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The critical role of early genetic diagnosis and phlebotomy treatment in preventing organ damage in hemochromatosis: modern diagnostic and therapeutic approaches

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ABSTRACT

Hemochromatosis, caused by the C282Y mutation in the HFE gene, is the most common inherited disorder of iron metabolism. Since there is no active iron excretion mechanism in the body, iron progressively accumulates in the liver, heart, pancreas and endocrine organs due to disorders in the hepcidin-ferroportin axis. The disease usually begins to show symptoms during the fifth decade of life, with the most common complaint being severe fatigue. If left untreated, hemochromatosis increases the risk of cirrhosis and hepatocellular carcinoma by around 20-fold. Transferrin saturation is considered together with ferritin elevation in diagnosis. Genetic testing targeting the HFE gene confirms the diagnosis and prevents unnecessary invasive interventions. In terms of measuring iron load in the liver, magnetic resonance imaging is the gold standard for non-invasive assessment. Therapeutic phlebotomy is still the cornerstone of treatment. Iron chelation therapy is the second option in cases where phlebotomy is contraindicated. Early diagnosis and treatment can prevent organ damage; however, late complications such as cirrhosis, hypogonadism, and arthropathy may be permanent. Hepcidin analogs and CRISPR technology are seen as promising treatment options in the future. With modern approaches, it is possible to detect the disease at an early stage and treat it effectively.

Keywords: Hereditary hemochromatosis, HFE gene mutation, phlebotomy, early diagnosis

INTRODUCTION

Hemochromatosis was first described as “bronze diabetes” by Armand Trousseau in 1865; later von Recklinghausen showed that this condition was associated with iron accumulation in the liver.[1,2] In 1935, Sheldon[3] demonstrated that the disease was a familial metabolic disorder. The first clue at the genetic level was identified in 1976 with the association with the HLA-A3 antigen,[4] and in 1996 it was shown that the C282Y mutation in the HFE gene was the main cause of the disease.[5] Today, as a result of these historical developments, hemochromatosis can be identified at an early stage through genetic tests, and periodic phlebotomy is an effective intervention that can prevent organ damage.[6]

Iron homeostasis is maintained by the balance between intestinal absorption, reticuloendothelial recycling, and limited physiological losses.[7,8] The reticuloendothelial system also supports iron levels by recovery from aging erythrocytes.[9] Losses through gastrointestinal epithelial turnover, dermal desquamation, and menstruation are minimal.[10] Since there is no active iron excretion mechanism in the body, systemic iron load is mainly regulated at the level of absorption via the hepcidin-ferroportin axis.[11] Disturbances in this regulatory system can cause a variety of clinical conditions ranging from iron deficiency anemia to iron overload syndromes such as hereditary hemochromatosis.[12] Hepcidin is a 25-amino acid peptide hormone synthesized in the liver and is the central regulator of this process.[11] Hepcidin binds to the ferroportin protein and withdraws iron transporters from intestinal enterocytes and macrophages, reducing absorption.[11] Hepcidin increases when iron stores are full (or in the presence of inflammation) and decreases in surgical blood loss, iron deficiency, or intensive erythropoiesis.[7]

Disruption in hepcidin levels constitutes the basic pathogenetic mechanism of hereditary hemochromatosis and other iron overload syndromes.[11] Mutations in the HFE, HJV, TFR2 and SLC40A1 genes either reduce hepcidin synthesis or prevent the action of hepcidin on ferroportin.[2] This leads to uncontrolled iron absorption from the intestines and excessive iron accumulation in the tissues. In cases of secondary hemochromatosis, hepcidin production is suppressed as a result of increased erythropoietic activity

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due to repeated erythrocyte transfusions (e.g. thalassemia intermedia) or impaired hepatocyte function in chronic hepatic diseases. As a result, hepcidin decreases, ferroportin activation continues and systemic iron accumulation occurs.[8]

ETIOLOGY

The cellular distribution of iron accumulation in primary and secondary hemochromatosis shows important differences in terms of diagnostics and clinical progression. Primary hemochromatosis is genetic and is characterized by systemic iron accumulation due to mutations. It is classically examined in four main types. The most common form, type 1 hereditary hemochromatosis, occurs in homozygous C282Y mutations of the HFE gene and shows autosomal recessive inheritance.[7] The H63D variant in the HFE gene has lower penetrance and usually contributes to the clinical picture in heterozygous combinations. Type 2 (juvenile) hemochromatosis, which is less common, is due to mutations in the HJV (hemojuvelin) or HAMP (hepcidin) genes and typically begins in adolescence.[13] Type 3 is due to mutations in the TFR2 (transferrin receptor 2) gene and is also inherited in an autosomal recessive manner.[14] In this variant, the disease may occur at an earlier age compared to cases with HFE mutations. Type 4 hemochromatosis is the only inherited form that is inherited in an autosomal dominant manner and is associated with mutations in the SLC40A1 gene.[15] This gene encodes the ferroportin protein, which transports iron out of the cell. The mutations in this type, which is often referred to as "ferroportin disease", lead to loss of ferroportin function or hepcidin resistance.

