REVIEW ARTICLE

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Hemochromatosis

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Hemochromatosis comprises a group of inherited disorders that can cause iron overload, which primarily affects the liver and joints and results from a failure in the regulation of the key liver-derived iron regulatory hormone hepcidin to respond to increasing iron stores.[1-3] Iron overload also occurs in transfusion-dependent and non–transfusion-dependent anemic disorders (e.g., thalassemia and myelodysplasia, respectively) and has been reviewed elsewhere[1-3]; iron overload caused by these disorders is no longer classified as hemochromatosis by the International BioIron Society.[1] Although the origins of hemochromatosis have been traced back to the Bronze Age,[4] the clinical sequelae have been characterized only since the beginning of the 19th century.[5-8] What has become apparent over the past 20 years is the heterogeneous clinical expression of hemochromatosis, including sex differences, as well as the nonspecificity of standard serum ferritin levels and transferrin saturation, resulting in diagnostic challenges (Fig. 1). This review focuses on hemochromatosis as currently defined, summarizes the literature, and provides an integrated approach to managing hemochromatosis.

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EPIDEMIOLOGY

Hemochromatosis is caused by several genetic disorders, the majority of which result in loss-of-function mutations in regulatory components of hepcidin synthesis (Table 1).[21] The cause of 95% of cases of hemochromatosis is a homozygous mutation in *HFE* (hemostatic iron regulator; chromosome 6p22.2, exon 4, c.845G→A, rs1800562), which results in a p.C282Y substitution and is termed HFE hemochromatosis (hereafter referred to as hemochromatosis).[2,11,12,21] This disorder affects approximately 1 in every 150 to 220 persons of northern European descent.[12,15,16,21,22] Simple heterozygosity for p.C282Y affects 1 in 7 persons, and the more minor p.H63D variant in *HFE* affects 1 in 3 persons of northern European descent.[1,12,21] Simple or compound heterozygosity for the p.C282Y and p.H63D variants or digenic inheritance of p.C282Y with another mutation in *HFE*, such as p.S65C, may cause mild elevations in serum transferrin saturation or ferritin levels but not clinically significant iron overload.[11,12,15-17] Pathogenic variants in genes encoding hemojuvelin, hepcidin, transferrin receptor 2, or ferroportin are rare and may cause non-HFE hemochromatosis (Table 1).[1] All are inherited in an autosomal recessive manner, with the exception of ferroportin mutations, which are autosomal dominant.

BIOCHEMICAL MANIFESTATIONS

Hemochromatosis may be characterized by elevations in serum transferrin saturation, ferritin levels, or hematologic measures.[21,23,24] Since iron-related laboratory measurements vary, a sustained elevation must be documented on multiple occasions. The earliest manifestations of hemochromatosis are elevations in serum

