Hereditary Hemochromatosis: an Inherited Abnormality of Iron Regulation

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ABSTRACT: Hereditary Hemochromatosis (HH) is an autosomal recessive genetic disease characterized by abnormalities in iron regulation, mostly due to mutations in the HFE gene, leading to increased iron absorption due to hepcidin deficiency. The classification of HH is based on the type of mutated gene, which must be distinguished from non-genetic conditions that cause secondary elevations in serum iron levels such as multiple transfusions and increased iron supplementation. Pathophysiological mechanisms of HH include increased absorption of iron in the upper intestine, decreased expression of the iron regulatory hormone hepcidin, altered function of the HFE protein, and tissue damage and fibrogenesis caused by iron overload. The human body is physiologically unable to excrete excess iron load so excess iron in serum will be deposited in various organs, causing organ dysfunction. The clinical manifestations of hemochromatosis vary widely depending on the location of iron deposition in the organ. The classic clinical triad of hemochromatosis is liver cirrhosis, skin pigmentation, and diabetes mellitus. Hemochromatosis can be screened for and diagnosed by examining serum ferritin levels, transferrin saturation, unsaturated iron-binding capacity, total iron-binding capacity, liver biopsy, magnetic resonance imaging, and genetic testing. The main treatment for hemochromatosis at this time is phlebotomy although other therapeutic methods can also be used to help lower iron levels and improve the patient's clinical course, such as therapy with chelating agents, *erythrocytopharesis*, and liver transplantation. If hemochromatosis is not treated, the patient can experience progressive liver damage leading to cirrhosis and hepatocellular carcinoma, and complications due to damage to various tissues and organs.

KEYWORDS: Hereditary Hemochromatosis, HFE gene mutations, Iron Regulation Abnormalities, Iron Overload

1. INTRODUCTION

Hereditary Hemochromatosis (HH) is an autosomal recessive genetic disease characterized by abnormal iron regulation in the body. According to the 2018 ACG Guidelines, HH is defined as an inherited condition of iron overload, which is characterized by excess iron absorption due to hepcidin deficiency leading to increased intestinal iron absorption. Meanwhile, according to the BioIron Congress held in Heidelberg in 2019, hemochromatosis is defined as a chronic iron overload condition caused by hepcidin deficiency or hepcidin resistance. This disease is mostly caused by mutations in the hemochromatosis (HFE) gene which was first identified in 1996. The human body is physiologically unable to excrete excess iron load so excess iron in serum will be deposited in various organs, causing organ dysfunction. Hemochromatosis is also called "Bronze Diabetes" because of its frequent manifestations in the form of skin hyperpigmentation, diabetes, and cirrhosis. The clinical manifestations of hemochromatosis vary widely depending on the location of iron deposition in the organ. Several signs and symptoms of hemochromatosis can include chronic fatigue, arthritis usually involving the II and III metacarpophalangeal joints, skin hyperpigmentation, liver cirrhosis, hepatocellular carcinoma, diabetes, arrhythmias, heart failure, decreased libido, and impotence. Hereditary hemochromatosis must be distinguished from non-genetic conditions that cause secondary elevations in serum iron levels such as multiple transfusions and increased iron supplementation.[1-8]

Hemochromatosis can be screened for and diagnosed by performing serum ferritin (SF) levels, transferrin saturation (TS), liver biopsy, magnetic resonance imaging (MRI), and genetic testing in patients suspected of having hemochromatosis. The main treatment for hemochromatosis today is phlebotomy although other therapeutic methods can also be used to help lower iron levels

and improve patient clinical outcomes, such as therapy with chelating agents, *erythrocytopharesis*, and liver transplantation. Death from hemochromatosis is caused by complications due to dysfunction of various organs such as hepatocellular carcinoma and heart failure.[2,7,8]