Secondary hemochromatosis develops due to acquired rather than genetic causes. The most common etiological factor is repeated erythrocyte transfusions due to diseases such as thalassemia major, sickle cell disease, and myelodysplastic syndrome.[16-18] Each erythrocyte unit contains approximately 200–250 mg of iron, which leads to systemic iron accumulation in the long term.[19] In addition, conditions with ineffective erythropoiesis (e.g. thalassemia intermedia) suppress hepcidin production, increase iron absorption from the intestines, and may lead to iron overload without transfusion.[20] Although rare, factors such as a high-iron diet, excessive oral iron intake, or consumption of iron-rich groundwater may also contribute to secondary iron overload.[21]

EPIDEMIOLOGY

Type 1 primary hemochromatosis is the most common autosomal recessive disorder of iron metabolism, especially in individuals of Northern and Western European descent. The homozygous form of the C282Y mutation in the HFE gene is seen in approximately 0.4–0.5% (1/200–1/250) of the populations in this region, while heterozygous carrier rate varies between 10–14%.[22] In contrast, non-HFE forms such as type 2 (juvenile), type 3 (TFR2-related), and type 4 (ferroportin disease) are quite rare; their prevalence varies between 1/100.000–1/1.000.000, and are frequently associated with isolated mutation clusters of Mediterranean, Middle Eastern, and Asian origin.[23]

Hereditary hemochromatosis due to the HFE gene is quite rare in Turkiye. In an epidemiological study, C282Y homozygous mutation was detected at a rate of 0.043% and heterozygosity at a rate of 2.5%. In the same study, H63D heterozygosity was detected in 24.1%, and it was reported that this variant was common but had low penetrance in the Turkish population.[24] Considering screening costs and the risk of creating "anxious healthy individuals", a national hemochromatosis screening program has not been implemented for the general population in any country. The optimal strategy today is targeted screening.

Sex is an important variable affecting clinical presentation. In women, menstrual blood loss can physiologically regulate iron balance among affected individuals, while in men, iron accumulation becomes symptomatic at an earlier age. Hereditary hemochromatosis is approximately 2–3 times more common in men than in women.[25]

PATHOPHYSIOLOGY

The Pathophysiology of Primary Hemochromatosis

The basic pathophysiological mechanism of primary hemochromatosis is the disruption of the hepcidin-ferroportin axis, which regulates systemic iron homeostasis. Under normal conditions, hepcidin, which is synthesized in hepatocytes, controls iron release from enterocytes and reticuloendothelial macrophages in the intestinal epithelium. Hepcidin interacts with ferroportin, allowing this protein to be removed from the cell membrane.[26] The C282Y mutation in the HFE gene reduces hepcidin production, leading to increased absorption of iron from the duodenum and uncontrolled release of iron from macrophages. This elevation overwhelms transferrin, resulting in non-transferrin-bound iron (NTBI) in the plasma.[27] Cellular damage caused by iron accumulation develops through the interaction of multiple pathophysiological mechanisms. These include oxidative stress, ferroptosis, inflammatory activation, hormonal dysfunction and immune suppression.[28] Increased reactive oxygen species cause damage to cell membranes, proteins and DNA. Ferroptosis is an important damage pathway especially in the liver and heart.[29]

The Pathophysiology of Secondary Hemochromatosis

Unlike hereditary forms, secondary hemochromatosis develops due to excessive iron intake or impaired erythrocyte turnover. The most common cause is repeated red blood cell transfusions in diseases such as thalassemia major, sickle cell disease or myelodysplastic syndrome.[16-18] The excess leads to accumulation of free iron (NTBI) and parenchymal organ damage. Another secondary loading mechanism is erythropoietic hemochromatosis, characterized by chronic erythropoietic stress and ineffective erythropoiesis. Ineffective erythropoiesis and chronic erythropoietin stimulation suppress hepcidin levels and increase intestinal iron absorption.[19]

Organ-Based Pathophysiological Effects

Although similar organ systems may be affected in primary and secondary hemochromatosis, the site of iron accumulation and the severity of damage are different. In the primary form, iron accumulates directly in parenchymal tissues such as the liver, pancreas, heart and endocrine organs, leading to severe damage in these tissues and a higher-paced progression.[30] In secondary hemochromatosis, iron is

primarily stored in the reticuloendothelial system (spleen, bone marrow, Kupffer cells). Parenchymal involvement develops later and is usually milder.[31]

Accumulation in hepatocytes eventually triggers fibrosis and micronodular cirrhosis. This process dramatically increases the risk of HCC. In some cohorts, the risk of HCC has been reported to be 20 times higher than in the general population.[32] The risk of developing cirrhosis is approximately 9-fold higher in individuals with HFE mutations.[33] Impairment of β-cell functions in the pancreas leads to decreased insulin secretion and the development of diabetes mellitus in around 40–50% of individuals with the homozygous C282Y mutation.[34] Iron overload not only reduces insulin secretion, but also increases insulin resistance. Pathological accumulation of iron in the heart tissue can lead to myocardial fibrosis, decreased contractility, and electrical conduction disorders.[35] Joint involvement leads to arthropathy that mimics degenerative joint diseases, but with calcium pyrophosphate dihydrate (CPPD) crystals in the synovial fluid.[36] Iron accumulation can lead to hormonal dysfunction in the pituitary, gonad, thyroid and pancreas. The most common endocrine disorder is hypogonadism, which can manifest with loss of libido, infertility, and amenorrhea.[37] Thyroid involvement can result in hypothyroidism.[38] More rarely, adrenal and parathyroid involvement can cause hypocortisolism or hypoparathyroidism.