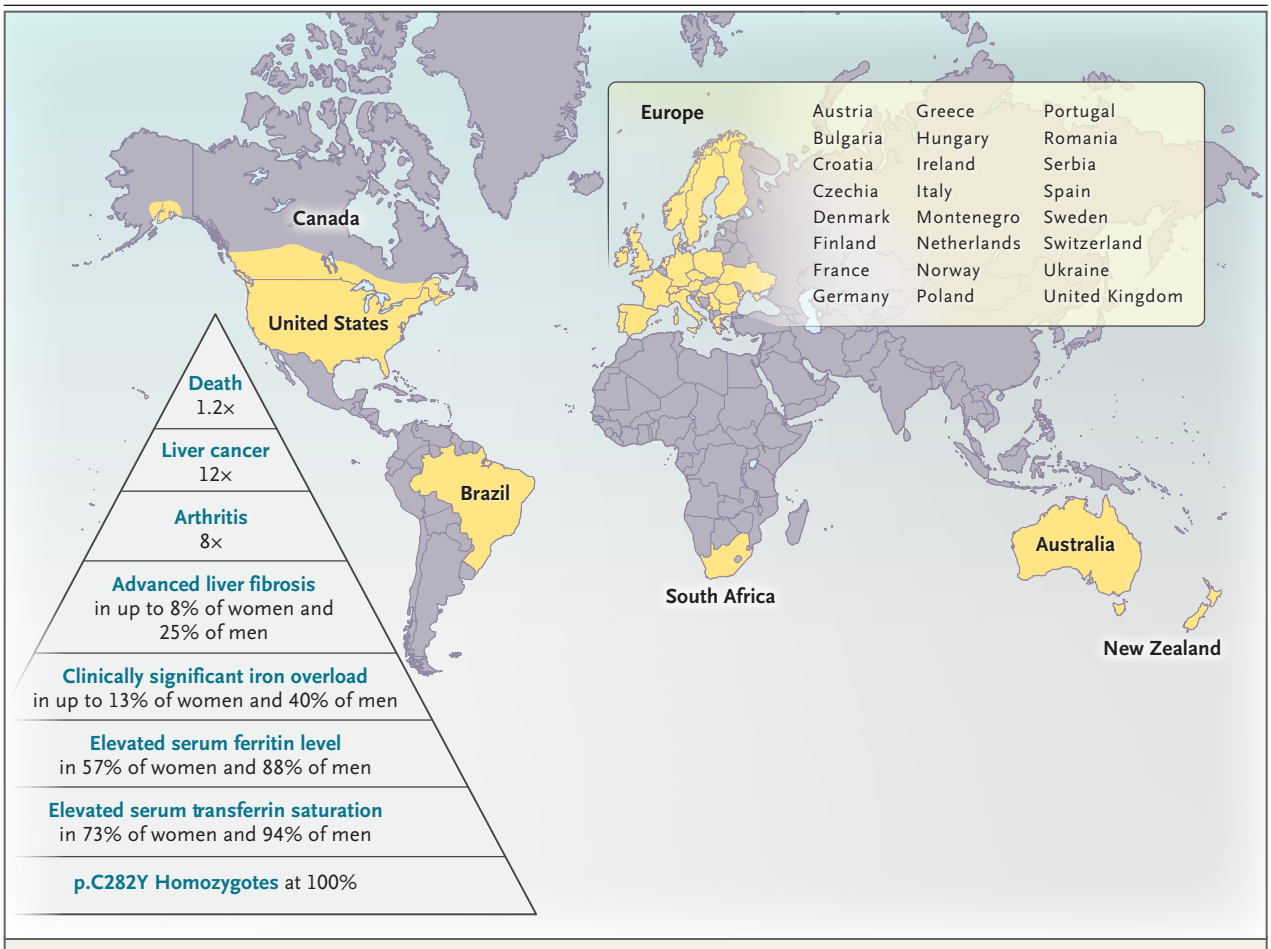

Figure 1. Global Distribution Heat Map and Spectrum of Expression of Hemochromatosis Due to *HFE* Mutation.

Although cases of hemochromatosis associated with *HFE* mutation were classically observed in the regions highlighted in yellow, global migration has distributed the disease more broadly, and it should be suspected in any person of northern European background. The data in the pyramid reflect the manifestations that would be expected in a cohort of persons with hemochromatosis. The increased risks of death and liver cancer are based on a comparison with an age- and sex-matched population of persons without *HFE* mutations. The risk of death is increased for men but not for women, on the basis of U.K. Biobank data[9]; the risk of liver cancer is also increased only for men. The risk of the typical arthropathy of hemochromatosis is increased by a factor of 8 for men and women, as compared with the risk among persons without *HFE* mutations.[10] Advanced liver fibrosis (defined as Scheuer fibrosis stage F3 or F4 [with stages ranging from F0 to F4, with higher stages indicating more clinically significant fibrosis] on liver biopsy) develops in up to 8% of women and 25% of men with hemochromatosis.[2,11-14] Clinically significant iron overload disease develops in up to 13% of women and 40% of men.[12,15-19] Serum ferritin levels are elevated above 300 μg per liter in 88% of men and above 200 μg per liter in 57% of women.[15] Serum transferrin saturation is elevated at 45% or higher in 94% of men and 73% of women.[12,15,20]

transferrin saturation, mean red-cell hemoglobin level, and red-cell volume.[23,24] These changes precede an elevation in the serum ferritin level.[2,13,21,23,24] The greatest abnormalities occur in persons who are homozygous for p.C282Y, followed by compound heterozygotes for p.C282Y and p.H63D, homozygotes for p.H63D, and simple heterozygotes, with men being affected to a greater extent than women.[11-13,15,23,25,26]

An elevation in transferrin saturation (45% or higher) has a sensitivity of 94% in men and 73% in women for the detection of p.C282Y homozygosity.[12,15,20] A serum ferritin level above 300 μg per liter in men has a sensitivity of 88%, and an elevation above 200 μg per liter in women has a sensitivity of 57%.[15] A transferrin saturation of less than 45%, combined with a serum ferritin level within the reference range, has an overall negative predictive value of 97% for men and women combined.[12,20] Approximately 8% of

Table 1. Classification of Hemochromatosis According to the Molecular Target.*

Variable	HFE Hemochromatosis	Non-HFE Hemochromatosis	
Molecular target	*HFE*	Genes encoding HJV, hepcidin, or TfR2	Gene encoding ferroportin
Frequency	Common; often due to p.C282Y homozygosity; in rare cases, due to compound heterozygosity	Very rare	Very rare
Population at risk	Northern European origin	Any population	Any population
Age group at clinical risk	Adults	Persons <30 yr of age (with HJV or hepcidin as target), or adults (with TfR2 as target)	Adults
Mechanism	Loss of function of target	Loss of function of target	Gain of function of target, resistance to hepcidin
Hepcidin production	Reduced	Reduced	Increased

* The classification is from Girelli et al.[1] HFE hemochromatosis is caused by mutation of *HFE* (most often the homozygous p.C282Y mutation), whereas non-HFE hemochromatosis is caused by mutation of the genes encoding hemojuvelin (HJV), hepcidin, transferrin receptor 2 (TfR2), or ferroportin.

