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NARRATIVE REVIEWS

Charles J. Kahi, Section Editor

Diagnosis and Treatment of Hemochromatosis

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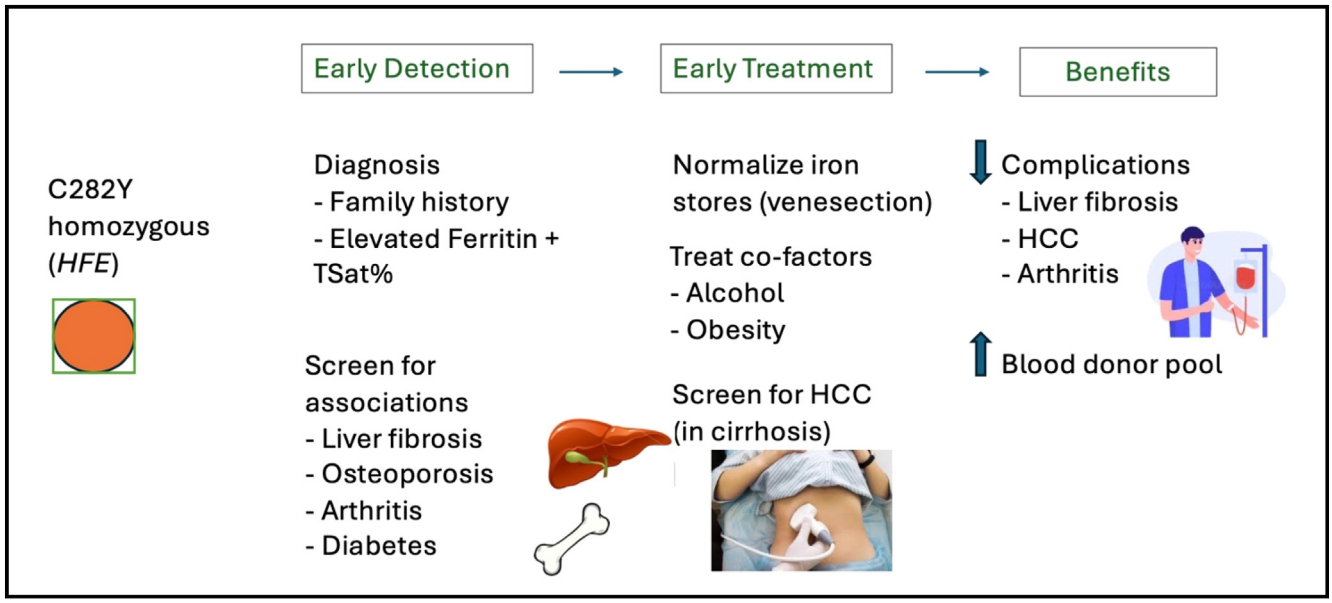

Hemochromatosis is not a new disease, and genetic variants for hemochromatosis have been identified in human fossils that are over 4000 years old in North Western Europe.[1] These variants were postulated to promote iron absorption as a survival benefit. In contrast, excess iron absorption can lead to serious complications, including arthritis, liver fibrosis, cirrhosis, primary liver cancer, and diabetes. In this review, the emphasis is on recent developments in the diagnosis and treatment of hemochromatosis, focusing on those homozygous for the C282Y variant in the *HFE* gene. In this condition, there is a clear need for earlier diagnosis, leading to earlier treatment, to prevent morbidity and mortality from iron overload.

Keywords: Haemochromatosis; Hemochromatosis; Iron Overload.

Epidemiology

Hemochromatosis is the most common genetic disease in persons of European ancestry. The prevalence of the typical genetic profile for hemochromatosis (C282Y homozygote, 845G ⟶A) is 1 in 227 in North American patients of European ancestry in the HEIRS study and 1 in 156 in northern England in the UK Biobank Study.[2,3] In Ireland, a study in which 1000 neonates were screened at birth for *HFE* variants revealed a prevalence of 1%, the highest rate in the world.[4] Although the C282Y variant is relatively common in certain populations, the clinical penetrance is far from absolute, and reports have varied widely depending on the definition of clinical penetrance used. More recent evidence from the UK Biobank has indicated that 1 in 5 males and 1 in 10 females will develop morbidity associated with hemochromatosis, changing the focus away from a condition previously believed to be without significant consequences.[3,5] Moreover, 1 in 10 males will develop severe liver disease unless identified early and treated.[6]

Diagnosis

If we reflect on a diagnostic methodology detailed by medical pioneers such as Sir William Osler, we would

Abbreviations used in this paper: APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; HCC, hepatocellular carcinoma; HEIRS, Hemochromatosis and Iron Overload screening; MRI, magnetic resonance imaging; NPV, negative predictive value.

