Diagnosis and management of hereditary haemochromatosis

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Hereditary haemochromatosis is an autosomal recessive genetic disease in which increased intestinal absorption of iron causes accumulation in tissues, primarily the liver, sometimes leading to organ damage. Liver deposits may result in cirrhosis and even death. A systematic review has shown that about 0.4% of people of northern European descent have the genetic mutation that increases the risk of developing haemochromatosis,[1] but the clinical penetrance of the mutation is much lower than the genetic prevalence. Symptoms and signs are initially non-specific, so the disease is often diagnosed at a late stage when substantial organ damage has already occurred. The challenge is to avoid both overdiagnosis and underdiagnosis. Since the discovery of the genetic mutation, new knowledge has come to light on the pathophysiology and course of the disease. This has led to new recommendations on diagnosis and treatment. In addition, new treatments are under evaluation. We review evidence from experimental and observational studies, systematic reviews, and guidelines to summarise for the general reader the clinical presentation, diagnosis, including early screening options, and management of hereditary haemochromatosis.

SOURCES AND SELECTION CRITERIA

Initially, we made an extensive search of Medline, Embase, and the Cochrane Library for papers published until December 2009 using both MESH headings and free text related to hereditary haemochromatosis. In addition, we retrieved national and international guidelines and checked the references of the papers that we obtained. The overall methodological quality of the papers was low. Although many reviews were available, they were mostly narrative. The more recent literature seems to be of better quality.

SUMMARY POINTS

- Hereditary haemochromatosis is an autosomal recessive disorder with a genetic prevalence of 0.4% in northern Europeans but a much lower clinical penetrance
- Those affected are at increased risk of cirrhosis of the liver and hepatocellular carcinoma
- Symptoms are often non-specific at presentation and include fatigue and arthropathy
- If transferrin saturation and serum ferritin are raised, test for C282Y mutation of the *HFE* gene
- First degree relatives of patients with clinically overt haemochromatosis can be screened for C282Y and H63D polymorphisms
- Regular phlebotomy is the main treatment, although newly developed therapeutic approaches show promise

What is hereditary haemochromatosis?

"Hereditary haemochromatosis" is a heterogeneous group of disorders (box) related to deficiency of the iron regulatory hormone hepcidin (fig 1).[2] Organs that may be affected by iron deposits include the liver, pancreas, joints, heart, skin, and gonads. Hereditary haemochromatosis must be distinguished from secondary forms of iron overload, such as those caused by repeated red blood cell transfusions or anaemia owing to ineffective erythropoiesis (fig 2). Although all lead to raised serum iron parameters, they are treated differently. Recent consensus from the European Association for the Study of the Liver (EASL) defines hereditary haemochromatosis as "C282Y homozygosity and increased body iron stores with or without clinical symptoms."[1]

A meta-analysis of 2802 people of European ancestry who had clinical iron overload found that 81% were homozygous for the C282Y mutation in the *HFE* gene on the short arm of chromosome 6. A smaller proportion (5%) were compound heterozygous for the C282Y/H63D mutations.[1] Several other mutations in the *HFE* gene have been described, but these are rare.[3] Here, we focus on C282Y homozygous haemochromatosis with increased body iron stores, which we refer to as haemochromatosis.

A systematic review of longitudinal prognostic studies found that 38-76% of homozygous people develop raised iron parameters, such as ferritin and transferrin saturation in the blood (biochemical penetrance).[4] However, clinical penetrance is lower—2-38% in men and 1-10% in women.[5 6] The lower clinical penetrance in women is thought to result from iron loss through menstrual bleeding and childbirth, although evidence is lacking. Genetic polymorphisms, antioxidant activity, inflammation, and environmental factors—such as alcohol misuse, steatosis, and coexisting viral infections—also seem to modify the risk of developing clinically overt disease.[7 8]

What are the presenting symptoms and signs?