p.C282Y homozygous women and 44% of p.C282Y homozygous men have serum ferritin levels above 1000 μg per liter, the threshold above which morbidity is significantly increased.[1,13,16,21,27] A limitation of using the serum ferritin level to detect p.C282Y homozygosity is that the level is also elevated in up to 40% of persons who have neither *HFE* variants nor iron overload, which most likely reflects the effect of obesity on serum ferritin values.[12,15,16,22,28] In p.C282Y homozygotes, there is a correlation between serum ferritin levels and body iron stores, as judged on the basis of the liver iron concentration, but serum ferritin levels are not correlated with the liver iron concentration in persons without hemochromatosis.[29] Thus, in the absence of known p.C282Y homozygosity or a secondary disorder of iron overload,[1,2,21] an elevated serum ferritin level is not proof of iron overload.

An elevation in the mean red-cell volume above 94 fl would identify 34% of all men and 62% of all women with hemochromatosis, an increase by a factor of more than 30, as compared with general population screening.[23,24] However, 4% of the general population has a mean red-cell volume above 94 fl; of these persons, 96% do not have p.C282Y homozygosity.[2,23,30] The main clinical advantage of this method of detection is that it provides additional screening benefits for the full blood examination.

SCREENING

General population screening for hemochromatosis has not been recommended because of variable and incomplete penetrance and lack of any proof of a resulting survival advantage.[2,13,30,31] However, a recent report on the U.K. Biobank study, which showed significantly increased mortality among men who were homozygous for p.C282Y as compared with men who did not have *HFE* variants, supports a reexamination of the usefulness of screening in susceptible male populations.[9] Screening is indicated in first-degree relatives of probands and is discussed in more detail below.[2,13]

CLINICAL MANIFESTATIONS

Our understanding of hemochromatosis has evolved since the original descriptions by Trousseau and von Recklinghausen.[32-34] Clinical cohort studies have shown significant morbidity and mortality.[6-8] Patients without advanced liver fibrosis were shown to have survival equivalent to that for healthy age- and sex-matched controls.[5,6] Simon and colleagues showed that hemochromatosis is inherited in an autosomal recessive fashion, in tight linkage disequilibrium with the HLA complex on chromosome 6p,[8,35] with the subsequent discovery of *HFE* by Feder et al.[36]

Homozygosity for p.C282Y causes disruption

of a disulfide bond and the conformation of HFE, affecting its interaction with β_2-microglobulin,[37] transferrin receptor 2, bone morphogenic protein receptor, and hemojuvelin.[21,38] The importance of this complex interaction became apparent with the discovery of hepcidin, the key liver-derived negative regulator of iron absorption from the gastrointestinal tract and iron release from body iron stores.[39,40] Hepcidin regulates iron release from cells by binding to its ligand, the key iron export protein ferroportin, which results in internalization and degradation of ferroportin.[41] Mutant HFE, hemojuvelin, transferrin receptor 2, and hepcidin lose the ability to up-regulate hepcidin synthesis, causing low serum hepcidin levels and providing the connection between the genetic mutations and the pathogenesis of iron overload (Fig. 2).[21,38,42,43] The extremely rare ferroportin gain-of-function cause of non-HFE hemochromatosis results in hepcidin resistance and increased hepcidin levels (Table 1).[1,21]

After the discovery of *HFE*,[36] population studies showed variable biochemical and clinical manifestations, which may not be progressive.[12,15,16,22] Cross-sectional cohort studies involving participants older than 85 years of age suggested that p.C282Y carriage was not associated with increased mortality.[44-47] However, a recent longitudinal population study has shown that men, but not women, who are homozygous for p.C282Y have a significantly increased mean risk of death by the age of 75 years, as compared with those who do not have *HFE* variants (19.5% vs. 15.1%).[9] This increased risk was not observed among persons with compound heterozygosity for p.C282Y and p.H63D or in those with simple heterozygosity.[9,16,17,48] Men and women who were homozygous for p.C282Y had an increased risk of sarcopenia, frailty, and chronic pain after the age of 60 years, as compared with persons who were not homozygous for the p.C282Y mutation, although the risk was higher among men than among women.[49] Among men but not women, homozygosity for p.C282Y was associated with an increase by a factor of 1.8 in the risk of dementia and delirium, as compared with an absence of *HFE* variants.[18]

Homozygosity for p.C282Y is associated with complications in up to 40% of men and 13% of women.[12,15-17,19,50] The variable biochemical and clinical penetrance is most likely due to multiple genetic and environmental modifiers of iron bioavailability, transport, and loading.[51] Men are likely to be at higher risk than women because of the absence of the protective effects of menstruation and pregnancy[52] or hormone-related differences in iron absorption.[53] Symptoms are nonspecific and often equally prevalent among persons with and those without hemochromatosis.[16,22] The most common symptom, fatigue, is observed primarily in men with serum ferritin levels that are higher than 1000 μg per liter.[16]