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consider a detailed medical history, physical examination, and appropriate blood tests, leading to confirmation of a diagnosis often by biopsy and/or imaging studies. Unfortunately, the signs and symptoms of hemochromatosis (specifically C282Y-linked hemochromatosis) are too non-specific to suggest a diagnosis of hemochromatosis. In C282Y-related hemochromatosis, the onset of clinical signs of iron overload may not occur until the 40s in men or 50s in women, who may be protected by physiologic blood loss through menstruation and pregnancy.[7] Although the clinical penetrance and severity of iron-related organ damage is greater in men than women, as evidenced by higher risks of liver cirrhosis and liver cancer, reported symptoms may not be significantly different between the 2 genders.

Diagnosis: Presentation

The most common non-specific symptoms include fatigue and arthralgias of the knuckles, affecting over one-half of individuals.[3] No symptoms are common in early hemochromatosis, but a family history of hemochromatosis may prompt testing in siblings who have the highest risk of being affected by the autosomal recessive condition. In most countries, the diagnosis of hemochromatosis is incidental; for instance, when a serum ferritin is ordered as a test for iron deficiency to investigate fatigue. Hemochromatosis may also be picked up as part of a blood workup for fatigue or arthritis, or for liver disease or diabetes; it may even be found incidentally on magnetic resonance imaging (MRI) for another indication, which demonstrates a 'black liver' secondary to iron overload. A high ferritin, an unexpected finding, in combination with a raised serum transferrin saturation, leads to genetic testing for *HFE* gene variants. In the largest population screening test to date (UK Biobank) using whole genomic testing, 451,270 participants in northern England were tested, and 1 in 156 were C282Y homozygotes.[2,3] In these homozygotes, a previous diagnosis of hemochromatosis had been made in only 12 % of men and 3.4 % of women. The average age at diagnosis in a cohort of 554 referred patients was 58.5 years for women and 61 years for men. This is strong evidence of a ***failure to diagnose*** hemochromatosis in clinical practice.

Diagnosis: Interpretation of Iron Studies (Serum Ferritin, Transferrin Saturation)

A paradox in hemochromatosis is that we miss the diagnosis in most cases (*missed diagnosis*), and we also over-diagnose hemochromatosis in patients with an elevation in serum ferritin who usually do not have hemochromatosis (*misdiagnosis*). In the Hemochromatosis and Iron Overload screening study (HEIRS),[2] participants from the United States and Canada were tested for serum ferritin, transferrin saturation, and the C282Y and H63D mutations of the *HFE* gene. All participants were notified of their results and offered counseling. There were 99,711 participants with 299 C282Y homozygotes reported in this multi-ethnic population. There were 12,993 participants (13%) with an elevated serum ferritin (>200 μg/L in women; >300 μg/L in men), 5997 participants (6%) with an elevated transferrin saturation (>45% in women, >50% in men). These results demonstrate that an elevated serum ferritin is extremely common, and it is a non-specific test, although the probability of being C282Y homozygous does increase with increasing ferritin levels for males and females (Figure 1).[8] For these reasons, patients should not be told that they have hemochromatosis or 'high iron levels' at their first sign of an elevated ferritin because most patients have elevations from much more common conditions including metabolic syndrome, fatty liver, daily alcohol use, obesity (termed metabolic hyperferritinemia[9]), and inflammation (Figure 2). It is important to screen individuals for these cofactors such as alcohol excess or the metabolic syndrome, which, when present, are associated with worse outcomes in patients with hemochromatosis.[10,11] There were no significant cases of non-*HFE* iron overload in the HEIRS study, and in that study, patients with an unexplained elevation in serum ferritin had extended genetic testing for rare iron overload genes.[12] Transferrin saturation had been touted as a possible screening test for hemochromatosis as it seems to reflect day-to-day iron absorption, which is increased in hemochromatosis. However, one important observation from the HEIRS study was that the test was not reproducible[13] and can vary considerably even within C282Y homozygotes and with circadian rhythm. It is best measured fasting and on more than one occasion to give a more representative value. Furthermore, the HEIRS study did not identify a threshold for transferrin saturation that would capture most C282Y homozygotes.[13] In a study of 3734 individuals in primary care in Scotland, cutoffs of ferritin $\geq$300 μg/L plus transferrin saturation >50% for males and ferritin $\geq$200 μg/L plus transferrin saturation >40% for females yielded modest detection rates for C282Y homozygosity of 18.8% (52/272) for males and 16.3% (68/415) for females.[14] In contrast, the combination of normal serum ferritin and a transferrin saturation <45% gives the greatest ability to 'rule out' hemochromatosis, with a negative predictive value (NPV) of 97%.[15] In practice, the typical recommendations to warrant *HFE* testing are a serum ferritin >200 μg/L in women and >300 μg/L in men along with a transferrin saturation >45%.[7] Once the initial diagnostic tests (ferritin, transferrin saturation, *HFE* testing) are done, further testing in a C282Y homozygote should include a full blood count, liver blood tests, including aspartate aminotransferase, alanine aminotransferase, bilirubin, creatinine, fasting blood glucose, hemoglobin A1c, alpha-fetoprotein, and an abdominal ultrasound. Biomarkers and elastography could be considered to estimate liver fibrosis. Cardiac testing is reserved for severe iron overload patients or patients with dyspnea. Bone, joint, and endocrine investigation can be guided by clinical presentation.

