Haemochromatosis

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Haemochromatosis is now known to be an iron-storage disease with genetic heterogeneity but with a final common metabolic pathway resulting in inappropriately low production of the hormone hepcidin. This leads to increase in intestinal absorption and deposition of excessive amounts of iron in parenchymal cells which in turn results in eventual tissue damage and organ failure. A clinical enigma has been the variable clinical expression with some patients presenting with hepatic cirrhosis at a young age and others almost asymptomatic for life. Research is unravelling this puzzle by identifying environmental factors—especially alcohol consumption—and associated modifying genes that modulate phenotypic expression. A high index of suspicion is required for early diagnosis but this can lead to presymptomatic therapy and a normal life expectancy. Venesection (phlebotomy) therapy remains the mainstay of therapy, but alternative therapies are the subject of current research.

Introduction

Haemochromatosis is the most common inherited genetic disease in European populations.1 Although multiple mutations can lead to the clinical syndrome (panel), the most common mutation is that in the HFE gene leading to the p.Cys282Tyr substitution.2 Individuals homozygous for this defect might develop iron overload and its clinical consequences. This mutation is present in roughly one in ten people of northern European descent. Thus, one in 200 people will be homozygous.3 Whether such people develop substantial iron overload depends on environmental and genetic factors, including sex, alcohol consumption, and blood loss. The fact that disease expression is greater in men is only partly explained by physiological blood loss with other probable genetic factors yet to be elucidated. Research is unravelling the relevant genetic factors associated with this disease. This disease is increasingly being recognised in its early stages by greater clinical awareness.4,5 By contrast with HFE-associated haemochromatosis, the non-HFE-associated forms (panel) are rare, although globally ubiquitous.

Pathophysiology

Genetic iron overload syndromes, such as haemochromatosis, result from either excessive cellular egress of iron or impaired iron recycling. Excessive iron egress might be secondary to either hepcidin deficiency or insensitivity of ferroportin to hepcidin. It results in the classic phenotype of haemochromatosis with increased transferrin saturation and parenchymal iron excess.

Hepcidin synthesis is a multistep process including several genes and proteins (figure 1). Hepcidin deficiency might be secondary to mutations of the HFE or TfR2 genes (adult haemochromatosis) and of the HJV or HAMP genes (juvenile haemochromatosis).6 It results in a common pathophysiological pathway (figure 1) and a common phenotype (figure 2), the severity of which depends on both the gene damaged and various yet poorly identified genetic and environmental cofactors. Hepcidin deficiency is responsible for excessive expression of ferroportin at the cell surface, which results in increased iron egress, especially from macrophages and intestinal cells, and then increased plasma iron and increased transferrin saturation, leading to the occurrence of non-transferrin bound iron (NTBI).7 NTBI is avidly taken up by hepatic, pancreatic, endocrine, and cardiac cells and causes parenchymal iron excess.

Insensitivity of ferroportin to hepcidin (type B ferroportin) results from a gain of function. A disease mutation in the ferroportin gene renders the ferroportin protein insensitive to hepcidin. Ferroportin accumulates at the cell surface resulting in excessive iron efflux from cells to plasma.8 Impaired iron recycling might be secondary to mutations of either the ferroportin or the ceruloplasmin gene. By contrast with hepcidin deficiency, this accounts for hyposideraemia and low transferrin saturation, and does not correspond to the classic presentation of haemochromatosis. Conversely, type A ferroportin disease results from a loss of function. The ferroportin protein is unable to carry iron, which results in iron accumulation within cells, especially macrophages.9 In this case, the main location of iron excess is mesenchymal.

To be delivered from cells to transferrin, iron must be oxidised. Ceruloplasmin acts as the only ferroxidase apart from enterocytes. The absence of ceruloplasmin results in iron accumulation in most organs, including the central nervous system, leading to aceruloplasminaemia.10,11 The main mechanism whereby iron exerts its deleterious effects is the generation of reactive oxygen species by promoting the Haber-Weiss reaction. Reactive
oxygen species are known to increase lipid peroxidation, which results in damage to cell organelles and DNA. Cells with strong antioxidant defences, such as macrophages, are more resistant to iron toxic effects than parenchymal cells. This explains why hepatocytes, endocrine, and cardiac cells are mainly affected by iron excess. However, organ damage is also modulated by genetic and environmental cofactors. With respect to the liver, the main result of parenchymal iron loading is the early activation of a fibrotic process, enhanced by associated alcohol consumption.