DIAGNOSIS AND CLINICAL FINDINGS

Patients with hereditary hemochromatosis usually do not manifest with overt symptoms until middle age. Even if present at an early stage, the symptoms are not specific; most patients may live for years with only complaints such as chronic fatigue (70% of cases), weakness, and joint pain.[39] Due to these non-specific symptoms, diagnosis is often delayed, increasing the risks for organ damage. While the disease manifests in the fifth or sixth decade of life, in women, symptoms may be delayed due to regular blood/iron loss with menstruation.[40] The disease can be diagnosed at an earlier stage if there is a family history or if high ferritin/transferrin saturation is detected in routine blood tests.

Most patients develop hepatomegaly and high liver enzymes, especially in advanced cases.[41] Jaundice is usually absent in the early stage, but may occur in advanced disease. Abdominal pain, tenderness in the right upper quadrant, hepatomegaly and splenomegaly are common findings. Cirrhosis may develop in the long term.[42] When cirrhosis occurs, prognosis is worsened and the risk of developing HCC increases greatly. It has been reported that the lifetime probability of developing HCC can reach 20% in patients with hemochromatosis.[43]

Excessive iron may accumulate in the pancreas, especially in the islets of Langerhans, leading to the development of diabetes. Diabetes prevalence in patients with hemochromatosis varies between 20–50%,[34] which is particularly high in individuals with advanced liver involvement. Regular phlebotomy treatment can improve blood sugar control even after diabetes develops; however, insulin requirement may continue in advanced cases.[44]

Hyperpigmentation is an early and common symptom of hemochromatosis. This bronze discoloration, observed in 70% of patients, is especially evident in the face and arm areas exposed to the sun and is due to increased melanin and dermal iron accumulation.[45] Dryness, thinning, ichthyosiform rashes on the skin, and hair loss throughout the body, especially in the pubic region, may be observed. Spoon nails are a characteristic dermatological finding, especially seen on the thumb and index finger, and are detected in approximately half of patients with hemochromatosis.[46]

Hemochromatosis can lead to a specific arthropathy due to the accumulation of calcium pyrophosphate crystals in the joints and chondrocalcinosis, which is especially evident in the 2nd and 3rd metacarpophalangeal joints. This condition, which clinically mimics osteoarthritis, can affect large joints such as the knee, hip, and spine, in addition to the hand joints. Joint complaints, unlike many other findings of hemochromatosis, usually do not regress with treatment and may be permanent.[47] Chronic iron accumulation and decreased bone mineral density due to hypogonadism are frequently seen in patients with hemochromatosis; therefore, bone mineral density studies are recommended, especially in individuals older than 40 years.[48]

Dilated or restrictive cardiomyopathy in the heart muscle may also be observed, and might present with shortness of breath, edema, arrhythmia, and conduction disorders.[49] Cardiomyopathy due to hemochromatosis may be the first symptom in young patients, and in some series, 15% of cases were found to manifest with cardiac symptoms.[50] While phlebotomy treatment initiated early can partially reverse cardiac impact, the damage becomes permanent in the late period.

Iron accumulation can cause hypogonadism, diabetes, and hypothyroidism. The most common endocrine complication is hypogonadotropic hypogonadism of pituitary origin. It progresses with loss of libido, erectile dysfunction, and gynecomastia in men, while females present with menstrual irregularities. Testicular involvement can also cause primary hypogonadism.[51] Thyroid involvement increases the risk of hypothyroidism, while adrenal and parathyroid involvement are rare.

Osteoporosis is also a common problem in patients with hemochromatosis. Approximately one quarter of patients have significant osteoporosis and more than 40% have osteopenia.[52] This decrease in bone density is associated with hypogonadism and high iron overload, and when necessary, treatments that protect bone health should be planned.

The accumulation of iron in macrophages restricts anti-pathogen activity. The risk of infection against siderophilic bacteria increases in individuals with hemochromatosis.[53] In particular, pathogens such as *Vibrio vulnificus*, *Listeria monocytogenes* and *Yersinia enterocolitica* can multiply rapidly in iron overload.[54] Since *V. vulnificus* infections can be fatal after consumption of raw seafood, it is recommended to avoid these foods.[55]

Hemochromatosis can rarely affect the central nervous system and cause movement disorders such as chorea or tremor as a result of iron accumulation in the basal ganglia. Evidence for these impacts usually come from case reports, and therefore, it is evident that neurological complications are rare and most patients do not develop significant central nervous system involvement.[56]

Hemochromatosis can be confused with many clinical conditions, especially in patients presenting with elevated ferritin. Secondary causes of hemochromatosis (e.g. chronic transfusions, hemolytic anemias, ineffective erythropoiesis) should be distinguished from the primary form. In addition, conditions such as viral hepatitis (especially HCV), MASLD, alcoholic liver disease, and dysmetabolic hyperferritinemia can also increase ferritin levels.[57] Transferrin saturation is usually normal in these cases. Iron parameters, genetic tests, clinical history, and concomitant disease findings should be evaluated together for diagnosis.

LABORATORY FINDINGS

In case of suspected hereditary hemochromatosis, the first evaluation is made with serum transferrin saturation and ferritin levels. Transferrin saturation exceeding 50% in men and 40% in women suggests iron overload.[48] EASL guidelines accept a transferrin saturation above 45% as being indicative of hereditary hemochromatosis.[43] This threshold value can capture 97.9-100% of individuals with C282Y homozygous mutation.[58] Transferrin saturation is not always reliable in assessing iron accumulation in secondary hemochromatosis. Therefore, it should be evaluated together with ferritin levels and, if necessary, tissue iron measurements.