Diabetes, bronzing of the skin, hepatomegaly, and arthropathy, especially of the second and third metacarpophalangeal joints, are typical presenting features. However, these are symptoms of advanced disease, and symptoms in early disease are non-specific. Case reports and observational studies have identified a wide range of other symptoms such as fatigue, arthropathy in other

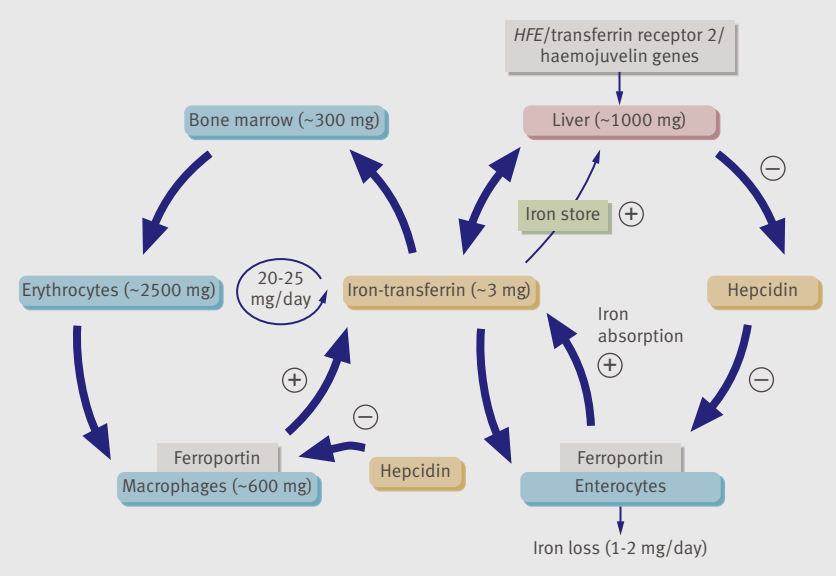

Fig 1 | Role of hepcidin in the pathophysiology of hereditary haemochromatosis. The largest flux of iron involves the recycling of iron from senescent erythrocytes out of macrophages for incorporation into erythroid precursors (all values are approximate). Liver and reticuloendothelial macrophages function as major iron stores. Only 1-2 mg of iron is absorbed and lost every day. Importantly, the total amount of iron in the body can be regulated only by absorption, while iron loss occurs only passively from sloughing of skin and mucosal cells and from blood loss. Defects in genes encoding proteins that regulate synthesis of the iron regulatory hormone hepcidin in hepatocytes result in a decrease of serum hepcidin concentrations. Hepcidin controls the plasma iron concentration by inhibiting iron export by ferroportin from duodenal enterocytes and reticuloendothelial macrophages. A decrease in hepcidin production results in raised plasma iron values and accumulation of iron in the body

joints, non-specific abdominal problems, erectile dysfunction, and cardiac problems.[9 10] All symptoms are thought to be caused by iron deposition in organs, although evidence on the relation between symptoms and the extent of iron overload is limited.[1 6 11-13] No studies have looked at the predictive value of combinations of symptoms. Thus, it is difficult to identify patients with haemochromatosis from their symptoms and signs, especially for generalists, who usually see patients with early, non-specific symptoms and signs rather than advanced disease.

How can haemochromatosis be distinguished from other diseases?

To treat patients correctly, clinicians need to distinguish haemochromatosis from other diseases that result in iron overload, from diseases that lead to high serum ferritin without iron overload, and from diseases that present in a similar way, particularly with liver dysfunction. The differential diagnoses are listed in the box.