**Risk factors and genetics**

**p.Cys282Tyr homozygosity**

In the general population, the allelic frequency of p.Cys282Tyr was reported to be as high as 6·2% in a pooled cohort of 127613 individuals from 36 screening studies with substantial variability across Europe, ranging from 12·5% in Ireland to zero in southern Europe. With respect to populations of northern European descent, the HealthIron longitudinal study using data from the Melbourne Collaborative Cohort study in Australia reported that in a population of 29676 individuals, p.Cys282Tyr homozygosity had an estimated prevalence of 0·68% (95 CI 0·59–0·78).

The prevalence of p.Cys282Tyr homozygosity in clinically recognised haemochromatosis was calculated as 80·6% in a meta-analysis including 2802 patients from 32 studies. Compound C82Y/His63Asp heterozygosity was reported in 5·3% of cases, and 19·4% of cases were not related to HFE. With respect to the prevalence of p.Cys282Tyr in selected groups, the results are more difficult to interpret. Some studies reported a higher frequency of p.Cys282Tyr in patients with well characterised chondrocalcinosis, in type 1 diabetes, in liver disease including hepatocellular carcinoma, and in prophyria cutanea tarda except in Italy. The penetrance of p.Cys282Tyr homozygosity is incomplete and varies widely from one study to another. This can be mainly attributed to methodological reasons: differences in the control population, selection biases, non-specificity of haemochromatosis-related symptoms, unavailability of confirmatory iron excess by liver biopsy, MRI, or the amount of iron removed, and absence of an accepted definition of the disease phenotype resulting in various definitions of penetrance. The studies from the groups of Worwood and Beutler were the first to avoid ascertainment bias by studying large populations.

Increased iron storage in young individuals (less than 30 years old) with p.Cys282Tyr homozygosity has been associated with mutations usually related to juvenile haemochromatosis, namely HAMP (hepcidin) and HJV (haemojuvelin). However, because of their low prevalence, these mutations cannot fully explain the variability of the p.Cys282Tyr homozygous phenotype. Polymorphisms in the haptoglobin (Hp) gene and in genes of the bone morphogenic protein (BMP) pathway were also...
Homozygosity can result in fully expressed disease (stage 4). ULN=upper limit of normal.

Different stages of the haemochromatosis phenotype. Not all patients will develop the full disease. Only Cys282Tyr homozygous patients.

Figure 2: Stages of haemochromatosis
Different stages of the haemochromatosis phenotype. Not all patients will develop the full disease. Only Cys282Tyr homozygous can result in fully expressed disease (stage 4). ULN=upper limit of normal.

Claimed to be substantial modifiers, but this was not subsequently confirmed.

Genome-wide association studies (GWAS) of Australian families of European descent showed that some transferrin single nucleotide polymorphisms (SNPs) can affect iron metabolism in p.Cys282Tyr homozygotes.

This was confirmed by a large GWAS of 474 unrelated French p.Cys282Tyr homozygotes that identified the rs3811647 polymorphism in the TF gene as the only SNP substantially associated with iron metabolism through serum transferrin and iron concentrations.

A GWAS by Benyamin and colleagues in European populations identified 11 genome-wide significant loci, including five novel loci (ABO, ARNTL, FADS2, NAT2, and TEX14) that had substantial effects on iron-related phenotypes. These novel loci affected either transferrin or ferritin. Another GWAS study by Stickel and colleagues reported a robust association between a variant in PCSK7 and cirrhosis in haemochromatosis with a large effect size. CYBRD1 has also been identified as a modulator of the iron-loading phenotype.

