, abdominal pain, and thirst. The liver is typically the first organ to be affected, and liver enlargement is present in the vast majority of symptomatic cases. About 90 percent of symptomatic cases experience excessive skin pigmentation, with a metallic or slate gray hue to the skin that results from increased melanin and iron. Diabetes occurs in more than half of cases, especially when there is a family history of diabetes. Other complications include arthritis, congestive heart failure, and low levels of sex hormones.

Any person with this constellation of symptoms (cirrhosis, diabetes, and increased skin pigmentation) should consider testing for HH. During diagnosis, it is particularly important for patients to let the physician know about dietary intake of iron, intake of ascorbic acid (which promotes iron absorption), alcohol ingestion, and family history. A number of individual tests might be recommended to

assess joint, liver (although many people with HH also have normal liver enzyme levels), and cardiac health.

Finally, total-body iron stores are measured. There are several ways to measure iron stores; physicians may, for instance, measure transferrin saturation or serum ferritin. People with untreated hemochromatosis typically have highly elevated serum ferritin.

If these tests are abnormal, genetic screening for HH is highly recommended. Newer genetic tests allow physicians to identify the genetic abnormalities that are associated with HH (e.g., the C282Y mutation). If this genetic abnormality is detected, all first-degree relatives of the affected person should also undergo screening for the abnormality, along with serum ferritin blood testing. Early treatment of HH allows for better long-term outcomes and normal life expectancy.

TREATMENT OPTIONS

The most effective therapy and treatment of choice for patients with HH is therapeutic phlebotomy (removal of either whole blood or red blood cells). The amount and frequency of phlebotomy will be determined by measurements of hemoglobin and serum ferritin. A ferritin measurement of more than 300 mg/mL is suggestive of iron overload that requires treatment.

Too-rapid removal of red cells will produce a drop in hemoglobin, resulting in anemia, even while total body iron stores remain elevated. The goal is to produce a very mild anemia, just sufficient so that iron is not further deposited in tissue but is used in hemoglobin production. It is not uncommon, however, for weekly phlebotomy treatments to last for one or two years. Afterward, phlebotomies may be done once every three months (Borgaonkar MR 2003).

An alternative to phlebotomy is chelation. During this procedure, a drug (such as deferoxamine) that binds to excess free iron is administered. Chelation is used in patients who cannot tolerate phlebotomy or who suffer from hemochromatosis caused by multiple blood transfusions. Although effective, chelation removes excess iron at a much slower rate than phlebotomy (about 10 to 20 mg per day, versus 200 to 250 mg per phlebotomy). Portable deferoxamine pumps are available to make administration of the drug easier.

In patients who already have organ damage at the time of diagnosis, supportive treatment of damaged organs is essential. Conventional pharmaceutical therapy for the management of complications such as hepatic failure, cardiac failure, and diabetes mellitus may also be required. Traditional pharmacologic treatments vary in their effectiveness at treating each of these conditions. For more information, see the following chapters:

- Liver Disease and Cirrhosis
- Atherosclerosis
- Diabetes

It is strongly advised that individuals with HH, including those without signs or symptoms but who are known to have the genetic markers for the disease, either reduce or abstain from alcohol consumption because it increases risk of cirrhosis tenfold in individuals with HH.

Antioxidant Treatments to Minimize Damage

Excessive iron, whether genetic or secondary to another condition, is known to cause high levels of damaging free radicals that contribute to endothelial dysfunction and the formation of scar tissue in vital organs such as the liver. Although antioxidant therapy isn't part of the conventional protocol, it is strongly recommended that people with any form of iron overload take proactive steps to maintain healthy antioxidant supplies. Also, because iron overload is linked to reduced energy generation within cells (as measured by the levels of adenosine triphosphate, the cell's main fuel source), it is important to maximize mitochondrial energy production (Britton RS et al 2002).

Vitamins E and A. Patients with HH have decreased antioxidant levels and increased lipid peroxidation. In one study, patients with HH had reduced levels of antioxidant vitamins (vitamins A, C, and E), so it is possible that supplementation with vitamins E and A may be beneficial (Young IS et al 1994). This finding is confirmed in a study that demonstrated vitamin E decreased lipid peroxidation and had a beneficial effect on liver fibrosis induced by iron overload.

Glutathione. Glutathione is one the body's main internal antioxidants. Glutathione levels are rapidly depleted in the event of severe oxidative stress, especially in the liver. Glutathione depletion in the liver is related to the development of cirrhosis and liver failure (Kidd P 2005). Although glutathione is available as a supplement, a number of nutrients can support glutathione synthesis.

N-acetylcysteine. N-acetylcysteine (NAC) has antioxidant and hepatoprotectant properties, and it is a precursor to glutathione. Because NAC is a precursor to L-cysteine and glutathione, it may provide protection against lipid peroxidation and protein oxidation. Evidence suggests that NAC may protect pancreatic beta cells and nerve cells in particular.

Milk thistle. Milk thistle (silymarin) is an antioxidant that protects and nourishes liver cells, stimulating protein synthesis and cellular regeneration. It is a powerful liver tonic, useful in prevention of cirrhosis of the liver and other liver disorders. It has been shown to be beneficial in the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis.

S-adenosyl-L-methionine. S-adenosyl-L-methionine (SAME) is a substrate of glutathione that may help protect the liver. SAME levels are diminished in liver disease, and studies have shown that they can be restored with supplementation. SAME has proven beneficial in the treatment of various forms of cirrhosis, hepatic fibrosis, and cholestases (Chawla RK 1990). In HH patients, SAME increases hepatic glutathione levels, supporting cellular antioxidant capacity.