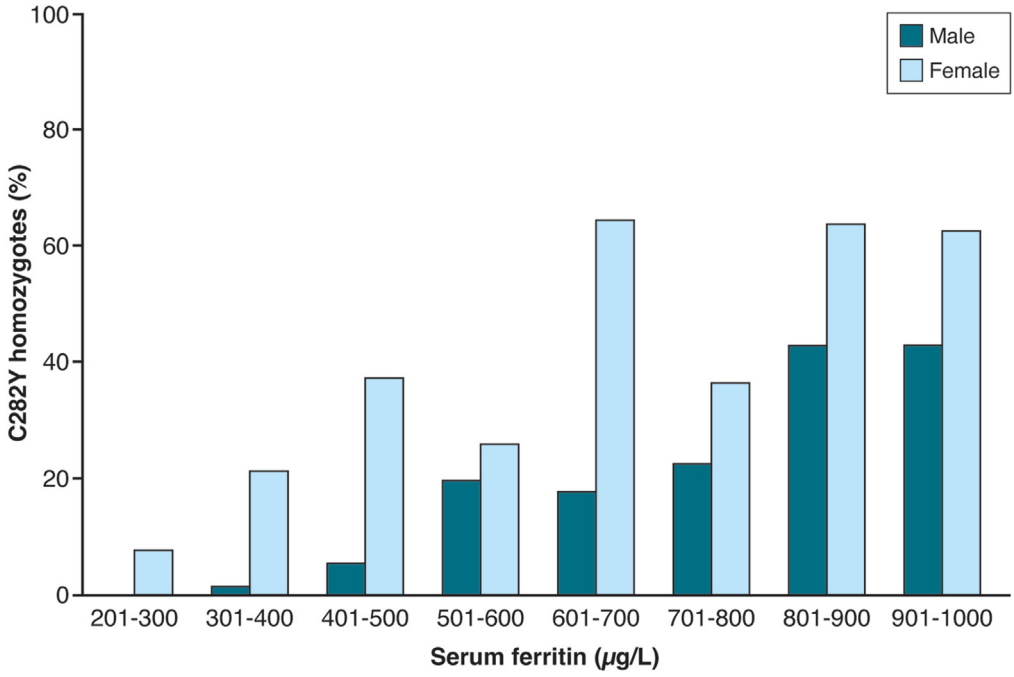

Figure 1. The probability of having C282Y hemochromatosis in 748 Caucasian participants with an elevated serum ferritin (>200 μg/L women; >300 μg/L men) and transferrin saturation (>45% women, >50% men).[8]