Hereditary Hemochromatosis is an autosomal recessive disease that most often occurs in Caucasians with a prevalence of 1 in 300-500 individuals. Hereditary Hemochromatosis types 2, 3, and 4 can be found in various parts of the world, but type 1 (HFE-related) is more common in northern European descent with a prevalence of about 2-4%. Hemochromatosis type 1 is estimated to occur in 6 out of 1000 in the Caucasian population. Meanwhile, the variant of hemochromatosis type 4 (*ferroportin* disease) was found to be highest in the African population (0.25%) although it was also found in the American population (0.039%), East Asian (0.033%), and non-Finnish European (0.03%). Clinical manifestations in males appear slightly earlier than in females.[1-3,9]

2. ETIOLOGY AND CLASSIFICATION

Hereditary Hemochromatosis occurs in homozygotes with mutations in the hemochromatosis gene (HFE). HFE is a membrane protein that undergoes heterodimerization with 2-microglobulin. Mutations in the HFE gene cause increased iron absorption despite normal dietary iron intake. The most common HFE gene mutations are C282Y and H63D mutations. Several types of HH can be classified into HFE-related and non-HFE-related. Non-HFE-related hemochromatosis is caused by mutations in genes other than C282Y, such as the hemojuvelin (HJV) gene, Hepcidin Antimicrobial Peptide (HAMP), and transferrin receptor-2 (TFR2). The types of hemochromatosis based on the underlying gene mutation can be seen in table 1.[2-13]

Table 1: Hereditary Hemochromatosis classification based on Etiology.[3]

Classification	Gene and Location	heritance Pattern	Protein Function	Clinical Manifestations	Iron Profile
Type 1A HH (homozygote)	HFE on 6p21.3 ation on HFE: 1. C282Y	Autosomal recessive	Hepcidin synthesis via BMP6, interaction with TFR1	Arthropathy, skin pigmentation, liver damage, diabetes litus, endocrine dysfunction, ardiomyopathy, hypogonadism	↑TS, ↑ferritin
Type 1B HH (compound heterozygote)	HFE on 6p21.3 ation on HFE: C282Y H63D	Autosomal recessive	Hepcidin synthesis via BMP6, interaction with TFR1	Arthropathy, skin pigmentation, liver damage, diabetes litus, endocrine dysfunction, ardiomyopathy, hypogonadism	↑TS, ↑ferritin
Type 1 C HH	HFE on 6p21.3 ation on HFE: 1. S65C	Autosomal recessive		Elevated serum iron (SI)/ferritin, no evidence of iron deposition in organs	↑TS, ↑ferritin
Type 2A juvenile HH	HJV (hemojuvelin) on 1p21	Autosomal recessive	Hepcidin synthesis, BMP coreceptor	Early-onset, <30 years, hypogonadism, cardiomyopathy	↑TS, ↑ferritin

Type 2B juvenile HH	HAMP (hepcidin) on 19q13	Autosomal recessive	Reduces iron efflux from erythrocytes	Early-onset, <30 years, hypogonadism, cardiomyopathy	↑TS, ↑ferritin
Type 3 HH	TFR2 (transferrin receptor 2) on 7q22	Autosomal recessive	Hepcidin synthesis, interaction with transferrin	Arthropathy, skin pigmentation, liver damage, diabetes litus, endocrine dysfunction, ardiomyopathy, hypogonadism	↑TS, ↑ferritin
Type 4A HH (FPN disease)	SLC40A1 (FPN) on 2q32 Loss-offunction FPN	Autosomal recessive	Export of iron in the duodenum	Iron deposition in the spleen, lower tolerance for phlebotomy, may have anemia	Normal or ↓TS
Type 4B HH (non-classical FPN disease)	SLC40A1 (FPN) on 2q32 Gain-of function, FPN cannot be internalized by hepcidin	Autosomal recessive	Resistance to hepcidin	Fatigue, joint pain	Normal or ↓TS

FPN=*ferroportin* ; HAMP=Hepatic Antimicrobial Protein; HH=Hereditary Hemochromatosis

According to the BioIron Congress, the four types of hemochromatosis can also be classified based on the mechanism of the hepcidin disorder that occurs, namely hemochromatosis related to hepcidin deficiency and hemochromatosis related to hepcidin resistance.[3,11]