The first tests to do in patients with suspected iron overload are measurement of iron and transferrin (which enables transferrin saturation to be calculated) and serum ferritin (fig 2).[1 5 9 14] *HFE* genetic testing is needed only in those with increased transferrin saturation and after exclusion of common causes of hyperferritinaemia: inflammation (check C reactive protein), chronic alcohol consumption, liver cell necrosis (alanine aminotransferase), metabolic syndrome (blood pressure, body mass index, triglycerides, and glucose), anaemia (haemoglobin, mean cellular volume, and ethnic background)

DIFFERENTIAL DIAGNOSIS OF HEREDITARY HAEMOCHROMATOSIS

Hereditary haemochromatosis

***HFE* associated hereditary haemochromatosis (type 1)**
C282Y homozygosity
C282Y/H63D compound heterozygosity
Other *HFE* gene defects

Non-HFE associated hereditary haemochromatosis
Haemojuvelin gene defect
Hepcidin gene defect
Transferrin receptor 2 gene defect
Ferroportin gene defect

Other hereditary forms of haemochromatosis
Hereditary H ferritin cataract syndrome
Haem oxygenase deficiency
Neonatal iron overload
Aceruloplasminaemia
Congenital atransferrinaemia or hypotransferrinaemia
Divalent metal transporter 1 gene defect

Secondary iron overload
Iron loading anaemias
Ineffective erythropoiesis
Thalassaemic syndromes
Sideroblastic anaemia
Myelodysplastic syndrome
Congenital dyserythropoietic anaemia
Parenteral iron overload (including multiple blood transfusions)

Other diagnoses
Metabolic syndrome
Obesity
Hypertension
Insulin resistance
Drug toxicity
Chronic haemodialysis
Chronic liver disease
Hepatitis
Alcohol misuse
Non-alcoholic steatohepatitis
Porphyria cutanea tarda
Liver cirrhosis
Iron overload in sub-Saharan Africa

as recommended by international guidelines (box).[1] If the patient is C282Y homozygous the diagnosis of HFE haemochromatosis can be established. In the absence of these mutations, perform magnetic resonance imaging to assess liver iron stores.[15] If liver iron is high and other diseases with liver iron loading, especially iron loading anaemias, have been excluded, perform molecular analysis for rare *HFE* mutations and mutations in the genes that encode haemojuvelin, hepcidin, transferrin receptor 2, and ferroportin, according to clinical, laboratory, and pathological features.[16]

People who present with symptoms of haemochromatosis and who are C282Y homozygous typically have higher than normal transferrin saturation and ferritin as a result of disrupted iron homoeostasis. The concentration of serum ferritin depends on the amount of iron stored in the body.