Additional antioxidant protection. Although the following antioxidants haven't been studied in HH specifically, it is known that iron overload causes a severe depletion of antioxidants due to a dangerous rise in free radicals. Thus, patients may wish to add the following antioxidants to their regimen: selenium, water-soluble quercetin, and lipoic acid.

Calcium, magnesium, and zinc. A practical way to lower iron is to interfere with its absorption from food. Minerals such as calcium, magnesium, and zinc have been shown to interfere with iron absorption (Murray M 1996).

The American Journal of Clinical Nutrition stated that if 300 mg calcium were taken with a meal, the amount of iron absorbed would be reduced by 40 percent. That is a simple and inexpensive way to reduce iron in the blood (Hallberg L 1998). To obtain 300 mg calcium, it is necessary to take a calcium supplement that supplies 300 mg elemental calcium. The best way to do this is to take one or two 1000-mg capsules of calcium citrate with every meal that contains iron.

Each 1000-mg calcium citrate capsule provides 200 mg elemental calcium. It is important to note that some people become tolerant to calcium-induced blockage of iron absorption after several months, so if calcium provides a sudden reduction in serum iron levels, patients should be certain it continues to work by having regular blood tests.

Tea Drinking

A study reported in the British journal Gut indicates that drinking black tea rich in tannin with meals can reduce iron absorption. The control group drank water with meals; the study group drank tea with meals. Intestinal iron absorption was measured by studying serum iron-binding capacity and serum ferritin. Results showed a significant reduction of iron in the study group as opposed to the control group. Thus, drinking black tea may reduce phlebotomy frequency in the management of patients with hemochromatosis (Kaltwasser JP et al 1998).

Green tea extract is a potent iron-chelating agent. Green tea is an antioxidant that helps remove excess iron from the liver. Hemochromatosis patients should take 4 to 10 green tea extract capsules with at least 300 mg active polyphenols per capsule.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Besides regular blood testing to monitor iron levels, patients can take a number of steps to help reduce iron absorption:

- Patients with HH should either limit their vitamin C supplementation to a maximum of 500 mg daily (Borgaonkar MR 2003) or avoid supplementation altogether (Young IS et al 1994). However, there is no restriction on the consumption of citrus fruits or vegetables (Borgaonkar MR 2003)
- Do not take iron pills, nutritional supplements, or multivitamins with iron.
- Do not eat cereals or other foods that are fortified with iron or foods such as liver and other organ meats, red meat, or spinach, which are high in iron (Borgaonkar MR 2003).
- Do not eat raw fish or raw shellfish; they may contain bacteria that are harmful to people with excessive iron. Cooking destroys the bacteria, so well-cooked fish and seafood are OK to eat.
- Severely limit or eliminate all alcohol.

Blood testing is an important component of hemochromatosis management. Patients with iron overload should get regular blood testing to monitor their iron levels, including levels of ferritin, transferrin saturation, and serum iron. The following levels suggest iron overload:

- **Ferritin:** More than 300 ng/mL
- **Transferrin saturation:** 50 to 100 percent

Additionally, blood testing for diabetes, especially the hemoglobin A1C test, which can measure mild elevations in blood glucose, is recommended. "Bronze diabetes" is closely associated with hemochromatosis.

The following supplements can interfere with iron's absorption or reduce the damage caused by excessive iron:

- **Vitamin E**—400 international units (IU) daily (with approximately 200 milligrams (mg) gamma tocopherol)
- **Vitamin A** (liquid, emulsified)—20,000 IU daily
- **L-glutathione**—250 to 1000 mg daily
- **NAC**—600 mg daily
- **Milk thistle extract** (*Silybum marianum*)—900 mg daily, standardized to contain 80 percent silymarin (720 mg), 30 percent silibinin (270 mg), and 4.5 percent isosilybin B (40.5 mg)
- **SAME**—400 to 1200 mg daily
- **Calcium citrate**—2000 mg with meals that may contain iron
- **Magnesium**—500 mg daily
- **Zinc**—30 mg daily
- **Selenium**—200 micrograms (mcg) daily
- **Quercetin**—500 mg daily (use only water-soluble quercetin for better absorption)
- **R-lipoic acid**—150 to 300 mg daily
- **Green tea extract**—725 to 2900 mg daily of an extract that provides at least 93 percent polyphenols

PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at www.LifeExtension.com.

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at www.LifeExtension.com.

HEMOCHROMATOSIS SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

Lipoic Acid

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

Milk Thistle

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Quercetin

- Quercetin can cause headache, mild tingling of the extremities, and gastrointestinal symptoms such as nausea.

SAMe

- Consult your doctor before taking SAMe if you have bipolar disorder. See your doctor frequently if you take SAMe and you have bipolar disorder.
- Consult your doctor before taking SAMe if you take antidepressants. See your doctor frequently if you take SAMe in place of or in addition to antidepressants.
- Consult your doctor before taking SAMe if you have cancer. Nucleic acid methylation patterns may change in people who have cancer and take SAMe.
- Do not take SAMe if you are undergoing gene therapy.
- SAMe can cause anxiety, hyperactive muscle movement, insomnia, hypomania, and gastrointestinal symptoms such as nausea and diarrhea.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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