The most frequent clinical manifestations are liver disease (advanced liver fibrosis or cirrhosis and primary liver cancer) and arthritis.[1,2,5,6,13] Oxidative stress–related tissue injury is responsible for the pathogenesis of the disease.[21,54] Among men but not women, the risk of liver disease is significantly increased, by a factor of 4.3, for p.C282Y homozygotes as compared with men who do not have *HFE* variants[17]; the risks of arthritis and colorectal cancer are doubled,[17,55] and the risks of pneumonia and diabetes mellitus are increased by a factor of 1.5.[17] Among women who are homozygous for p.C282Y, the risks of colorectal cancer and breast cancer are doubled[55] and the risk of arthritis is increased by a factor of 1.3, as compared with women who do not have *HFE* variants.[17] Although it is not clear whether the predispositions to colorectal and breast cancers are *HFE*- or iron-related, epidemiologic observations indicate that iron elevation is a risk factor for breast cancer.[56]

LIVER DISEASE

Advanced liver fibrosis or cirrhosis (Scheuer fibrosis stage F3 or F4 [with stages ranging from F0 to F4, with higher stages indicating more clinically significant fibrosis] on liver biopsy, respectively; hereafter termed advanced liver fibrosis)[14] is rare in persons under the age of 45 years who do not have other liver disorders; it occurs in about 8% of women and 25% of men with hemochromatosis.[2,11-13,57] Risk factors include excessive alcohol consumption, diabetes mellitus, arthritis, serum ferritin levels exceeding 1000 μg per liter, platelet levels of less than 200×10^9 per liter, elevated aspartate aminotransferase (AST) levels, a liver iron concentration greater than 200 μmol per gram, and total mobilizable iron stores on therapeutic phlebotomy of more than 9.6 g.[19,20,27,57-59] Men who are homozygous for p.C282Y have a lifetime risk of primary liver cancer that is 12 times as great

as the risk in men who do not have *HFE* variants (7.2% vs. 0.6%).[9] There is no significant association between p.C282Y homozygosity and liver cancer in women.[9] Patients with advanced liver fibrosis are at greatest risk for primary liver cancer (hepatocellular carcinoma or cholangiocarcinoma)[5,6,60] and should undergo routine cancer surveillance with liver ultrasonography at 6-month intervals. Surveillance is generally long-term, since the risk of hepatocellular carcinoma persists while cirrhosis persists.[1,2,13,21] Regression of advanced liver fibrosis to Scheuer stage F2 or lower has been associated with a significant reduction in the long-term risk of hepatocellular carcinoma, although the majority of cases of cirrhosis persist after treatment.[60] When such regression has been proved, clinicians may consider cessation of surveillance for hepatocellular carcinoma. Serum iron levels at the upper end of the reference range, but in the absence of iron overload, have been reported to be a risk factor for primary liver cancer, supporting a direct role of iron in carcinogenesis.[56] Furthermore, therapeutic phlebotomy significantly reduces the risk of cancer, adding further credibility to the role of iron in the development of cancer.[61]

ARTHRITIS

Hemochromatosis-related arthritis was first described in 1964.[62] It affects at least 24% of persons and is a major cause of disability and reduced quality of life.[10,63] Classically, arthropathy affects the metacarpophalangeal joints, followed by the hip, ankle, radiocarpal, elbow, shoulder, and knee joints, as well as the lumbar spine.[10,63] It can be challenging to discriminate between hemochromatosis-related arthropathy and degenerative osteoarthritis (also known as type 1 polyarticular osteoarthritis).[10] Type 1 polyarticular osteoarthritis, characterized by Heberden's or Bouchard's nodes with prominent interphalangeal joint, knee joint, and great toe metatarsophalangeal joint involvement, occurs just as often in patients with hemochromatosis as in those without the disorder.[10] However, type 2 polyarticular osteoarthritis, characterized by arthropathy of the second to fifth metacarpophalangeal joints or bilateral large-joint arthropathy (involving radiocarpal, elbow, hip, knee, or ankle joints), is 8 times as common in patients with hemochromatosis as in those without the disorder.[10] It is unclear why arthropathy affects only a subgroup of people with hemochromatosis. Arthritis may occur at any point during the natural history of hemochromatosis, even after successful therapeutic phlebotomy.[2,10] Risk factors for arthritis include increased age, advanced liver fibrosis, serum ferritin levels exceeding 1000 μg per liter, and serum transferrin saturation above 50% for at least 6 years.[64,65] Persons with hemochromatosis and arthritis have a significantly higher mean red-cell volume than those who have hemochromatosis without arthritis or who have other forms of arthritis (e.g., rheumatoid arthritis or osteoarthritis) in the absence of *HFE* variants.[66]

Liver disease and arthritis tend to occur concomitantly. Hemochromatosis-related arthritis is more likely with a higher iron load or more advanced liver disease.[67,68] A recent study involving patients with well-characterized hemochromatosis clearly showed that arthritis was strongly associated with advanced liver fibrosis; 84% of the study participants with Scheuer stage F3 or F4 fibrosis had arthritis.[58] Thirty-four percent of the study participants with arthritis had Scheuer stage F3 or F4 fibrosis, whereas only 5% of participants without arthritis had F3 or F4 fibrosis. The absence of arthritis had a 95% negative predictive value for advanced liver fibrosis.