When studying a small group of 35 p.Cys282Tyr homozygotes with extreme phenotypes (22 with severe iron overload defined as severe on composite criteria and 13 with normal or mildly increased iron stores), McLaren and colleagues identified a GNPAT (glyceronephosphate O-acyltransferase) variant associated with severe iron overload. This has been followed by similar studies in other countries with somewhat conflicting results. Besson-Fournier and colleagues genotyped the GNPAT variant (rs11558492) in 284 unrelated HFE p.Cys282Tyr homozygous patients recruited in the south of France. They followed the enrolment strategy with regard to extreme phenotypes and included the restrictions on alcohol consumption. They replicated the finding of an enrichment of GNPAT rs11558492 in HFE p.Cys282Tyr homozygous men with a severe phenotype. By contrast, in a study of 264 men from the Irish hereditary haemochromatosis population, Ryan and colleagues identified that GNPAT p.S19G was not associated with a high iron phenotype, defined as a serum ferritin concentration of more than 1000 μg/L. Method and statistical differences could well explain the different findings. Similarly, the findings were not confirmed in a large series from France.

Additionally, some HLA haplotypes have been reported to improve survival in p.Cys282Tyr homozygotes, possibly owing to less severe iron overload and earlier age at diagnosis.

**Sex**

Male p.Cys282Tyr homozygotes display biochemical and symptomatic haemochromatosis more often and to a greater degree than their female counterparts. The HealthIT study showed that 28.4% of men had documented iron-overload-related disease compared with only 1.2% of women. Aguilar-Martinez and colleagues similarly reported in a French Mediterranean registry that biological and clinical penetrance was higher in men (19%) than women (13%). They also identified that men were diagnosed earlier than female p.Cys282Tyr homozygotes and that a higher proportion of men had clinically overt haemochromatosis.

The protective effect in women has been attributed to physiological iron loss during menstruation and pregnancy, the antioxidant effect of oestrogen, and sex-specific HFE and non-HFE genetic modifiers.

Importantly, serum ferritin concentrations substantially increase after menopause.

**Environmental factors**

Excessive alcohol consumption contributes to the progression of symptomatic haemochromatosis. Hepatic oxidative effects of iron and alcohol are cumulative. Consumption of more than 60 g of alcohol per day has been associated with substantially higher levels of serum iron and ferritin.

Fletcher and colleagues described a nine-fold increase in cirrhosis in p.Cys282Tyr homozygotes who drank more than 60 g of alcohol per day compared with those who drank less than 60 g of alcohol per day, consistent with the findings of Loréal and colleagues in 1992 and of Adams and Agnew in 1996.

Hepatic steatosis is also a cofactor in liver injury in haemochromatosis and can be related to excess alcohol, obesity and metabolic syndrome, and viral infection.

Finally, p.Cys282Tyr homozygotes with coexistent hepatitis C infection have been reported to develop cirrhosis at an earlier stage and lower hepatic iron concentration compared with individuals without hepatitis C.

Dietary modulators of haemochromatosis have also been studied. Non-citrus fresh fruits have been found to have a protective effect against iron loading in men but not in women. Conversely, haemoglobin iron intake...
including red meat is correlated with increased iron loading.\textsuperscript{39,45} Citrus fruit consumption had no substantial effects in either sex.\textsuperscript{45} Individuals with haemochromatosis who are blood donors were found to have lower serum ferritin than non-donors.\textsuperscript{39}

**Penetrance of other HFE genotypes**

Compound (p.Cys282Tyr/His63Asp) heterozygotes might have increased transferrin saturation and serum ferritin concentrations indicating a slight increase in liver iron concentration. However, iron-overload-related disease is rare and no more prevalent compared with HFE wild-type controls,\textsuperscript{46} unless cofactors such as alcohol or steatosis are involved.

On the basis of a large study of 41038 individuals attending a health appraisal clinic in the USA by Beutler and colleagues,\textsuperscript{8} it can be assumed that other genotypes (p.Cys282Tyr heterozygosity, His63Asp heterozygosity, and His63Asp homozygosity) do not result in clinically relevant modifications of iron metabolism even if they are associated with a slight increase in serum ferritin concentrations or transferrin saturation when considering large populations. Some exceptional private mutations (rare genetic mutations that are usually found only in a single family or a small population) have been reported, which, when associated with p.Cys282Tyr heterozygosity, might be responsible for severe iron overload.\textsuperscript{47,48}

**Clinical presentation, signs, and symptoms**

The classic well known clinical manifestations of haemochromatosis are hepatic cirrhosis, diabetes, and skin pigmentation (figure 3).\textsuperscript{49} This clinical picture is now not representative of most individuals with haemochromatosis.\textsuperscript{50} It is rare, nowadays, to encounter advanced symptomatic disease and is usually seen in individuals with a serum ferritin concentration exceeding 1000 μg/L.