While ferritin is a biomarker reflecting intracellular iron stores, it is also an acute phase reactant. Therefore, ferritin levels may increase independently of iron overload in conditions such as inflammation, infection, liver diseases, malignancies and metabolic disorders. In the literature, it has been reported that only approximately 10% of patients with elevated ferritin levels have true iron overload.[6] Transferrin saturation below 45% and serum ferritin within the normal range have a negative predictive value of approximately 97% in excluding the possibility of significant iron overload.[40] Ferritin >300 µg/L in men and >200 µg/L in women and concurrent high transferrin saturation are suggestive of hereditary hemochromatosis and may necessitate genetic testing.[43]

In hemochromatosis, mild increases in ALT and AST levels are usually seen due to liver iron accumulation. These increases usually do not exceed 2 times the normal level.[57] It is notable that enzyme levels may further increase in advanced stages of the disease, especially with fibrosis or cirrhosis.[21] In adults with unexplained and persistent mild transaminase elevation, screening for hemochromatosis is recommended.

Owing to the impact of hemochromatosis on the pancreas and glucose intolerance, screening for diabetes is recommended in individuals suspected of having hemochromatosis. Erythrocyte lifespan may be shortened in patients with hemochromatosis due to hemolytic processes or frequent phlebotomy applications. This causes HbA1c to underestimate the mean glucose level.[59] Therefore, HbA1c may not be reliable in the diagnosis and follow-up of diabetes in individuals with hereditary hemochromatosis. It may be beneficial to prioritize direct measurement methods such as fasting glucose, fructosamine test and OGTT in this patient population.[60]

HFE gene mutation analysis is the basic confirmatory test for the diagnosis of hereditary hemochromatosis. The C282Y mutation is the most common cause, especially in individuals of Northern European origin, and is detected in homozygous form in more than 80% of cases.[61] The second most common mutation, H63D, usually contributes to the disease in the form of combined heterozygosity with C282Y. For this reason, it is recommended to perform HFE genetic testing in patients with high transferrin saturation and/or ferritin and to investigate C282Y and H63D mutations.[62] Detection of HFE mutation confirms the diagnosis of hereditary hemochromatosis, thus avoiding unnecessary advanced invasive procedures (such as liver biopsy). If there are no HFE mutations but clinical findings are strong, advanced analysis for rare genes such as TFR2, HAMP, HJV, and SLC40A1 can be considered.[23] However, in the adult population, diagnosis can be made only with the HFE test in >90% of cases.[63]

Hormonal evaluation should be performed in patients with high ferritin or iron overload. In men, morning total testosterone and LH/FSH levels should be checked; in women, menstrual status should be questioned and pituitary-gonadal axis tests should be performed if necessary. If there is clinical suspicion, thyroid function tests, fasting glucose and HbA1c should be added to the evaluation.

IMAGING MODALITIES

Magnetic resonance imaging (MRI) is the reference imaging method for quantitative and non-invasive evaluation of liver iron accumulation, especially since it avoids the need for invasive biopsy. Accumulation in organs such as the heart, pancreas and pituitary gland can also be detected.[64] MRI is used to determine the severity of iron accumulation even in genetically-diagnosed hereditary hemochromatosis and helps predict the risk of organ damage.[65] High iron accumulation in the liver and low iron accumulation in the spleen suggests primary hemochromatosis; accumulation in the spleen supports secondary causes.[66]

Echocardiography is the first-line imaging method for the evaluation of iron-related cardiomyopathies (dilated/restrictive) in hemochromatosis. The EASL 2022 guideline recommends that all patients with severe hemochromatosis who have symptoms of heart disease should undergo transthoracic echocardiography together with an ECG and, if necessary, support it with cardiac MRI (T2-MRI).[48] Cardiac MRI (T2-MRI) is important for early diagnosis and intervention, especially in juvenile cases.[67] Treatment initiated with early diagnosis can partially reverse cardiac dysfunction. Chest radiography may also provide supportive evidence for advanced heart failure findings.

Liver biopsy has been considered the "gold standard" for measuring liver iron in hemochromatosis for many years and is also considered the most sensitive method for determining the degree of tissue damage caused by iron.[68] Histological examination of liver tissue with Perls Prussian blue staining shows a classic iron distribution in hereditary hemochromatosis. Iron accumulation is seen predominantly in hepatocytes and also in bile duct epithelial cells, with minimal presence in some reticuloendothelial elements (e.g., Kupffer cells). This parenchymal iron accumulation pattern is typical of most cases of hereditary hemochromatosis and helps distinguish it from secondary iron overload.[69] In cases of transfusion-related hemosiderosis or chronic hemolytic anemia, iron accumulation occurs primarily in Kupffer cells, with limited involvement of hepatocytes. Thus, the presence

of iron primarily in hepatocytes on liver biopsy supports the hereditary form, whereas excessive iron in macrophages suggests secondary causes.[31]

The 2011 AASLD guideline recommended liver biopsy to assess the risk of cirrhosis in patients with hereditary hemochromatosis who have serum ferritin >1000 µg/L or elevated liver enzymes.[57] The EASL 2022 guideline recommends non-invasive methods such as transient elastography (Fibroscan), FIB-4 and APRI instead of routine biopsy.[48] In patients with very high ferritin levels, the degree of liver fibrosis is first investigated with these non-invasive tests. If advanced fibrosis/cirrhosis cannot be definitely excluded with non-invasive methods or if the results are contradictory, biopsy is indicated.[48] In modern management, liver biopsy is reserved for cases where the diagnosis of cirrhosis cannot be confirmed with clinical and non-invasive tests. The iron concentration and fibrosis score (e.g. METAVIR) obtained with biopsy are still valuable in determining the stage of the disease.[70]