OTHER CLINICAL MANIFESTATIONS

A variety of other conditions occur with hemochromatosis, including hyperpigmentation, diabetes mellitus, hypogonadotropic hypogonadism, and cardiomyopathy.[2,13,17,21] Persons with hemochromatosis are also at increased risk for infection with *Vibrio vulnificus* and opportunistic organisms.[69] These conditions are usually managed according to the standard of care and in addition to the usual treatment of iron overload. Cardiomyopathy is one of the rare complications that is potentially reversible with iron-removal therapy.[34]

RECOMMENDED APPROACH TO CLINICAL ASSESSMENT

There are three common scenarios in which a clinical assessment for hemochromatosis should be performed: a positive family history in the absence of symptoms; elevated serum transferrin saturation, ferritin levels, or aminotransferase levels in the absence of symptoms; or the presence of symptoms (Fig. 3).[2,13,21]

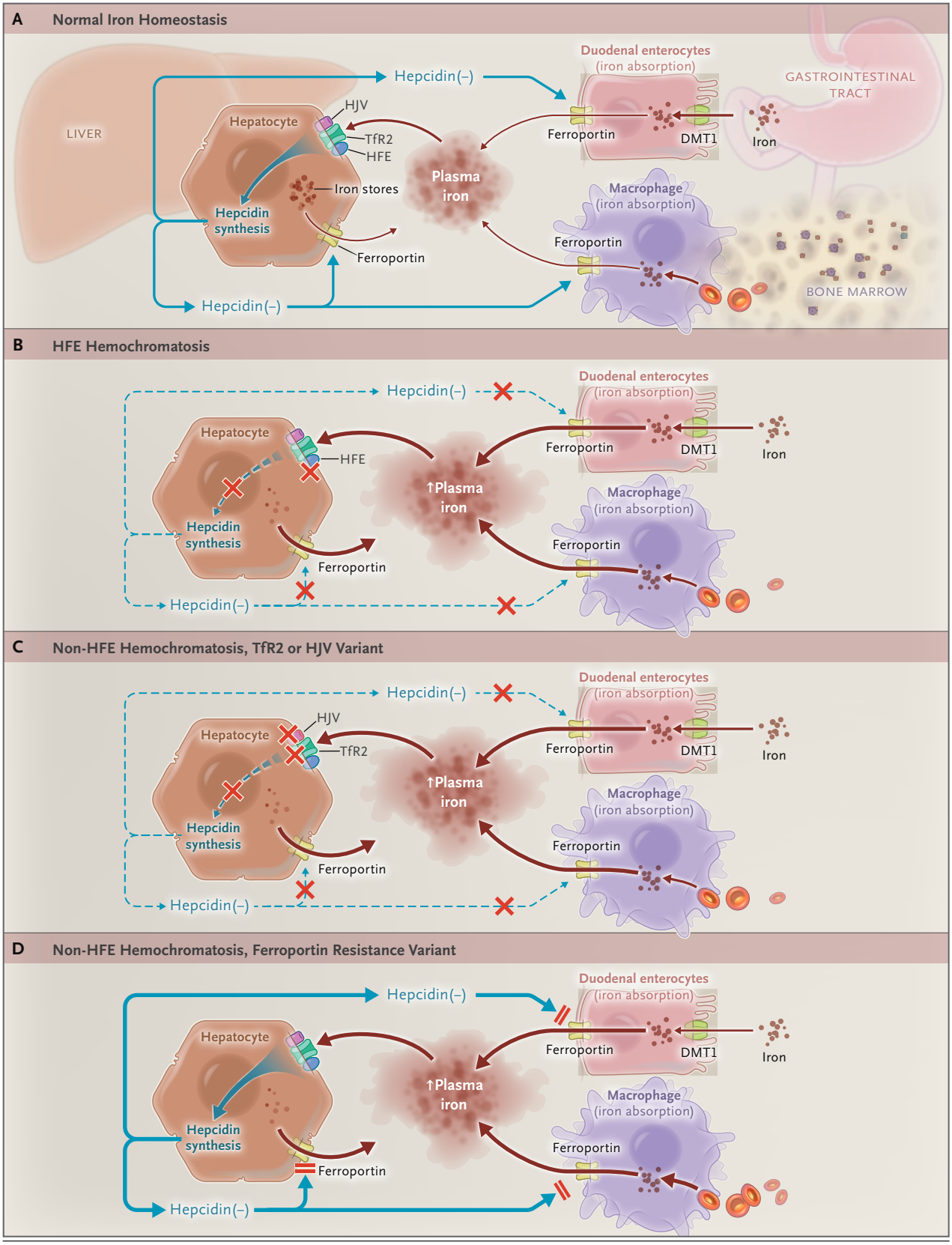

Figure 2 (facing page). Mechanisms Underlying Iron Overload Due to Hemochromatosis.