Diagnosis: Testing for C282Y Variant in the HFE *Gene*

As a condition that is readily identifiable and treatable, the argument of screening for hemochromatosis remains pertinent today. When the C282Y genetic test became widely available in 1997, initial concerns were raised regarding the detection of C282Y homozygotes without iron overload, the potential genetic discrimination, and the cost of testing. In the HEIRS study, 12% of the newly identified male C282Y homozygotes, and 43% of the newly identified female homozygotes had a normal serum ferritin.[2] There were no cases of genetic discrimination reported in the first year of the study.[16] The cost of genetic testing for a single mutation (C282Y) which can be done without polymerase chain reaction amplification (Invader assay), is reported to be as low as USD $5. This may not be the charge in a commercial laboratory, but it is clear that the cost of C282Y testing is not prohibitive, and in most cases, is less than the cost of serum ferritin and transferrin saturation. There have been at least 7 studies using genetic testing as a screening test for hemochromatosis.[2,17–20] The test is reproducible, inexpensive, widely available, and can be done on a saliva sample. A difficult issue has been defining the logistics of a screening program. Most economic analysis studies have shown cost-effectiveness with population screening for hemochromatosis,[21,22] but have modeled targeted screening in groups such as those northern European ancestry or only men, which could be unappealing to public policy makers.[23] Screening through a simple request for a saliva sample for hemochromatosis in a mail-back program may also not be a constructive approach. In Northern Ireland, the patient support organization mailed 36,000 people information about free genetic tests for hemochromatosis with instructions, and only 360 requested the test.[24] The acceptance rate of the genetic test to screen for hemochromatosis in the first study using the genetic test for screening in 2000 in Canada was 97%, but these were blood donors with a recruiter on site.[13] Whole genome sequencing may offer an additional mechanism by which C282Y homozygosity/hemochromatosis could be detected were it to become more commonly used in clinical practice; indeed, hemochromatosis has been a Tier 1 genetic result since 2021, in which notification of the result to the patient is recommended.[25]

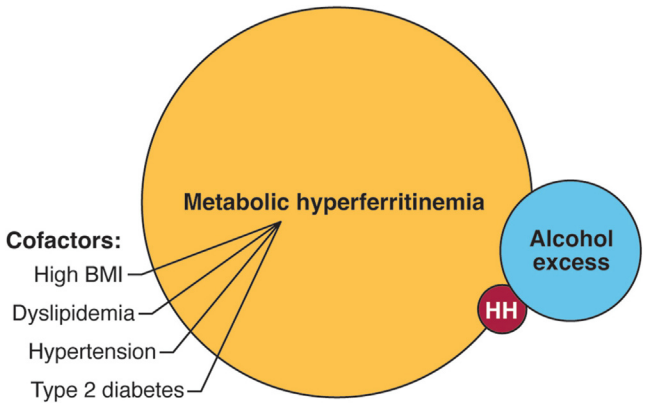

Figure 2. Relative proportion of typical causes of an elevated serum ferritin in practice.

The diagnosis of hemochromatosis can begin with a history of fatigue or arthralgias, a family history of the condition, or as incidental finding of elevated ferritin or transferrin saturation. After reviewing the family history, alcohol use, the individual's body mass index, and the ancestry of the patient, it may be appropriate to order the *HFE* (C282Y) genetic test. Specialist referral can then be to a hepatologist, gastroenterologist, hematologist, or a genetics clinic (Figure 3).

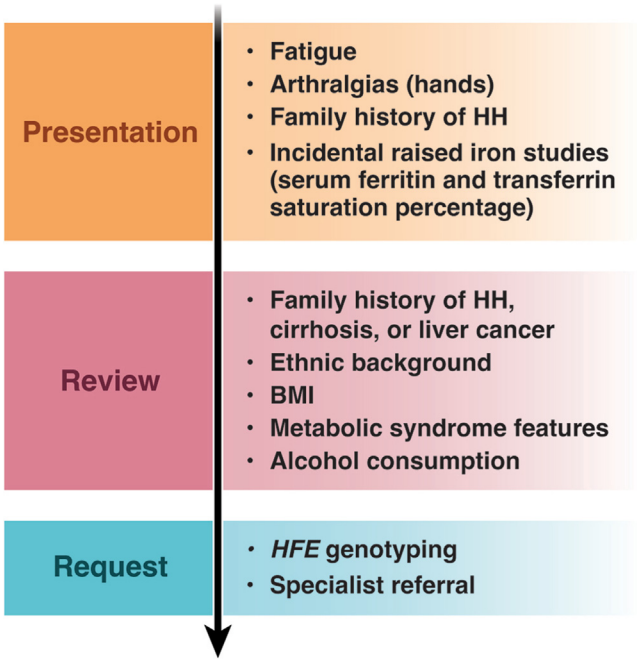

Figure 3. Diagnostic pathway for hemochromatosis.