Ferritin, transferrin saturation and/or HFE genetic testing is recommended for first-degree relatives of individuals diagnosed with hereditary hemochromatosis. The ACG, AASLD and EASL guidelines recommend genetic counseling and family screening.[40,48,57]

TREATMENT

The main treatment for primary hemochromatosis is regular therapeutic phlebotomy. Phlebotomy gradually depletes iron stores by removal of blood at intervals; this method is usually easy, cheap and extremely effective. During the induction phase, 450–500 ml of blood is taken at weekly intervals to reduce the ferritin level to ~50 µg/L. This level is then maintained with less frequent phlebotomies during the maintenance period (once a month or every few months).[71] In patients with high iron overload, it may take months to reach the target, and dozens of phlebotomies may be required.[72] Appropriately initiated early treatment is effective in preventing complications such as cirrhosis and HCC. Significant improvements in findings such as hyperpigmentation, insulin resistance and fatigue can be achieved with phlebotomy. However, advanced complications such as cirrhosis, hypogonadism, and arthropathy are often irreversible.[73]

Erythrocyte apheresis is an iron-reducing treatment method applied by selectively removing erythrocytes from peripheral blood and returning plasma, improving tolerability. Randomized controlled trials have shown that this method reduces serum ferritin levels more rapidly than conventional phlebotomy and reduces the total number of sessions.[74] In addition, in cases that do not respond to phlebotomy, erythrocyte apheresis combined with low-dose erythropoietin can be applied.[74]

Iron chelation is performed with drugs that chemically bind and remove accumulated iron in the body. This is a second-line treatment option, especially in cases of primary hemochromatosis where phlebotomy is contraindicated or intolerable.[40,72] In addition, in cases of secondary hemochromatosis due to transfusions (e.g. thalassemia major), chelation is the primary treatment method since phlebotomy cannot be applied.[75] Chelators such as deferoxamine (i.v./s.c.), deferasirox (oral), and deferiprone (oral) bind iron and increase its excretion via urine or feces. Due to potential toxicities, treatment should be carried out in experienced centers and with close biochemical monitoring.

Liver transplantation should be considered in patients with hemochromatosis who develop advanced fibrosis, cirrhosis, or HCC. Current data show that transplantation outcomes have improved significantly in this group. In a study covering the period 2003–2019, it was reported that 1- and 5-year survival rates in patients who underwent liver transplantation due to hereditary hemochromatosis were similar to the general transplant patient population.[76] Since the risk of HCC continues in the presence of advanced fibrosis or cirrhosis, screening with ultrasonography and AFP levels should be performed throughout life.

Hepcidin-based treatments (e.g. Rusfertide/PTG-300) and oral ferroportin inhibitors have emerged as alternative pharmacological options to phlebotomy in recent years. Hepcidin analogs have been shown to lower iron parameters and reduce the need for phlebotomy in phase 2 studies.[77] With genetic engineering approaches such as CRISPR/Cas9, HFE gene mutations have been successfully corrected in mouse models, with success in reducing iron accumulation in the liver.[78] Although these strategies have the potential for permanent treatment in the future, they have not yet been put into clinical practice. Currently, phlebotomy remains the standard treatment.

If left untreated, hemochromatosis can lead to progressive organ damage and serious complications such as cirrhosis and HCC. The main factors that determine prognosis are the presence of cirrhosis at the time of diagnosis, high ferritin levels, male sex, advanced age, alcohol use and concomitant metabolic diseases.[79] In patients diagnosed and treated at an early stage, the life expectancy is similar to healthy individuals; however, the risk of HCC and mortality is significantly increased in those presenting with cirrhosis. Therefore, iron-reducing treatment should be continued even in cirrhotic patients and regular HCC screening should be performed.[48]

CONCLUSION

Taken together, treatment of hemochromatosis is not limited to phlebotomy alone, but requires a holistic approach that includes patient education, lifestyle changes, and multidisciplinary follow-up.

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The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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REFERENCES