Iron is normally stored in the liver and bone marrow (Panel A). Absorption of orally ingested iron from the gastrointestinal tract occurs in the duodenum. Hepcidin regulates absorption of iron from the duodenum through negative regulation of the iron-export protein ferroportin. Hepcidin production is regulated by iron stores in the liver and signaling involving the HFE, hemojuvelin (HJV), and transferrin receptor 2 (TfR2) proteins. Increased production of hepcidin in response to iron results in a reciprocal reduction in iron absorption. In HFE hemochromatosis (Panel B), the absence of HFE leads to a loss of iron-regulated hepcidin production, reduced serum hepcidin levels, and consequential failure of ferroportin down-regulation and iron absorption. As a result, iron absorption is inappropriately increased. The absence of hepcidin also results in loss of iron from bone marrow stores. In non-HFE hemochromatosis due to an absence of TfR2 or HJV, there is a similar loss of iron-regulated hepcidin production (Panel C). In rare cases, non-HFE hemochromatosis is due to mutations in ferroportin, which cause ferroportin to resist the negative regulatory effects of hepcidin (the parallel red lines indicate resistance to hepcidin binding), resulting in inappropriately increased iron absorption from the duodenum, even when hepcidin levels increase appropriately in response to increasing liver iron levels (Panel D). The thickness of the arrows indicates the relative changes in iron flux among the gastrointestinal tract, blood, liver, and bone marrow. DMT1 denotes divalent metal transporter 1.

ASYMPTOMATIC PERSONS WITH A POSITIVE FAMILY HISTORY

For children of a known p.C282Y homozygote who are under 18 years of age, the accepted approach is to obtain the genotype of both parents, since disease onset before 18 years of age is extremely rare.[2,13,70] If one of the parents does not have the p.C282Y mutation, there is no risk of p.C282Y homozygosity in the offspring.[2,70,71] For persons who are 18 years of age or older or if genotyping of parents is not available, genetic testing should be undertaken at the earliest convenience to detect p.C282Y homozygosity (associated with a high risk of iron overload), compound heterozygosity for p.C282Y and p.H63D (associated with a low risk of iron overload), or simple heterozygosity for p.C282Y or p.H63D (indicating no increase in the risk of iron overload). Serum transferrin saturation and ferritin levels should be measured only in high-risk and low-risk patients; if values are elevated, further workup should proceed as described below for the clinical workup in symptomatic persons. If serum ferritin levels are not elevated, a repeat measurement should be performed in 5 years to detect progression.[2,13] In p.C282Y homozygous persons who are 55 years of age or older and have serum ferritin levels within the reference range, surveillance can cease, since it is highly unlikely that iron overload would ever evolve.[72] In women, serum ferritin levels generally plateau 10 to 20 years after menopause, at values that do not exceed 400 μg per liter, a level too low to result in disease.[52] Homozygotes for p.C282Y should be given advice concerning screening of first-degree relatives and standard-of-care surveillance for colorectal and breast cancer.[55,70]

ASYMPTOMATIC PERSONS WITH ELEVATED IRON-RELATED LABORATORY MEASUREMENTS

Serum transferrin saturation, ferritin levels, or aminotransferase levels are commonly elevated in the general population. Elevated serum transferrin saturation and ferritin levels are observed in up to 6% and 40% of adults, respectively.[12,15,16,22,28] Up to 14% of adults have elevated serum alanine aminotransferase (ALT) levels.[73,74] For persons of northern European ancestry who have elevated serum transferrin saturation or ferritin levels, the most appropriate investigation is testing for p.C282Y, as described above (Fig. 3). For persons with abnormal aminotransferase levels, serum transferrin saturation and ferritin levels should be measured. If values are elevated, persons of northern European ancestry should undergo genetic testing for p.C282Y. Those who are found to be homozygous for p.C282Y, as well as persons who are not of northern European ancestry but who have elevated serum transferrin saturation and ferritin levels, should be evaluated as described in the following section. It is rare to find clinically significant iron overload in persons of northern European ancestry who have elevated serum transferrin saturation or ferritin levels in the absence of p.C282Y homozygosity.[29]

SYMPTOMATIC PERSONS

Assessment should be undertaken to determine the risk of end-organ damage, especially liver disease and arthritis. Risks of arthritis, advanced liver fibrosis, and the subsequent development of primary liver cancer increase with progressive iron loading, particularly when the serum ferritin levels exceed 1000 μg per liter (Fig. 3). Hemo-