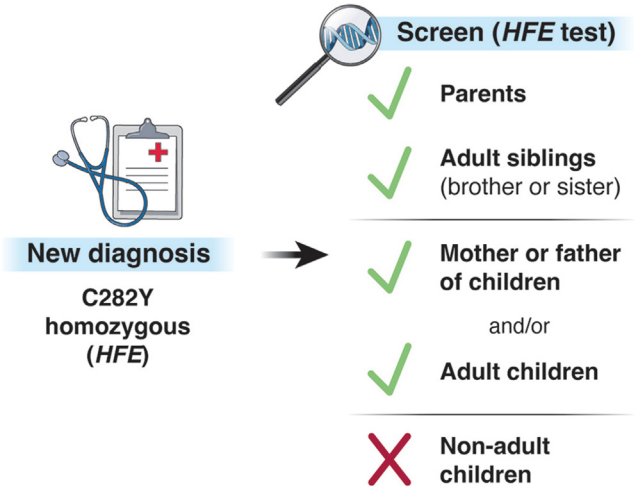

Figure 4. Approach to family screening following a diagnosis of hemochromatosis.

Diagnosis: Approach to a Newly Diagnosed Case

A new diagnosis of hemochromatosis in a C282Y homozygote should include a family history, and siblings and parents should be instructed to request a *HFE* (C282Y) genetic test. Adult children may also be tested, or alternatively, the partner/parent of the children may be tested, and if negative for the C282Y variant, then the children do not need testing in the future (Figure 4). Screening of non-adult children is not recommended.

Upon diagnosis, the initial serum ferritin for an individual with hemochromatosis remains the best noninvasive marker of iron burden, the likelihood of iron-related complications, and the expected number of phlebotomies required to achieve 'de-ironing.' Serum ferritin is also the most useful indicator of liver disease risk. For instance, those with a serum ferritin >1000 μg/L are much more likely to have severe liver fibrosis than those that do not; one small French study of 77 C282Y homozygotes found advanced (F3/F4) fibrosis on liver biopsy in 1 in 5 patients with a ferritin >1000 μg/L and/or increased liver transaminases.[26]

Diagnosis: Importance of Assessment for Liver Fibrosis

All patients with hemochromatosis should be screened for liver fibrosis, as liver disease will affect approximately 20% of adult male C282Y homozygotes.[5] Typically, a baseline abdominal ultrasound is performed to assess for concomitant hepatic steatosis, as well as for evidence of cirrhosis, portal hypertension, and liver cancer. MRI liver is not required for diagnosis in C282Y homozygotes with evidence of biochemical iron excess but is an accurate and sensitive means to determine iron burden, which can guide therapy in those without conventional C282Y-related hemochromatosis.[7,27] Liver fibrosis detection may be done with blood-based fibrosis markers such as the Fibrosis-4 (FIB-4) or aspartate aminotransferase to platelet ratio index (APRI) scores, which are commonly used in other causes of chronic liver disease and have some limited data in hemochromatosis. In one retrospective study of 181 patients with *HFE*-associated hemochromatosis who had liver biopsies, an APRI score >0.44 or a FIB-4 score >1.1 showed good ability to detect advanced fibrosis (area under the receiver operating characteristic curve, 086–0.88).[28] In the same study, and APRI score of <0.37 or a FIB-4 score of <0.73 gave a NPV of 88.6% and 92% for advanced liver fibrosis, respectively. Transient elastography, an alternative noninvasive tool for liver fibrosis assessment, was found by Legros et al to have a high NPV for ruling out advanced fibrosis in C282Y homozygotes with a liver stiffness of <6.4kPa.[26] However, a more recent study demonstrated a poor correlation between APRI or FIB4 scores and liver stiffness values in C282Y homozygotes but did not have liver biopsies as a comparison.[29]

Diagnosis: Extra-hepatic Manifestations

Aside from liver disease, other areas where iron-related harm may manifest include bones/joints, heart disease, and diabetes. In the UK biobank, male C282Y homozygotes had an odds ratio of 2.30 (95% confidence interval [CI],1.49–3.57) for osteoporosis compared with the control population.[3] An excess of arthritis has been consistently reported in C282Y homozygotes, with 27.9% males requiring joint replacement over their lifetimes as compared with 17.1.% of those without *HFE* variants.[5]

Given these associations, it is important to consider a baseline bone density dual x-ray absorptiometry scan in C282Y homozygote adults >40 years of age, x-rays of the hands for patients with symptomatic arthropathy, and to consider orthopedic or rheumatology specialist input.