1. Trousseau A. Lectures on clinical medicine. vol 2. Lindsay & Blakiston; 1873.
2. Pietrangelo A. Non-HFE hemochromatosis. *Hepatology*. 2004;39(1):21-29. doi:10.1002/hep.20007
3. Ramage H, Sheldon JH. Haemochromatosis: 1, the content of the tissues in iron and sulphur 2. the results of spectrographic examination with especial reference to copper and calcium. *QJM: Int J Med*. 1935;4(2):121-129.
4. Simon M, Bourel M, Fauchet R, Genetet B. Association of HLA-A3 and HLA-B14 antigens with idiopathic haemochromatosis. *Gut*. 1976;17(5): 332-334. doi:10.1136/gut.17.5.332
5. Feder J, Gnirke A, Thomas W, et al. A novel MHC class I–like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet*. 1996;13(4):399-408. doi:10.1038/ng0896-399
6. Adams PC, Barton JC. A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation. *J Hepatol*. 2011;55(2):453-458. doi:10.1016/j.jhep.2011.02.010
7. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr*. 2017;106(Suppl 6):1559S-1566S. doi:10.3945/ajcn.117.155804
8. Frazer DM, Anderson GJ. The regulation of iron transport. *Biofactors*. 2014;40(2):206-214. doi:10.1002/biof.1148
9. Weiss G. Iron, infection and anemia--a classical triad. *Wien Klin Wochenschr*. 2002;114(10-11):357-367.
10. Gulec S, Collins JF. Molecular mediators governing iron-copper interactions. *Annu Rev Nutr*. 2014;34(1):95-116. doi:10.1146/annurev-nutr-071812-161215
11. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. *Annu Rev Nutr*. 2006;26(1):323-342. doi:10.1146/annurev.nutr.26.061505.111303
12. Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372(19): 1832-1843. doi:10.1056/NEJMra1401038
13. Hamdi-Rozé H, Ben Ali Z, Ropert M, et al. Variable expressivity of HJV related hemochromatosis: "Juvenile" hemochromatosis? *Blood Cells Mol Dis*. 2019;74:30-33. doi:10.1016/j.bcmd.2018.10.006
14. De Gobbi M, Roetto A. *TFR2*-Related Hemochromatosis. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; 2005.
15. Zhang W, Xu A, Li Y, et al. A novel SLC40A1 p.Y333H mutation with gain of function of ferroportin: a recurrent cause of haemochromatosis in China. *Liver Int*. 2019;39(6):1120-1127. doi:10.1111/liv.14013
16. Hsu CC, Senussi NH, Fertrin KY, Kowdley KV. Iron overload disorders. *Hepatol Commun*. 2022;6(8):1842-1854. doi:10.1002/hep4.2012
17. Yildirim N, Unal S, Yalcinkaya A, Karahan F, Oztas Y. Evaluation of the relationship between intravascular hemolysis and clinical manifestations in sickle cell disease: decreased hemopexin during vaso-occlusive crises and increased inflammation in acute chest syndrome. *Ann Hematol*. 2022;101(1):35-41. doi:10.1007/s00277-021-04667-w
18. Valent P, Krieger O, Stauder R, et al. Iron overload in myelodysplastic syndromes (MDS) - diagnosis, management, and response criteria: a proposal of the Austrian MDS platform. *Eur J Clin Invest*. 2008;38(3): 143-149. doi:10.1111/j.1365-2362.2007.01915.x
19. Rasel M, Hashmi MF, Mahboobi SK. Transfusion iron overload. StatPearls [Internet]. StatPearls Publishing; 2024.
20. Gardenghi S, Marongiu MF, Ramos P, et al. Ineffective erythropoiesis in beta-thalassemia is characterized by increased iron absorption mediated by down-regulation of hepcidin and up-regulation of ferroportin. *Blood*. 2007;109(11):5027-5035. doi:10.1182/blood-2006-09-048868
21. Taher AT, Musallam KM, Cappellini MD. Guidelines for the management of non-transfusion-dependent β-thalassaemia. 3rd ed. Nicosia (Cyprus): Thalassaemia International Federation; 2023.
22. Milman NT, Schioedt FV, Junker AE, Magnussen K. Diagnosis and treatment of genetic HFE-hemochromatosis: the Danish aspect. *Gastroenterology Res*. 2019;12(5):221-232. doi:10.14740/gr1206
23. Turshudzhyan A, Wu DC, Wu GY. Primary non-HFE hemochromatosis: a review. *J Clin Transl Hepatol*. 2023;11(4):925-931. doi:10.14218/jcth.2022.00373
24. Karaca H, Güven K, Önal M, Gürsoy Ş, Başkol M, Özkul Y. The prevalence of primary hereditary hemochromatosis in central Anatolia. *Turk J Gastroenterol*. 2013;24(1):43-50. doi:10.4318/tjg.2013.0579