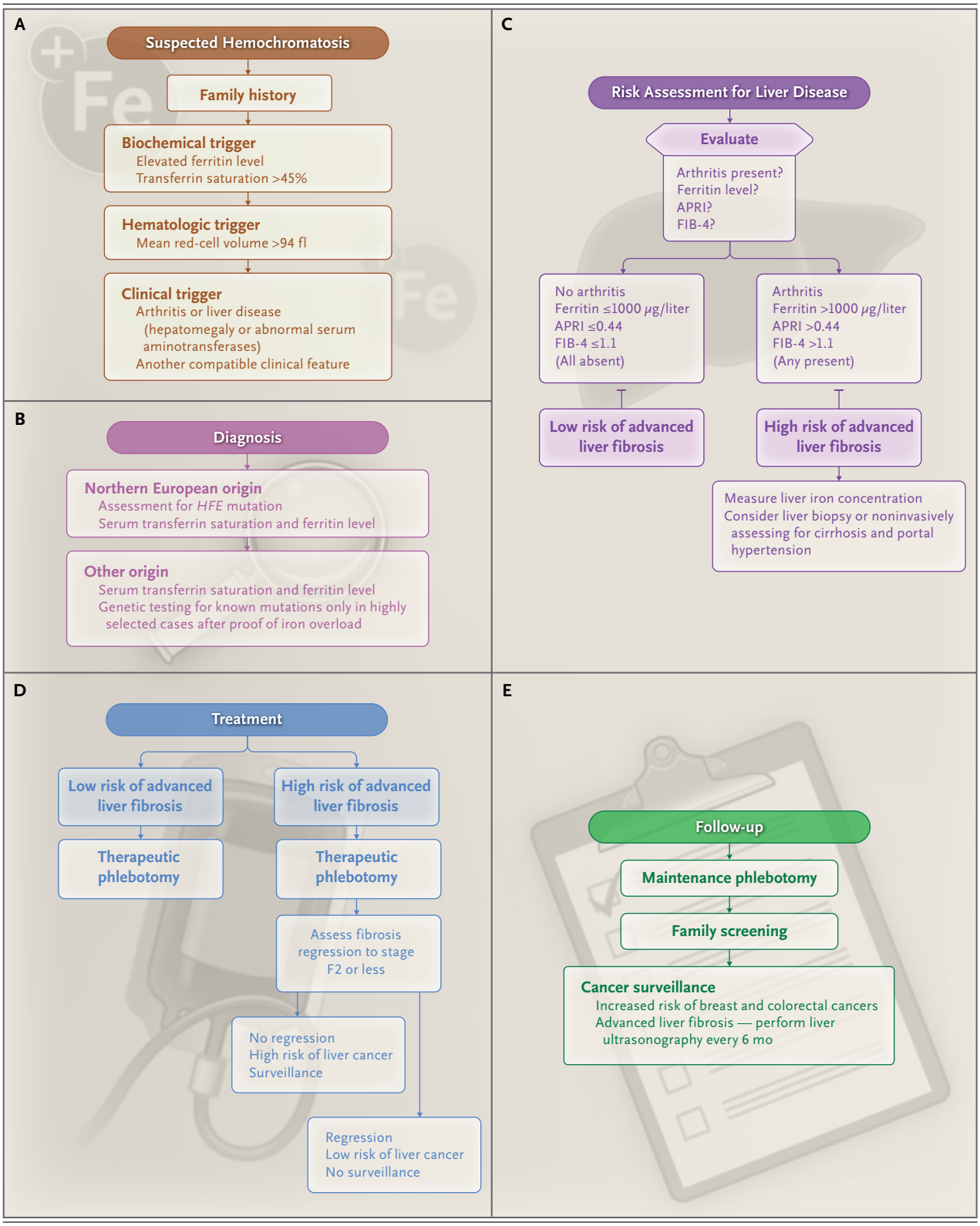

Figure 3 (facing page). Recommended Key Steps in the Clinical Evaluation of Hemochromatosis.

The steps describing when to suspect hemochromatosis are shown in Panel A, how to diagnose hemochromatosis in Panel B, and how to assess for liver disease in Panel C. Panel D shows treatment, and Panel E shows follow-up. The risk of colorectal cancer is twice as high among persons who are homozygous for p.C282Y as among those who do not have *HFE* variants; the risk of breast cancer is twice as high among women who are homozygous for p.C282Y. APRI denotes aspartate aminotransferase–to-platelet ratio index, and FIB-4 Fibrosis-4 index.

chromatosis-related arthritis is a very useful clinical predictor for the presence of advanced liver fibrosis, as noted above.[58,67,68] For persons who are homozygous for p.C282Y and have additional risk factors for liver disease, an assessment for liver disease at lower ferritin values may be warranted.[2,13] Quantitation of the liver iron concentration and assessment of the stage of liver fibrosis are critical in assessing the risk of advanced liver fibrosis and primary liver cancer and should be routinely performed in all persons who have serum ferritin levels exceeding 1000 μg per liter or arthritis or who are otherwise judged to be at risk because of additional factors, including unexplained hepatomegaly and elevated serum aminotransferase levels.