From a cardiac viewpoint, it is estimated that <3% C282Y homozygotes will have cardiomyopathy, predominantly in those with a serum ferritin >1000 μg/L.[30] Although there is no exact serum ferritin cutoff to trigger cardiac testing, in young patients presenting with severe iron overload or in any individual with serum ferritin levels >2000 μg/L, the assessment of cardiac function through echocardiogram or axial imaging is warranted. Indeed, cardiac iron overload can be the presenting feature of hemojuvelin disease (juvenile hemochromatosis, related to *HJV* rather than *HFE* variants, with an onset in early adulthood).

Finally, the UK biobank study also demonstrated a significant excess of delirium, dementia, and Parkinson's disease, but not depression, in male C282Y homozygotes.[5,31] Iron in the brain has been reported in C282Y homozygotes with advances in MRI brain imaging.[32] The implications of these findings and the potential impact on early detection and potentially preventative treatment require further study and consideration.

The use of MRI for evaluating hepatic iron deposition is variable, and limited by cost and access to MRI. In the setting of a persistently elevated serum ferritin and transferrin saturation and a normal *HFE* test, and once metabolic hyperferritinemia or alcohol excess have been excluded (which explain the significant majority of cases), a MRI liver can be considered to assess for parenchymal iron overload. This is typically requested by a specialist in iron-related disorders, and reserved for those with evidence of significant biochemical iron excess. The technical aspects of MRI liver iron concentration estimates continues to evolve with improved R2*sequence analysis and rapid result reporting from in-line analysis.[33]

Hemochromatosis: Treatment

The management of hemochromatosis utilizes the medieval treatment of blood removal to decrease body iron stores. To focus treatment on those at need, it is essential to have a correct diagnosis, which includes C282Y genetic testing and, in non-C282Y homozygotes, proof of iron overload (Table 1). It has been demonstrated in France in a multicenter study that most patients receiving venesections for presumed iron overload, are not C282Y homozygotes and do not have iron overload.[34] The early hypothesis that many of these cases would have genetic mutations in other iron genes has not been demonstrated, and the most common diagnosis is the metabolic syndrome without iron overload.

Once a diagnosis has been established, treatment should not be delayed, given the numerous reported benefits associated with normalization of iron stores, not limited to an improvement in fatigue, the reversal of liver fibrosis, and a reduced risk of diabetes, liver cirrhosis, liver cancer, and death.[35,36] Moreover, treatment should be initiated as a matter of urgency in symptomatic patients or in those with significant iron overload (eg, serum ferritin >1000 μg/L). Treatment should also not be withheld from patients with mildly increased iron stores, as patients with moderate elevations in serum ferritin (eg, 300–500 μg/L) have been shown to benefit from venesection, with a reported reduction in cardiovascular disease and extra-hepatic malignancies.[37] Ultimately, patients should be encouraged to attend for voluntary blood donation once de-ironed, as transfusion services now accept blood from patients with hemochromatosis in many countries, with a positive effect on the blood donor pool.[38]

C282Y Homozygote

A C282Y homozygote with an elevated serum ferritin can be assumed to have iron overload and should be offered phlebotomy treatment. Patients are typically treated by weekly 500 mL phlebotomy by an experienced team until the serum ferritin is in the low normal range. Many studies suggest a target serum ferritin of 50 μg/L. This number was arbitrarily chosen because it was anticipated that some patients would not return for follow-up and allowed possibly for a slow rise of serum ferritin over time. A patient survey from France suggested that aggressive phlebotomy therapy to also decrease the transferrin saturation would reduce symptoms in some patients.[39] This strategy places patients on the verge of iron deficiency, requires more intensive follow-up by the treating physician, and is difficult to implement in routine practice. There can be non-expressing C282Y homozygotes with a normal serum ferritin and transferrin saturation discovered through family or population screening studies. Adult patients with a normal ferritin at the time of diagnosis are unlikely to develop iron overload later in life and can have periodic screening of ferritin every few years.[40] The side effects of phlebotomy at an experienced treatment center are very low. The most common are local effects around the needle insertion, including pain, redness, and inability to find a good vein.[41] Syncope and fatigue can occur. Volume depletion can be minimized by the use of a salt-containing sport drink.