25. Porter JL, Rawla P. Hemochromatosis. StatPearls. StatPearls Publishing Copyright© 2025, StatPearls Publishing LLC.; 2025.
26. Muñoz M, Villar I, García-Erce JA. An update on iron physiology. *World J Gastroenterol*. 2009;15(37):4617-26. doi:10.3748/wjg.15.4617
27. Ryan E, Ryan JD, Russell J, et al. Correlates of hepcidin and NTBI according to HFE status in patients referred to a liver centre. *Acta Haematol*. 2015;133(2):155-161. doi:10.1159/000363490
28. Feng S, Tang D, Wang Y, et al. The mechanism of ferroptosis and its related diseases. *Mol Biomed*. 2023;4(1):33. doi:10.1186/s43556-023-00142-2
29. Ru Q, Li Y, Chen L, Wu Y, Min J, Wang F. Iron homeostasis and ferroptosis in human diseases: mechanisms and therapeutic prospects. *Signal Transduct Target Ther*. 2024;9(1):271. doi:10.1038/s41392-024-01969-z
30. Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. *Vox Sanguinis*. 2009; 97(3):185-197. doi:10.1111/j.1423-0410.2009.01207.x
31. Siegelman ES, Mitchell DG, Rubin R, et al. Parenchymal versus reticuloendothelial iron overload in the liver: distinction with MR imaging. *Radiology*. 1991;179(2):361-366. doi:10.1148/radiology.179.2.2014275
32. Elmberg M, Hultcrantz R, Ekbom A, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology*. 2003;125(6):1733-1741. doi:10.1053/j.gastro.2003. 09.035
33. Fletcher LM, Dixon JL, Purdie DM, Powell LW, Crawford DH. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology*. 2002;122(2):281-289. doi:10.1053/gast.2002.30992
34. Moczulski DK, Grzeszczak W, Gawlik B. Role of hemochromatosis C282Y and H63D mutations in HFE gene in development of type 2 diabetes and diabetic nephropathy. *Diabetes Care*. 2001;24(7):1187-1191. doi:10.2337/diacare.24.7.1187
35. Ahmed S, Peterson SJ, Parikh MA, Frishman WH. Cardiovascular manifestations of hemochromatosis: a review of pathophysiology, mechanisms, and treatment options. *Cardiol Rev*. 2025;33(4):359-364. doi:10.1097/crd.0000000000000622
36. Mitton-Fitzgerald E, Gohr CM, Williams CM, Rosenthal AK. Identification of common pathogenic pathways involved in hemochromatosis arthritis and calcium pyrophosphate deposition disease: a review. *Curr Rheumatol Rep*. 2022;24(2):40-45. doi:10.1007/s11926-022-01054-w
37. Pelusi C, Gasparini DI, Bianchi N, Pasquali R. Endocrine dysfunction in hereditary hemochromatosis. *J Endocrinol Invest*. 2016;39(8):837-847. doi:10.1007/s40618-016-0451-7
38. Edwards CQ, Kelly TM, Ellwein G, Kushner JP. Thyroid disease in hemochromatosis. Increased incidence in homozygous men. *Arch Intern Med*. 1983;143(10):1890-1893.
39. Świątczak M, Raczak A, Świątczak A, et al. Fatigue assessment in patients with hereditary hemochromatosis: first use of the popular diagnostic tools. *J Clin Med*. 2024;13(18):5544. doi:10.3390/jcm13185544
40. Kowdley KV, Brown KE, Ahn J, Sundaram V. Correction: ACG clinical guideline: hereditary hemochromatosis. *Am J Gastroenterol*. 2019; 114(12):1927. doi:10.14309/ajg.0000000000000469
41. Barton JC, Barton JC, Patel N, McLaren GD. Abdominal pain and cirrhosis at diagnosis of hemochromatosis: analysis of 219 referred probands with HFE p.C282Y homozygosity and a literature review. *PLoS One*. 2021;16(12):e0261690. doi:10.1371/journal.pone.0261690
42. Grosse SD, Gurrin LC, Bertalli NA, Allen KJ. Clinical penetrance in hereditary hemochromatosis: estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. *Genet Med*. 2018; 20(4):383-389. doi:10.1038/gim.2017.121
43. Beaton M, Guyader D, Deugnier Y, Moirand R, Chakrabarti S, Adams P. Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology*. 2002;36(3):673-678. doi:10.1053/jhep.2002.35343
44. Thielen V, Radermecker RP, Philips JC, Paquot N, Scheen AJ. Hereditary hemochromatosis and diabetes mellitus: diagnostic approach and clinical evolution. *Revue Medicale De Liege*. 2005;60(5-6):448-454.
45. Cawley EP, Hsu YT, Wood BT, Weary PE. Hemochromatosis and the skin. *Arch Dermatol*. 1969;100(1):1-6.