Individuals with p.Cys282Tyr homozygosity might present with abnormal iron tests with or without clinical symptoms, and with or without proven evidence of iron overload because of the non-specificity of increased serum ferritin concentrations. The presentation of haemochromatosis with diabetes and liver disease has become rare, except when metabolic syndrome or chronic alcoholism are implicated. In an Italian retrospective review\textsuperscript{50} of a prospectively collected cohort of patients with haemochromatosis diagnosed between 1976 and 2007, patients diagnosed in 2007 or later had milder iron overload and lower prevalence of cirrhosis and extrahepatic manifestations, such as diabetes, arthropathy, cardiopathy, and diabetes. Individuals with normal serum ferritin concentrations at diagnosis are unlikely to develop symptoms of haemochromatosis,\textsuperscript{51} as reported by Asberg and colleagues who showed that p.Cys282Tyr homozygotes had low morbidity compared with control groups overall.\textsuperscript{52,53–55}

Whether iron overload is progressive in individuals with biochemical abnormalities only at diagnosis is not yet known. It is suggested that serum ferritin concentrations might rise but that end-organ damage is uncommon.\textsuperscript{28,31,33–35}

With time, clinically expressed haemochromatosis has become less frequent.\textsuperscript{4} The most common symptom of haemochromatosis is chronic fatigue. Arthropathy has been more and more recognised as a key feature
of haemochromatosis during the past few decades. Symptoms can develop early in men, before 30 years of age, and usually after menopause in women. Chondrocalcinosis or damage to the second and third metacarpophalangeal joints and to the proximal interphalangeal joints are the more frequent and typical localisations, but all joints might be damaged, including ankles, hips, and knees, which results in a high frequency of joint replacement—mainly hip—in patients with haemochromatosis compared with the general population.

Bone disease was also confirmed as a rather frequent complication in haemochromatosis. With the use of bone assessment with dual-x-ray absorptiometry, three studies identified a prevalence of osteoporosis ranging between 25·3% and 34·2%. Similarly, but before the availability of HFE testing, peripheral and vertebral fractures were reported in patients with haemochromatosis.

With time, other symptoms have become less common. Recent studies reported the prevalence of cirrhosis in male p.Cys282Tyr homozygotes to be only 2·7%. The same figure is true for diabetes—several studies have reported no significant difference in the prevalence of diabetes in p.Cys282Tyr homozygotes compared with controls. In a large population-based screening project in Norway, 4% of men diagnosed with haemochromatosis (according to phenotypic data only) reported impotence. Cardiac disease is not significantly increased in p.Cys282Tyr homozygotes compared with controls. Additionally, Beutler and colleagues showed that skin pigmentation was no more prevalent compared with controls. However, they did not encounter advanced symptomatic disease.

Haemochromatosis impairs the functional outcome (fatigue, arthropathy, osteoporosis) rather than survival. This is an important issue because iron-related arthropathy can develop even when serum ferritin concentrations are moderately increased by contrast with other symptoms, which are more likely to occur in individuals with serum ferritin concentrations of more than 1000 μg/L.

**Diagnosis**

With the readily available testing for HFE and increased awareness of the disorder, most patients are now diagnosed at an early stage before the development of symptomatic disease (figure 3). Patients are often detected at health checks with clinical symptoms compatible with but unrelated to haemochromatosis, especially chronic fatigue and arthralgia or through family screening. The commonest symptom at this stage is lethargy and early abnormal tests often indicate raised serum transaminase levels or serum ferritin concentrations. Observation of patient history should focus especially on alcohol ingestion, iron intake, and the ingestion of large doses of ascorbic acid.