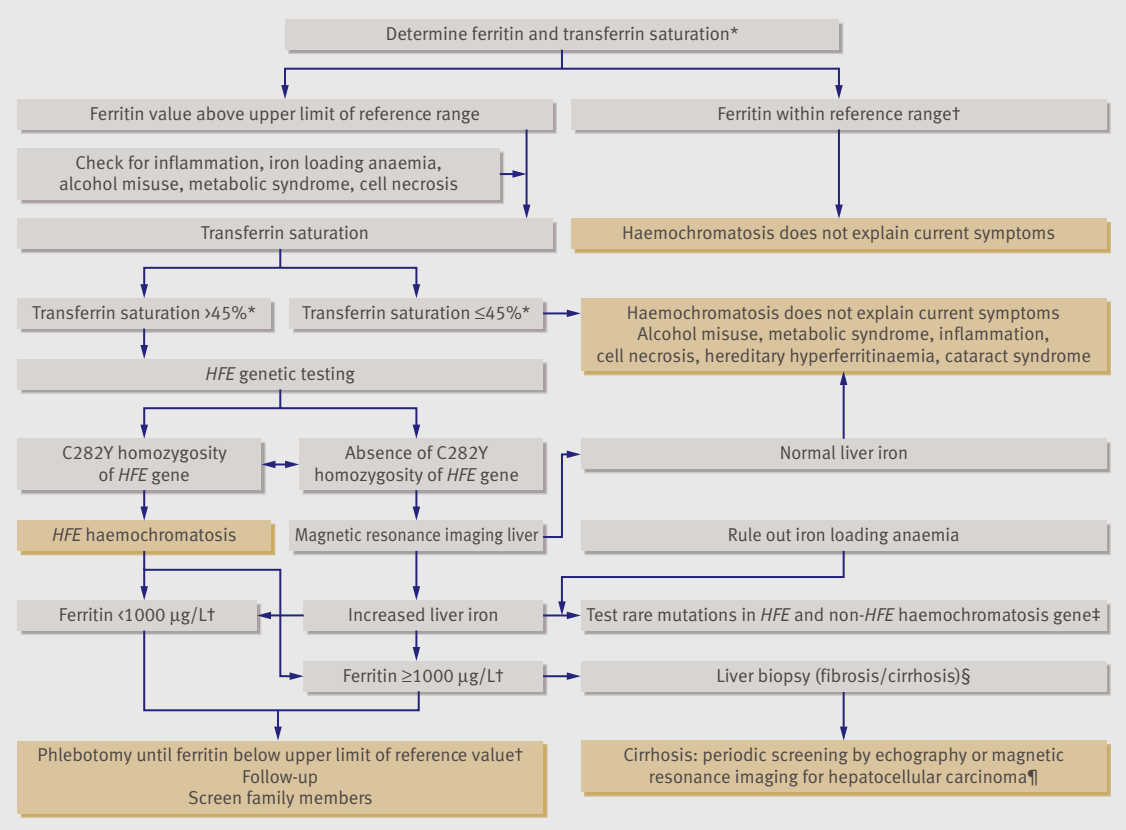

Fig 2 | **Diagnostic flowchart for patients with suspected haemochromatosis. *The reference range for transferrin saturation is 15-45%. †The ferritin range differs between laboratories and methodologies used. Usual upper reference values are about 300 µg/L and 200 µg/L for men and women, respectively. ‡If rare *HFE* mutations are present the diagnosis is *HFE* haemochromatosis; if mutations in the genes for the transferrin receptor 2, haemojuvelin, hepcidin, or ferroportin are detected the diagnosis is non-*HFE* haemochromatosis; in the presence of any of these mutations, treat patients the same as those with *HFE* haemochromatosis regarding phlebotomy, screening relatives, and periodic screening of the liver in those with liver cirrhosis. §Iron overload in the liver may also result from end stage cirrhosis; in exceptional cases, further diagnostic considerations then depend on cellular and nodular distributions of iron and associated findings such as fibrosis on liver biopsy. ¶In the absence of cirrhosis, regular screening by echography or magnetic resonance imaging is not indicated**

With high iron load ferritin is usually high, and this may correlate with the development of signs and symptoms of iron overload.[12]

PATIENT'S STORY

The first symptom was painful swelling of my hand, for which I was referred to a rheumatologist. He suspected haemochromatosis because of my bronzed skin and ordered the relevant tests. In retrospect, this explains my "fatty liver" that had been diagnosed by a screening test at work. After the diagnosis I was treated with frequent phlebotomies, which made me so tired that I could no longer work full time. Currently, my worst problem is pain in my hips and finger. None of the available painkillers is effective. Furthermore, I have fatigue, which means that I have to plan my activities carefully. Thirdly, I have erectile dysfunction. Fortunately, my wife and I have found other ways to reach intimacy. My children and my sisters have been screened for the mutation and had their iron parameters measured. Luckily, none of them are affected. I used to undergo phlebotomies biweekly. However, since I have been given esomeprazol my iron parameters remain stable and I no longer need to be bled. I worry about symptoms that might arise in the future, such as problems with my heart.

Transferrin saturation

Transferrin saturation is the proportion of the iron transport protein transferrin that is saturated with iron; it is calculated as follows: ((serum iron (µmol/L):25)/transferrin (g/L))×100%. In haemochromatosis, transferrin saturation is generally increased throughout the day, and a non-fasting measurement will detect high values. Transferrin saturation is raised as a result of innately low hepcidin, which leads to increased iron uptake from the intestine and iron release by reticuloendothelial macrophages.[17] Transferrin saturation can also be high in people with iron loading anaemias, those taking iron tablets or multivitamins containing iron, patients with hepatitis, and people who misuse alcohol.