In those with established cirrhosis, 6-monthly ultrasound and alpha-fetoprotein levels for hepatocellular carcinoma (HCC) screening is mandatory, given a significant increased risk. This is the most devastating, and life-threatening complication of hemochromatosis, typically affecting men. Data from the UK Biobank has revealed a hazard ratio of 10.5 (95% CI, 6.6–16.7) for hepatic malignancies in C282Y homozygous males.[42] Moreover, the type of HCC seen in hemochromatosis tends to be more poorly differentiated and associated with worse outcomes.[43] In addition, hemochromatosis is a known cause of non-cirrhotic HCC, and the merits of HCC screening can be considered in those with liver

Table 1. Clinical Guide

• Phlebotomy treatment should be offered to all C282Y homozygotes with an elevated serum ferritin (>200 μg/L in women; > 300 μg/L in men).
• Non-expressing C282Y homozygotes (those without elevated serum ferritin levels) need observation not treatment, and voluntary blood donation should be encouraged.
• Maintenance therapy can be personalized, and the need for maintenance and the interval for phlebotomy will vary by age, sex, and the initial ferritin at presentation.
• Voluntary blood donation is the ideal solution for a patients in the maintenance phase of therapy.
• Non-C282Y homozygotes with a significantly elevated ferritin and transferrin saturation could have MRI liver to determine if iron overload is present before initiating venesection therapy.
• Cirrhotic patients require a more intensive follow-up plan including abdominal ultrasound every 6 months to screen for HCC.
• Patients should be advised to notify their siblings and adult children to be tested for hemochromatosis.

HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

Table 2. Hemochromatosis 2024 Update

• Serum ferritin is a non-specific test.
• Transferrin saturation has wide biological variability, which limits its value as a screening test.
• Metabolic hyperferritinemia, rather than iron overload, is the most common cause of a raised serum ferritin in practice.
• Do not tell patients they have hemochromatosis until the genetic test reveals a C282Y homozygote.
• Compound heterozygotes (C282Y/H63D) or H63D homozygotes rarely develop iron overload or any clinical symptoms.
• Do not order venesections or advanced genetic testing (hemojuvelin, transferrin receptor 2, hepcidin, ferroportin, BMP6) in patients with a suspicion of iron overload and negative *HFE* mutations unless iron overload is established (eg, by MRI liver).

MRI, magnetic resonance imaging.

fibrosis, a family history, or concomitant risks for progressive liver disease.

Other HFE *Genotypes*

This group can include compound heterozygotes (C282Y/H63D) and H63D homozygotes (H63D/H63D). Large population-based studies have shown that individuals with these genotypes do not experience an increase in mortality or morbidity and can be reassured.[2,3,44] Mild elevations in serum ferritin has been demonstrated in some individuals but are almost always associated with other risk factors like metabolic syndrome, obesity with fatty liver, or daily alcohol consumption.[42] Mild biochemical iron overload can be seen in C282Y/H63D compound heterozygotes in approximately 10% of cases and in 1% of H63D homozygotes.[2] Furthermore, 10% of C282Y heterozygotes can demonstrate mild increases in serum ferritin or transferrin saturation, but not of clinical significance.[1] Although venesection has not been proven to be of benefit in such patients, the most pragmatic and reasonable approach to normalizing iron stores is to promote voluntary blood donation and to treat other metabolic risk factors.

Elevated Serum Ferritin Normal HFE *Genetic Testing*

This is a very large group of patients in the general population, and they rarely are found to have iron overload. In those with evidence of significant biochemical iron overload and negative *HFE* testing, an MRI liver is preferred to a trial of phlebotomy to preserve intravenous therapy center facilities for higher priority needs.[34] If MRI liver demonstrates iron overload, the patient should be referred to a center experienced in advanced genetic testing (such as for ferroportin, hemojuvelin, hepcidin, transferrin receptor 2, BMP6 mutations, and hypoceruloplasminemia).

Erythrocytaphoresis

This method is a type of automated red blood cell exchange. It is a pump-driven system similar to plasmapheresis, and it has been shown to be an efficient method of removing iron while maintaining blood volume. Each procedure can remove up to 800 mL and remove 2.3 times the amount of iron compared with a 500 mL phlebotomy. The procedure has more supply costs per treatment, but fewer treatments are required. It has been used in several European centers[45] and can be used with acceptable safety in experienced centers. It is the only treatment for iron overload that has been studied in a randomized participant-blinded study.[46] In this project, mildly affected C282Y homozygotes were compared between those with iron removed and a placebo group that had the pheresis treatment without iron removal. Many measures were unchanged between the 2 groups, and there was a small improvement in fatigue.