Serum ferritin concentration alone is not a reliable predictor because it can be normal in the early phase of the disease and its specificity is poor. Increased serum ferritin concentrations are identified in many common conditions such as chronic alcoholism, metabolic syndrome, inflammatory syndrome, and diseases with cell necrosis. The serum iron concentration and percentage saturation of transferrin are increased early, and their specificity is better than that of serum ferritin, but remains reduced by false-negative and false-positive rates related to alcohol excess and end-stage liver disease. However, a persistent fasting serum transferrin saturation of more than 45% is an early sign of homozygosity for haemochromatosis and should be considered and followed by HFE testing.

**Differential diagnosis**

In the differential diagnosis of haemochromatosis, transferrin saturation becomes important (figure 3). In haemochromatosis, the percentage of serum transferrin saturation might fluctuate but is frequently increased. If not, an alternative diagnosis should be considered, especially inflammation, cell necrosis, alcohol-related damage, or metabolic syndrome (fatty liver disease). If these are excluded and the serum ferritin concentration is substantially increased, then rarer causes might be involved—eg, ferropoortin disease or aceruloplasminaemia (figure 3).

**Screening for haemochromatosis**

**Family screening**

Once the diagnosis is established in an individual, it is important to counsel and screen other family members, especially first-degree relatives (parents, siblings, and children). Testing for p.Cys282Tyr alone or with the H163A substitution is suggested in those with abnormal iron ferritin. Because of the frequency of asymptomatic forms, genotyping is now widely proposed as an initial test. For children of an identified proband, testing for HFE substitutions in the other parent is helpful because if normal, the child is merely an obligate heterozygote and at no risk. For practical purposes, children need not be checked before they are 18 years old unless the serum ferritin concentration is very high (eg, more than 1000 μg/L), which could be an indication of juvenile haemochromatosis or other rarer forms.

**Screening in the general population**

The worldwide consensus is that general screening is not recommended for several reasons—ie, cost, the threat of discrimination (sometimes still with respect to insurances), and the substantial rate of false-positive or false-negative results when using transferrin saturation or serum ferritin concentration as screening tests.

**Management**

Once the diagnosis of HFE haemochromatosis has been made, the question is whether additional tests are needed to assess the effects of the disease. If serum ferritin
concentrations are less than 1000 μg/L, most clinicians propose to test the patient for diabetes (fasting serum glucose) and not to perform other tests unless there are clinical or biochemical abnormalities. With respect to liver assessment, Guyader and colleagues showed that patients with no hepatomegaly, serum ferritin concentrations of less than 1000 μg/L, and normal serum aspartate transaminase were always free of bridging fibrosis and of cirrhosis and did not warrant liver biopsy. Therefore, if serum ferritin concentrations exceeded 1000 μg/L, a more systematic assessment was recommended. The place of MRI in diagnosis is still a debated topic.

It is important to determine whether severe fibrosis or cirrhosis is present and, in case of increased transaminase levels, to seek another cause of liver disease. This still relies upon liver biopsy in the absence of a definitively proven non-invasive alternative. Serum hyaluronate was proposed by Crawford and colleagues as a potent surrogate marker of fibrosis and of cirrhosis and did not warrant liver biopsy. If serum ferritin concentrations exceeded 1000 μg/L, a more systematic assessment was recommended. The place of MRI in diagnosis is still a debated topic.

Role of HFE in other liver diseases

HFE substitutions and increased hepatic iron might contribute to other liver diseases. For example, porphyria cutanea tarda might be precipitated or aggravated by iron, which accentuates the clinical manifestations. In non-alcoholic steatohepatitis, there is some evidence of increased expression of the disease because of the presence of HFE substitution and also some evidence that iron removal can be beneficial. However, this subject remains controversial. In chronic hepatitis C virus infection, some studies have shown aggravation by iron and that it is reasonable to perform venesection therapy before initiating antiviral therapy. HFE substitutions are not increased in frequency in alcoholic liver disease. End-stage liver disease is sometimes associated with iron overload of the degree seen in haemochromatosis. Alcohol ingestion suppresses hepatic hepcidin secretion. Additionally, haemolysis might also play a part. A large population study has shown that individuals homozygous for p.Cys282Tyr are at increased risk of breast and colorectal cancer but confirmatory evidence is awaited.