46. Akbarialiabad H, Jamshidi P, Callen JP, Murrell DF. Dermatologic manifestations of hereditary hemochromatosis: a systematic review. *J Eur Acad Dermatol Venereol*. 2025;39(5):976-986. doi:10.1111/jdv.20098
47. Husar-Memmer E, Stadlmayr A, Datz C, Zwerina J. HFE-related hemochromatosis: an update for the rheumatologist. *Curr Rheumatol Rep*. 2014;16(1):393. doi:10.1007/s11926-013-0393-4
48. Zoller H, Schaefer B, Vanclooster A, et al. EASL clinical practice guidelines on haemochromatosis. *J Hepatol*. 2022;77(2):479-502. doi:10.1016/j.jhep.2022.03.033
49. Aronow WS. Management of cardiac hemochromatosis. *Arch Med Sci*. 2018;14(3):560-568. doi:10.5114/aoms.2017.68729
50. Joshi PK, Patel SC, Shreya D, et al. Hereditary hemochromatosis: a cardiac perspective. *Cureus*. 2021;13(11):e20009. doi:10.7759/cureus.20009
51. Young J. Endocrine consequences of hemochromatosis. *Presse Med*. 2007;36(9 Pt 2):1319-25. doi:10.1016/j.lpm.2007.01.041
52. Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int*. 2009;20(4):549-555. doi:10.1007/s00198-008-0701-4
53. Thwaites PA, Woods ML. Sepsis and siderosis, Yersinia enterocolitica and hereditary haemochromatosis. *BMJ Case Rep*. 2017;2017:bcr2016218185. doi:10.1136/bcr-2016-218185
54. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. *Int J Infec Dis*. 2007;11(6):482-487. doi:10.1016/j.ijid.2007.04.007
55. Kanamori Y, Tanaka M, Itoh M, et al. Iron-rich Kupffer cells exhibit phenotypic changes during the development of liver fibrosis in NASH. *iScience*. 2021;24(2):102032. doi:10.1016/j.isci.2020.102032
56. Nielsen JE, Jensen LN, Krabbe K. Hereditary haemochromatosis: a case of iron accumulation in the basal ganglia associated with a parkinsonian syndrome. *J Neurol Neurosurg Psychiatry*. 1995;59(3):318-321. doi:10.1136/jnnp.59.3.318
57. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(1):328-43. doi:10.1002/hep.24330
58. McLaren CE, McLachlan GJ, Halliday JW, et al. Distribution of transferrin saturation in an Australian population: relevance to the early diagnosis of hemochromatosis. *Gastroenterology*. 1998;114(3):543-549. doi:10.1016/s0016-5085(98)70538-4
59. Nakatani R, Murata T, Usui T, et al. Importance of the average glucose level and estimated glycated hemoglobin in a diabetic patient with hereditary hemolytic anemia and liver cirrhosis. *Intern Med*. 2018;57(4):537-543. doi:10.2169/internalmedicine.9135-17
60. Sonagra AD, Zubair M. Laboratory evaluation of hereditary hemochromatosis. StatPearls [Internet]. StatPearls Publishing; 2023.
61. Le Gac G, Mons F, Jacolot S, Scotet V, Férec C, Frébourg T. Early onset hereditary hemochromatosis resulting from a novel TFR2 gene nonsense mutation (R105X) in two siblings of north French descent. *Br J Haematol*. 2004;125(5):674-678. doi:10.1111/j.1365-2141.2004.04950.x
62. McDonnell SM, Phatak PD, Felitti V, Hover A, McLaren GD. Screening for hemochromatosis in primary care settings. *Ann Intern Med*. 1998;129(11_Part_2):962-970. doi:10.7326/0003-4819-129-11_part_2-199812011- 00007
63. Girelli D, Busti F, Brissot P, Cabantchik I, Muckenthaler MU, Porto G. Hemochromatosis classification: update and recommendations by the BIOIRON Society. *Blood*. 2022;139(20):3018-3029. doi:10.1182/blood.2021011338
64. Zhang J, Liu K, Sun Y, Yu J. Magnetic resonance spectroscopy for quantification of liver iron deposition in hereditary hemochromatosis of a Chinese family: four case reports. *Medicine*. 2022;101(46):e31742. doi:10.1097/md.0000000000031742
65. Low G, Huang G, Dharmana H, Moloo Z, Fu W. Re: PC Adams. Genetic testing for hemochromatosis: diagnostic or confirmatory test for iron overload? *Can J Gastroenterol Hepatol*. 2015;29(3):165-166. doi:10.1155/2015/523876
66. İdilman İS, Akata D, Özmen MN, Karçaaltıncaba M. Different forms of iron accumulation in the liver on MRI. *Diagn Interv Radiol*. 2016;22(1):22-28. doi:10.5152/dir.2015.15094
67. Assis RA, Kay FU, Conti FM, et al. The role of magnetic resonance imaging-T2* in the evaluation of iron overload early in hereditary hemochromatosis. A cross-sectional study with 159 patients. *Am J Hematol*. 2015;90(12):E220-221. doi:10.1002/ajh.24189
68. Castiella A, Zapata E, Alústiza JM. Non-invasive methods for liver fibrosis prediction in hemochromatosis: one step beyond. *World J Hepatol*. 2010;2(7):251-255. doi:10.4254/wjh.v2.i7.251
69. Salomao MA. Pathology of hepatic iron overload. *Clin Liver Dis (Hoboken)*. 2021;17(4):232-237. doi:10.1002/cld.1051
70. Cathcart J, Mukhopadhya A. European Association for Study of the Liver (EASL) clinical practice guidelines on haemochromatosis. *Frontline Gastroenterol*. 2023;14(4):282-286. doi:10.1136/flgastro-2022-102296
71. Adams PC, Ryan JD. Diagnosis and treatment of hemochromatosis. *Clin Gastroenterol Hepatol*. 2025;23(9):1477-1485. doi:10.1016/j.cgh.2024.10.041
72. Girelli D, Marchi G, Busti F. Diagnosis and management of hereditary hemochromatosis: lifestyle modification, phlebotomy, and blood donation. *Hematology Am Soc Hematol Educ Program*. 2024;2024(1):434-442. doi:10.1182/hematology.2024000568
73. Singh P, Mortimore G, Hicks K, et al. Venesection treatment in haemochromatosis–current best practice from the BSG/BASL Special Interest Group. *Frontline Gastroenterol*. 2025:flgastro-2025-1. doi:10.1136/flgastro-2025-103172
74. Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the writing committee of the American Society for Apheresis: the ninth special issue. *J Clin Apher*. 2023;38(2):77-278. doi:10.1002/jca.22043
75. Cheng L, Tang X, Fu P, Liu F. Secondary haemochromatosis in a haemodialysis patient. *Singapore Med J*. 2015;56(7):e124-126. doi:10.11622/smedj.2015116
76. Lymberopoulos P, Prakash S, Shaikh A, et al. Long-term outcomes and trends in liver transplantation for hereditary hemochromatosis in the United States. *Liver Transpl*. 2023;29(1):15-25. doi:10.1002/lt.26539
77. Kowdley KV, Modi NB, Peltekian K, et al. Rusfertide for the treatment of iron overload in HFE-related haemochromatosis: an open-label, multicentre, proof-of-concept phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1118-1128. doi:10.1016/s2468-1253(23)00250-9
78. Rovai A, Chung B, Hu Q, et al. In vivo adenine base editing reverts C282Y and improves iron metabolism in hemochromatosis mice. *Nat Commun*. 2022;13(1):5215. doi:10.1038/s41467-022-32906-9
79. Barton JC, McLaren CE, Chen WP, et al. Cirrhosis in hemochromatosis: independent risk factors in 368 HFE p.C282Y homozygotes. *Ann Hepatol*. 2018;17(5):871-879. doi:10.5604/01.3001.0012.3169