The reference range for transferrin saturation is 15-45%; expert consensus considers 45% to be the upper limit of normal in a non-fasting situation,[1 9] although higher cut-off values are sometimes recommended for population screening programmes.[18]

Serum ferritin

Serum ferritin is an indirect measure of body iron stores and is increased in patients with iron overload, viral infections, other inflammatory conditions, the metabolic

ONGOING RESEARCH

- New chelators, hepcidin agonists, proton pump inhibitors, and calcium antagonists are under evaluation. Clinical trials are needed to assess their clinical value
- The predictive value of various combinations of symptoms for the presence of haemochromatosis
- The optimal screening approach
- Parameters that could help determine the optimum frequency of phlebotomy and the quantity of blood taken at each session, including the optimum target value of serum ferritin
- Non-invasive alternatives to liver biopsy as an indicator of liver damage
- Greater understanding of how the synthesis of hepcidin is regulated in the liver may provide insight into the reasons for low clinical penetrance and provide markers that could help predict penetrance in C282Y homozygotes
- International and national evidence based clinical practice guidelines must be developed and implemented because differences between centres cause anxiety among patients

TIPS FOR NON-SPECIALISTS

- Haemochromatosis usually starts with non-specific symptoms and signs. Although evidence is lacking, consider testing for the disease in patients who have had unexplained symptoms for several months
- First test for serum ferritin, serum iron, and transferrin, then calculate the transferrin saturation value. If serum ferritin and transferrin saturation are both high, refer the patient to a specialist in haemochromatosis (usually a gastroenterologist)
- Repeated phlebotomy is the cornerstone of treatment, although new treatments are under development
- Population screening is not indicated. Screening of first degree relatives with symptomatic haemochromatosis is indicated
- If treated adequately, patients with symptomatic haemochromatosis have a normal life expectancy

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

European Iron Club (www.euro-iron.org)—European organisation for professionals interested in iron metabolism

International BioIron Society (www.bioiron.org)—International organisation for professionals interested in iron metabolism

Lee PL, Beutler E. Regulation of hepcidin and iron-overload disease. *Annu Rev Pathol Mech Dis* 2009;4:489-515

Weiss G. Genetic mechanisms and modifying factors in hereditary hemochromatosis. *Nat Rev Gastroenterol Hepatol* 2010;7:50-8.

American Association for the Study of Liver Diseases. Practice guidelines. www.aasld.org/practiceguidelines/Pages/PracticeGuidelinesAlpha.aspx

European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol* 2010;53:3-22

Resources for patients

The European Federation of Associations of Patients with Haemochromatosis (www.european-haemochromatosis.eu)—Provides links to patient organisations in several countries

American Hemochromatosis Society (www.americanhs.org)—Provides education and support for patients

Up-to-Date (www.utdol.com/patients/content/topic.do?topicKey=~jO3tricadskc9/#H25)—Overview about haemochromatosis

Haemochromatosis Society UK (www.haemochromatosis.org.uk/home.html)—Provides help, support, and information for those affected by haemochromatosis

syndrome, cancer, and chronic liver disease (for example, as a result of alcohol misuse); it is also raised in patients on dialysis and as a result of drug toxicity. Many immunochemical methods are available to measure serum ferritin. We recommend using local reference values because the inter-laboratory coefficient of variance of serum ferritin concentrations is high, 6-13% (source: Foundation of quality control of medical laboratory diagnostics (SKML) data on interlaboratory variance of serum ferritin from about 270 Dutch laboratories in 2009). Upper reference values are about 300 µg/L and 200 µg/L for men and women, respectively.