Long-term management

Therapeutic venesection

All international guidelines agree that excess iron should be treated with venesection and that the usefulness of other therapies is limited. In the absence of randomised controlled trials, recommendations are based upon the clinical evidence that iron removal before the onset of cirrhosis and diabetes is associated with reduced morbidity and mortality and that some features including hepatic fibrosis might be improved by venesection therapy. Recommendations vary with respect to the level of iron burden at which therapy should be proposed, the endpoint of initial venesection, and the optimum maintenance therapy (table). However, the worldwide consensus is to treat patients early, as soon as serum ferritin concentrations are above the upper limit of normal, and to aim at low to normal body iron stores in the long term (serum ferritin concentrations of 50–100 μg/L). All guidelines agree to check haemoglobin before each venesection and serum ferritin concentrations less frequently—eg, on a monthly basis as long as ferritin concentrations remain above the upper limit of normal and, thereafter, every two venesections. The periodicity or volume of venesections should be adapted to maintain haemoglobin concentrations above 11–12 g/dL and the serum ferritin concentration between 50 and 100 μg/L. The criteria for testing, endpoint, and goal for initial and maintenance therapy are summarised in table.
Some methods might help to improve tolerance. Pain at puncture point might be prevented with local anaesthetic. The kneading of a rubber ball might help to develop the venous net when insufficient. The patient is recommended to drink a large volume of water at the time of venesection and, in case of reduced flow, prescription of 75 mg of aspirin on the morning before venesection is helpful. If venesection is not tolerated during the maintenance phase, then decreased iron delivery (spontaneous restrictions in diet, tea consumption, treatment with proton pump inhibitor) or blood loss should be considered.

Pregnancy removes about 1 g of iron from the mother. Therefore, venesections must be stopped in the pregnant woman and serum ferritin monitored to correct iron deficiency.66 In older patients, the need for venesection usually decreases irrespective of associated blood loss, but there is no indication to abandon therapy unless cardiovascular or haematological contraindications occur.

Results are excellent with respect to general health (early fading of fatigue), skin pigmentation, and biochemical liver function tests (normalisation of serum transaminase saturation).67 Evolution of joint symptoms is more unpredictable: two-thirds of patients are either improved or stabilised, but a third either worsen or develop joint disease despite therapy.67 Improvement of glucose tolerance might occur during venesection therapy, but diabetes, particularly when requiring insulin, is not reversed by iron removal.49 Hepatic fibrosis has been shown to regress substantially in 50% of cases of severe fibrosis and in 30% of cases of cirrhosis,101 but whether regression is associated with a reduced risk of hepatocellular carcinoma is uncertain.

By contrast, established cirrhosis is irreversible and, after iron removal, such individuals remain at increased risk of the development of primary hepatocellular cancer.74,102,103 Therefore, in cases of initial severe fibrosis or cirrhosis, maintenance of ultrasound screening every 6 months remains the rule, even when some fibrosis regression has occurred.101

If treated with venesection in the pre-cirrhotic stage, individuals with haemochromatosis have normal life expectancy. In 1985, Niederau and colleagues indicated that haemochromatosis-related mortality is associated mainly with major complications of liver cirrhosis and liver cancer and that deaths caused by cardiomyopathy and diabetes were also increased in patients with haemochromatosis.168 A meta-analysis concluded that the rate of death from any cause was not increased in p.Cys282Tyr homozygotes.52 But again, this analysis did not include many cases of advanced symptomatic disease.

Data for survival and causes of death in a large series of 1085 treated p.Cys282Tyr homozygotes followed up for 8-3 years (SD 3·9) indicated that only patients with initial serum ferritin concentrations higher than 2000 µg/L had increased mortality, mainly related to liver diseases, and those with initial serum ferritin concentrations between the upper limit of normal and 1000 µg/L had decreased overall mortality in relation to reduced cardiovascular and extra-hepatic cancer-related mortality.69 Such results support a beneficial effect of early and sustained management of patients with iron excess, even when mild to moderate. Delayciki and colleagues67 have expressed the need for a controlled clinical trial investigating the need for treatment in patients with only moderately increased serum ferritin between the upper limit of normal and 1000µg/L. The Mi-iron trial,68 which is currently in progress, addresses this issue.