Dietary Therapies

Patients are often very interested in dietary therapies, and this view is reinforced by many internet patient support groups. It is not possible to have an iron-free diet. An iron-reduced diet has been studied and has

Table 3. Future Developments and Controversial Areas

• Population screening for hemochromatosis using the C282Y genetic test. There is hesitancy among geneticists to screen neonates for adult diseases in which many will never develop symptoms. Neonatal screening has been studied in France and Australia.
• If whole genomic testing becomes common, it could lead to a large number of new C282Y homozygotes who should be notified as per recommendations from the American College of Medical Genetics.[23] Whole genome testing is being studied in the UK Biobank study and the National Institutes of Health All of Us study.
• Noninvasive markers for liver fibrosis and liver-related complications in hemochromatosis need further study to optimize cutoffs.
• Prediction of HCC in patients with hemochromatosis needs further study.
• Mini-hepcidin therapies are parenteral and do not mobilize storage iron. They reduce intestinal iron absorption and have been suggested to be used after iron depletion by venesections to reduce the need for maintenance therapy.
• Gene editing could eventually become a treatment of choice, but in the early days of gene therapy, it is more likely to be tried in diseases without adequate treatments and more severe complications.

HCC, hepatocellular carcinoma.

had a minor effect in reducing serum ferritin. Iron supplementation of common foods by iron was a popular marketing tool in the 1950s, but removal of these supplements in Scandinavia has been studied with small effects on population health.[47] English tea with every meal can reduce iron absorption. There are several studies on the use of oral iron binding compounds that can reduce iron absorption.[48,49] Inhibition of gastric acid by proton pump inhibitors can also reduce iron absorption but not enough to manage a patient with hemochromatosis without phlebotomy.[50]

Therapies That May Reduce the Need for Maintenance Therapy

In our current understanding of the pathogenesis of iron overload in hemochromatosis, hepcidin dysregulation plays a central role. For this reason, synthetic minihepcidin was developed as a parenteral therapy for hemochromatosis. However, it became apparent in animal models that hepcidin therapy did not mobilize excess liver iron but did decrease intestinal iron absorption.[51] Newer concepts of therapy have considered an initial period of phlebotomy to iron depletion followed by parenteral hepcidin injections to decrease the need for maintenance phlebotomy.[52,53] There are several potential flaws in the rationale for combination therapy. It assumes that patients or providers are dissatisfied with phlebotomy therapy. This is incorrect, and many patients enjoy phlebotomy treatment, including the psychosocial aspects of meeting other patients and families with hemochromatosis. There are many patients that will not require maintenance therapy. This is particularly true in young women who present with a serum ferritin <1000 μg/L. In 1991, a treatment study that did not offer maintenance therapy found that 52% did not have significant iron re-accumulation over a 4-year observation period.[54] Any study of an expensive biological hepcidin therapy would need to be compared with a phlebotomy group, and a cost analysis will always favor phlebotomy because a blood donation can be considered a benefit rather than a cost. A study group of no phlebotomy if ferritin does not rise above the reference range would help define the need for maintenance therapy.

Chelation Therapy

Deferasirox is the only oral iron chelator that has been studied in the treatment of hemochromatosis.[55] It is an oral therapy that has been approved for secondary iron overload associated with anemia. It has not been approved for the treatment of hemochromatosis. The study was difficult to recruit to, which suggests that most patients with hemochromatosis are satisfied with phlebotomy therapy or concerned regarding the potential side effects. Iron reduction was less efficient than with phlebotomy, and adverse effects were frequently reported. Chelators have rarely been used in combination with phlebotomy in life-threatening cases of hemojuvelin disease with cardiac dysfunction.

Summary

The diagnosis of hemochromatosis has evolved from the use of non-specific iron blood tests (serum ferritin) and tests with unreliable reproducibility (transferrin saturation) to simple genetic tests (C282Y test) and advanced imaging (MRI liver, elastography) (Table 2).

The treatment of hemochromatosis by phlebotomy has stood the test of time and is a very safe and cost-effective treatment. Biological therapies with minihepcidins or gene editing using CRISPR technology are on the horizon (Table 3) but must be tested against phlebotomy.

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Conflicts of interest
The authors disclose no conflicts.