Genetic testing

When symptoms and serum iron parameters suggest haemochromatosis genetic testing is indicated. A systematic review found sensitivity and specificity of C282Y homozygosity to be above 90% and almost 100%, respectively, for the presence of an iron overload phenotype in white northern Europeans.[19]

A recent prospective population based cohort study showed that documented iron overload disease is rare among C282Y/H63D compound heterozygotes.[20] An advantage of genetic testing in patients with signs of increased iron stores is the certainty of the diagnosis, and this has important implications for treatment and counselling of first degree relatives. If a symptomatic patient is a C282Y homozygote, screening of first degree relatives for the presence of the genotype may be indicated.[21]

Magnetic resonance imaging and liver biopsy

If the diagnosis is still unsure after blood analysis and testing for the C282Y and H63D polymorphisms of the *HFE* gene, magnetic resonance imaging might be helpful. A reliable, quantitative imaging technique for the detection of iron in the liver is available.[15] If the expertise or facilities to offer the technique is lacking, tissue from a liver biopsy may be analysed to look for iron deposits. If the concentration of iron deposits is below the cut-off value, haemochromatosis can be excluded, but if it is above, genetic testing for rare haemochromatosis mutations is indicated.[9]

What is the prognosis for patients with haemochromatosis?

A meta-analysis found that C282Y homozygous patients with clinically ascertained haemochromatosis have an increased risk of developing liver disease (odds ratio 3.9, 99% confidence interval 1.9 to 8.1) and hepatocellular carcinoma (11, 3.7 to 34).[11] A population screening survey of 65 238 people showed that the absolute risk of liver damage is about 5% in homozygous men and less than 1% in women.[22] Patients with either of these complications have a reduced life expectancy. However, observational studies of patients who received adequate and timely treatment, of people identified by population screening, and of previously undiagnosed family members of patients with haemochromatosis show that overall mortality is not higher than in the general population.[5 23-25]

Is screening indicated?

Population screening

The relatively high prevalence of the C282Y homozygous genotype in European populations led several authors to recommend population screening.[26 27] However, the low clinical penetrance means that many people would be incorrectly diagnosed with haemochromatosis when not clinically unwell, which could be harmful and could lead to problems with obtaining medical insurance. A systematic review therefore concluded that population

screening is not recommended because the harms exceed the benefits.[28]

Screening those with haemochromatosis related diseases

New EASL guidelines recommend considering genetic testing for patients with porphyria cutanea tarda, well defined chondrocalcinosis, hepatocellular carcinoma, late onset type 1 diabetes, and those presenting with a combination of unexplained chronic liver disease and raised transferrin saturation. Although the evidence is limited, these diseases are associated with a higher prevalence of C282Y homozygosity.[1]

Screening people with a positive family history

Screening first degree relatives of patients diagnosed with haemochromatosis is another option. A modelling study showed that for patients with two or more children, the most cost effective approach is to test the patient's spouse first and test the children only if the spouse is heterozygous. For one child or siblings, direct testing for the mutation is the most cost effective strategy.[21] The value of testing for the C282Y mutation is still unclear because of the unknown risk of developing biochemical or clinical signs of haemochromatosis even in homozygotes. This is even more the case when testing for C282Y/H63D compound heterozygosity. This is because the chance of finding this genotype in relatives of a C282Y homozygous proband is relatively high (the population frequency of the H63D mutation is 20%); documented iron overload in people with this genotype is rare[20]; and disease penetrance in the absence of comorbid factors is low, as is shown in an observational study.[29]

However, an observational study of first degree relatives of C282Y homozygous patients found that haemochromatosis related symptoms are more common than in controls and that their level of iron overload may be predicted by disease severity in the index patient.[25 30] Because the first symptoms develop during adulthood, the choice of whether or not to test can be postponed until children are grown up and can decide for themselves.

How is hereditary haemochromatosis treated?