Alternative therapies
Iron chelators might be exceptionally indicated for initial iron removal only in patients with no superficial vein available or with contraindication to venesection.67 Deferasirox, a new oral chelator, has been shown to eliminate iron excess effectively in patients with HFE haemochromatosis but at the expense of some renal and hepatic side-effects and financial cost.109 Erythrocytapheresis is an effective therapy but is not widely available, is costly, and does not remove iron faster than venesection.109 In the future, new therapies such as mini hepaticins, BMP6 agonists, and TMPRSS6 antagonists should be applicable to humans, but it is likely that venesection will remain the mainstay of treatment because of its efficacy, tolerance, and low cost.

Other forms of genetic iron overload
In type A ferroportin disease, venesection remains the mainstay of treatment but might be poorly tolerated, requiring spacing out venesections. The therapeutic target of serum ferritin concentrations less than 50–100 µg/L is probably too low because of the risk of anaemia.111

In aceruloplasminaemia, venesection is usually poorly tolerated, and iron chelation might be necessary.112 Conversely, in juvenile haemochromatosis, iron-related cardiac burden might indicate urgent and intensive iron removal using both venesection and iron chelation.111

Diet
No evidence exists to support dietary interventions in patients with haemochromatosis; however, a systematic review by Moretti and colleagues113 concluded that dietary modifications that modulate iron intake or bioavailability might affect iron accumulation and that dietary modifications encourage patients’ active involvement in their management. A broadly healthy diet is recommended. Tea drinking114 and non-citrus fruit14 intake have been reported as possibly reducing the rate of iron accumulation and might be used. Alcohol is a major hepatotoxic factor.115,116 It has also been shown to reduce hepcidin synthesis.117-119 Therefore, withdrawal of alcohol consumption or severely curtailing its use (one standard drink per 24 h period) should be the rule
during initial venesection therapy and thereafter in cases of cirrhosis. In the absence of severe fibrosis, a reasonable alcohol intake might be permitted.

**Drugs and vaccinations**

Due to the potential cardiac toxic effects in patients with excess iron, vitamin C supplementation is contra-indicated during the initial phase of therapy. In the case of hypogonadism, substitution with androgens should be cautioned because of potential hepatotoxic effects. Patients should also be immunised against hepatitis A and B, and, in case of cirrhosis, against pneumococcus.

**Organ damage**

The management of hepatic and extra-hepatic complications has no specific therapy. Liver transplantation might be necessary in the case of hepatocellular carcinoma or end-stage liver disease, knowing that this latter condition rarely occurs in the absence of hepatotoxic cofactors, mainly excessive alcohol intake and hepatitis co-infection. Early reports suggested that post-transplant survival was reduced because of heart disease, infection, and malignancy. A study of 18 transplanted p.Cys282Tyr homozygotes did not confirm these findings and showed that liver transplantation normalised hepcidin secretion and prevented the recurrence of hepatic iron overload. Thus, this confirmed that the basic defect in HFE-associated (and indeed other hepcidin-related) haemochromatosis lies in the liver.

**Controversies and uncertainties**

There is much debate about when treatment should be initiated. The international guidelines published by both the American and European Liver Associations advocate that therapy should be commenced when the serum ferritin concentrations are above the upper limit of normal. However, no strong evidence exists to substantiate this, and present research might change this recommendation.