Quantitation of the liver iron concentration aids in predicting the risk of fibrosis. Historically, quantitation was undertaken invasively by means of liver biopsy, but more recently, reliable methods of noninvasive measurement have been described.[1,2,13,20,75] Practical noninvasive methods include retrospective calculation of the iron removed on the basis of the number and volume of therapeutic phlebotomies undertaken to reduce the serum ferritin level to 50 to 100 μg per liter[13] and magnetic resonance imaging (MRI). Several MRI techniques for estimating liver iron deposition and correlations with biochemical measurements in liver-biopsy specimens have been described.[76-80] Allowing for substantial heterogeneity of iron deposition within the liver and the attendant limitations of comparing biopsy-based methods of assessment with imaging methods,[77,81,82] MRI provides good clinical value for quantification of iron overload[2,76,77] and is also accurate for quantification of myocardial iron deposition.[83] Of the published MRI methods for measuring the liver iron concentration, only that described by St. Pierre et al.[77] has been approved for human use by regulatory authorities in the United States, Europe, and Australia. The liver iron concentration can also be measured biochemically after liver biopsy.[1,2,11,13]

Advanced liver fibrosis can be detected by means of liver biopsy or noninvasive approaches, and an assessment for advanced fibrosis is critical in determining the prognosis and the risk of hepatocellular carcinoma. Validated noninvasive approaches include serum biomarker panels and elastography.[84,85] The AST-to-platelet ratio index (APRI), calculated as (AST ÷ the upper limit of the normal range) × 100 ÷ the platelet count, and the Fibrosis-4 index, calculated as (age × AST) ÷ (platelet count × $\sqrt{\text{ALT}}$), accurately detect liver-biopsy–diagnosed advanced liver fibrosis in patients with hemochromatosis, with an accuracy of more than 80%; the APRI is useful for monitoring fibrosis regression during treatment.[84] Hepascore (an algorithm based on age; sex; and serum levels of bilirubin, α_2-macroglobulin, hyaluronic acid, and γ-glutamyltransferase) and transient elastography were shown in a recent study to be limited in their clinical usefulness, since they underdiagnose advanced liver fibrosis, except in persons with serum ferritin levels that exceed 1000 μg per liter.[85] If judged to be clinically appropriate, liver biopsy may be recommended for a definitive diagnosis in persons with serum biomarker values that are consistent with advanced liver fibrosis.[2,13] All persons with advanced liver fibrosis are at high risk for primary liver cancer and require cancer surveillance.[1,2,5,13,60]

TREATMENT

Treatment has been shown to result in clinical improvement in persons with hemochromatosis who have elevated serum ferritin levels.[2,13,86] The mainstay of treatment is phlebotomy; dietary restriction of iron intake offers little or no proven benefit in routine management.[1,2,13,87] Avoidance of raw seafood (to reduce the risk of infection with *V. vulnificus*) and reduction of alcohol consumption (to reduce the risk of advanced liver fibrosis) should occur in conjunction with phlebotomy treatment.[88] Therapy is divided into

treatment and maintenance phases. Treatment consists of weekly phlebotomy until a target serum ferritin level of 50 to 100 μg per liter is reached.[2,13] Thereafter, maintenance therapy is undertaken to stabilize the target serum ferritin level. Most often, this requires phlebotomy every three months, but the required frequency is highly variable and needs to be individualized. Currently, phlebotomy therapy is reserved for persons with elevated serum ferritin levels who have a proven iron overload disorder, polycythemia vera, or porphyria cutanea tarda.[89,90] There is no good evidence for the usefulness of phlebotomy treatment in persons with elevated ferritin levels that are due to other conditions, such as fatty liver disease.[91,92]

Treatment reduces fatigue, improves cognition,[86,93] and reduces liver fibrosis.[19,60,84,93] Improvements in patients with liver fibrosis occur across the spectrum of fibrosis.[19,60,84,93] Cirrhosis regresses with adequate phlebotomy therapy in up to 23% of persons, with 18% having regression to a Scheuer stage of F2 or lower, a level associated with a significant reduction in the long-term risk of primary liver cancer.[60] There is no clear evidence that phlebotomy therapy reduces the risk of primary liver cancer, alleviates established arthritis, or is effective in treating diabetes mellitus secondary to hemochromatosis, if cirrhosis persists.[93]

For persons for whom routine phlebotomy therapy is associated with unacceptable adverse events, several alternatives exist. Erythrocytapheresis selectively depletes the red-cell mass, and fewer episodes of treatment are required than with routine phlebotomy.[94-96] Alternatively, chelation therapy may be considered.[97]

CONCLUSIONS

Hemochromatosis is a common disorder with variable clinical manifestations that differ between men and women. The disorder is associated with increased mortality among men. Timely clinical ascertainment through family screening and evaluation of persons with suggestive biochemical or clinical features will reveal disease at the earliest opportunity. All persons with hemochromatosis and elevated serum ferritin levels should receive treatment. The main causes of illness are liver disease and arthritis. Key advances in the delineation of arthritis and noninvasive biomarker panels for detecting advanced liver fibrosis provide new approaches for assessment. Persons with advanced liver fibrosis should receive treatment and undergo long-term surveillance for liver cancer. The risk of liver cancer is substantially reduced among patients with cirrhosis in whom fibrosis regresses to stage F2 or lower with treatment. All adults with hemochromatosis should be informed of the risk of breast or colorectal cancer and should receive appropriate screening advice.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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