Phlebotomy

Haemochromatosis is usually treated with phlebotomy. Each 500 mL of blood contains 0.25 g of iron. The concentration of iron above which phlebotomy is indicated is not clear. A meta-analysis has shown that serum ferritin concentrations above 1000 µg/L may cause cirrhosis of the liver.[11] A consensus based approach is to start treatment when serum ferritin rises above local reference values (about 300 µg/L and 200 µg/L for men and women, respectively).[1] However, not all patients with raised serum ferritin show further increases.[31] Therefore, for patients with moderately raised serum ferritin a "watchful waiting" approach, with phlebotomy only when their serum ferritin increases progressively, might be an alternative to regular phlebotomy.[32]

The optimum frequency of phlebotomy and quantity of blood taken are unclear, but expert consensus suggests that 500 mL of blood should be taken each week in the depletion stage, guided most usually by serum ferritin and haemoglobin values.[1 9] The procedure used is similar to that for blood donations. If phlebotomy results in anaemia, or adverse consequences of hypovolaemia, frequency of bleeding or volumes of blood taken can be adjusted.

No evidence is available to help set a target value for serum ferritin. Some authors recommend aiming for 50 µg/L or even lower.[1] However, it might be better to aim for values within the normal range because these might be better tolerated by patients, result less often in anaemia, and prevent an increase in intestinal iron uptake caused by further lowering of hepcidin as a result of intensive blood letting.[33] The maintenance stage is reached when serum ferritin drops below the target value. The optimum frequency of phlebotomy will depend on the patient's symptoms and response to treatment, the serum ferritin value at diagnosis, and patient preferences.

An observational study reported that adherence to phlebotomy was greater than 90%.[34] The main negative effects were problems with venous access and the time consuming nature of the treatment.[35] Observational studies have shown that fibrosis of the liver may be reversed by phlebotomy. The effects on symptoms have not been evaluated extensively, and reviews show that treatment can improve some symptoms, such as fatigue and skin pigmentation, but not others, such as arthralgia.[1 9 36] In addition, evidence that treatment improves survival is limited because the low absolute risk of death from cirrhosis or hepatocellular carcinoma makes it difficult to show an effect using observational data.[23] A randomised clinical trial to evaluate the effect of phlebotomy would probably be considered unethical and would be complicated because of variable penetrance.

Iron chelation

Currently, the only routinely available alternative to phlebotomy is iron chelation, which is more costly and has more side effects. In iron chelation with desferrioxamine ferric ions are bound into ferrioxamine complex and eliminated from the body via the urine. Side effects include gastrointestinal symptoms, dizziness, visual and auditory impairments, muscle cramps, tachycardia, and thrombopenia. Experts recommend chelation with desferrioxamine only when phlebotomy is contraindicated—for example, when venous access cannot be obtained and in patients with circulatory problems (such as heart failure or anaemia).

Therapeutic erythrocytapheresis

Therapeutic erythrocytapheresis is the removal of erythrocytes only rather than whole blood that could become an alternative to phlebotomy. Preliminary results show that erythrocytapheresis leads to a fourfold reduction of phlebotomy sessions. More than twice as much iron can be removed per session and side effects are reduced.[37]

What can patients do to influence the disease?

Whether avoiding dietary iron reduces iron storage has not been investigated. Expert consensus opinion is that patients should avoid iron containing food supplements.[1] Patients might want to limit alcohol consumption,

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- Diagnosis and management of juvenile idiopathic arthritis (*BMJ* 2010;341:c6434)
- Oesophageal cancer (*BMJ* 2010;341:c6280)

especially when not yet iron depleted, because alcohol has a toxic effect on the liver and may also suppress hepcidin expression, as summarised in two reviews.[1 38] However, dietary advice that is too strict may reduce quality of life or even reduce adherence.

How do we monitor patients with haemochromatosis?

Patients are monitored mainly to guide the timing of treatment and detect liver damage. Serum ferritin is the main parameter used because an observational study found that it correlates with symptoms and the risk of complications. A cross sectional study showed that when serum ferritin is less than 1000 µg/L the risk of serious liver damage is below 1%.[39] Serum ferritin levels above 1000 µg/L are, according to international consensus, an indication for liver biopsy because of the risk of cirrhosis.[1 9] When a liver biopsy shows cirrhosis, periodic screening for hepatocellular carcinoma becomes mandatory. This can be done with echography or magnetic resonance imaging.

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