The optimum concentrations of serum ferritin and transferrin saturation for maintenance therapy are also debated. All guidelines recommend to obtain and then to maintain normal body iron stores. However, in the absence of evidence-based data, the definition of low body iron stores remains vague, consisting of serum ferritin concentrations of 50 μg/L, between 50 μg/L and 100 μg/L, or within the normal range, with no consideration for the value of transferrin saturation (table). Despite normal serum ferritin concentrations being achieved, sustained increased transferrin saturation and then toxic non-transferrin bound iron might persist. Whether this could relate to chronic fatigue and the worsening or development of arthritis under maintenance therapy remains uncertain. Thus, it is desirable to maintain serum transferrin saturation below 50%. Whether both substitutions—p.Cys282Tyr and His63Asp—should be tested initially is somewhat controversial. Testing both at the same time might lead to confusion because His63Asp has been clearly shown to be associated with mild features of haemochromatosis in case of compound heterozygosity and with concomitant morbidities only. Therefore, some experts recommend testing for His63Asp only in p.Cys282Tyr heterozygotes with suspicion of increased iron stores. However, in a young individual with unexplained increases in transferrin saturation, testing for compound heterozygosity might avoid unnecessary other investigations. The two-step procedure is not significantly more expensive.

MRI has been shown to be a reliable means to detect and quantify visceral iron excess, especially in the liver and spleen. Decrease in MRI hepatic signal is well correlated with increase in hepatic iron concentration within a wide range from 100 μmol/g to 350 μmol/g dry weight. Beyond this range, it is much less accurate. Additionally, it might lead to false-positive results because of technical concerns or associated steatosis. The more usual indication of MRI is the suspicion of iron excess in a non-p.Cys282Tyr-homozygous patient. In the p.Cys282Tyr homozygote, MRI can be used in case of suspected heavy iron overload to detect macroscopic preneoplastic or neoplastic iron-free foci.

When liver biopsy should be performed is also controversial. Now that hepatic iron concentration can be estimated with reasonable accuracy (serum ferritin concentration with or without MRI), the role of liver biopsy is to confirm or exclude cirrhosis of the liver. This is because of its prognostic implications. Thus, indications are confined to patients with a serum ferritin level of 1000 μg/L or more, especially with abnormal liver enzymes. It can also be used to confirm liver iron concentrations when important. Forthcoming studies of non-invasive assessment of hepatic fibrosis by biochemical markers and elastometry should restrict the role of liver biopsy in the management of haemochromatosis.

**Contributors**

JWF, YD, and RCS designed and wrote the manuscript. YD edited the manuscript. RCS checked the references.

**Declaration of interests**

We declare no competing interests.

**References**

1. Hepcidin deficiency causes
   a. Internalization of ferroportin, effectively closing iron excretion
   b. Over-expression of ferroportin resulting in increased iron egress
   c. Over-expression of ferroportin resulting in accumulation of iron in the RES
   d. Increased transferrin saturation

2. Ferroportin disease type B (hemochromatosis type 4)
   a. Is associated with normal hepcidin levels
   b. Presents with high ferritin but low iron and transferrin saturation
   c. Most of the iron is accumulated in hepatocytes
   d. Is caused by insensitivity of ferroportin to hepcidin

True or False

3. Patients with hemochromatosis only develop arthropathy in the small joints of the hands

4. Alcohol, HCV infection and fatty liver disease all increase risk of cirrhosis in patients with homozygote C282Y mutation

5. Phlebotomy prevents progression of joint disease associated with hemochromatosis

6. Only patients with homozygote hemochromatosis who have ferritin >1,000 or elevated AST levels need to undergo staging for liver fibrosis

7. Long-term goals of phlebotomy are to lower ferritin to 50-100 ug/L and a hemoglobin <11g/dL

8. In ferroportin disease type B (type 4 hemochromatosis), the ferroportin transporter is insensitive to hepcidin

9. Two mechanisms that can lead to iron overload include overexpression of hepcidin production or insensitivity of ferroportin to hepcidin

10. Transferrin saturation >45% should trigger testing for HFE, but can be caused by chronic alcoholism or end-stage liver disease of any cause

11. Individuals who are homozygote for the C282Y mutation will invariably develop iron overload over their lifetime.

12. Adult hemochromatosis and juvenile forms both share the same pathophysiology: hepcidin deficiency

13. Aceruloplasmenia is associated with parenchymal iron overload, as ceruloplasmin is the only ferroxidase capable of delivering iron to transferrin

14. S65C mutations and homozygote H63D mutations do not cause clinically significant iron overload. Compound C282Y and H63D heterozygotes develop liver damage only when comorbidities exist.

15. Vitamin C supplements are contraindicated during the early phase of hemochromatosis therapy