3. PATHOGENESIS

There are 4 main categories of pathophysiological mechanisms of HH, namely increased absorption of iron in the upper intestine, decreased expression of the iron regulatory hormone hepcidin, altered function of the HFE protein, and iron-induced tissue damage and fibrogenesis.[14-17]

The body absorbs 1-2 mg Fe each day from the intestinal lumen through the duodenal villi which involve intestinal membrane proteins, namely *Ferrireductase* (DcytB) and Divalent Metal Ion Transporter (DMT1). *Ferrireductase* will convert Fe^{3+} to Fe^{2+} then DMT1 carries Fe^{2+} from the intestinal lumen to the duodenal villi. Fe^{2+} is then absorbed into the bloodstream by *ferroportin*. *Hephaestin* will convert Fe^{2+} back into Fe^{3+} in the blood and will bind to apo transferrin to form transferrin which is a Febinding protein in the blood. Transferrin will transport Fe to be carried to the liver and bone marrow. Fe reabsorption through duodenal crypts involves *β*-2 microglobulin, transferrin receptor-2 (TfR2), and HFE protein by converting Fe^{3+} to Fe^{2+} in the process of endocytosis. Mutations of the HFE protein (C282Y) can disrupt the binding.[15,16]
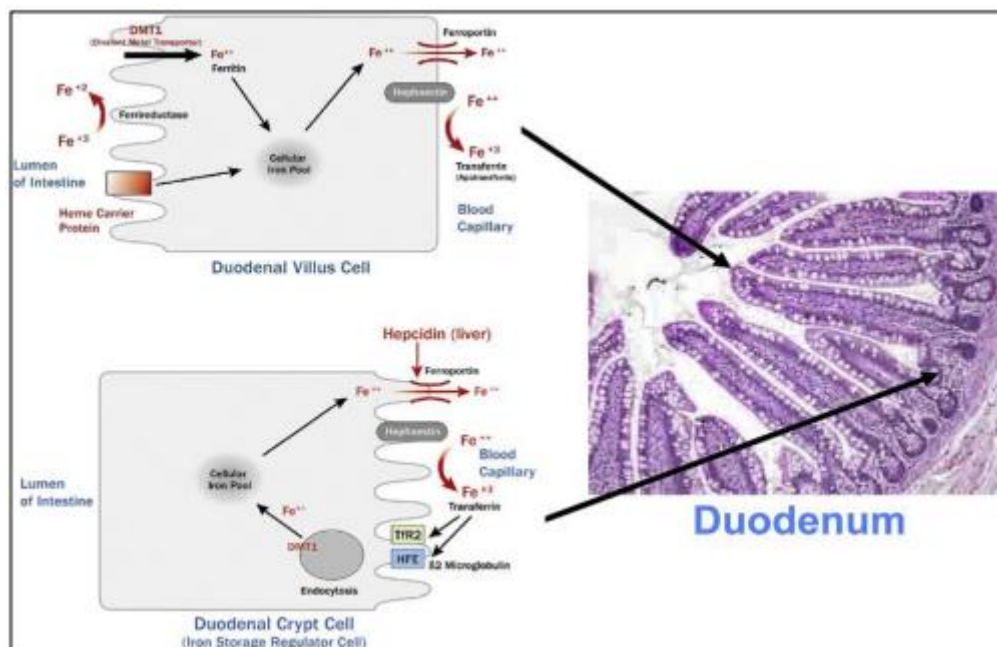
Figure 1: Fe metabolism in the intestine. [15]

Hereditary Hemochromatosis occurs when there is a defect in the regulation of intestinal iron absorption, resulting in iron accumulation. The main effect of the action of hepcidin on *ferroportin* occurs at two sites, namely the *duodenocytes* and macrophages in the spleen. The action of hepcidin causes a decrease in plasma iron concentration by interfering with duodenal iron absorption and splenic iron release from erythrocyte degradation. Thus, decreased hepcidin synthesis by the liver will cause *hypohepcidinemia*, which in turn causes *hypersideremia* through hyperabsorption of iron and increased recycling of iron in the spleen. The circulating iron in the plasma is then taken up by transferrin, whose total iron-binding capacity is greater than the physiological iron concentration. This is indicated by the normal partial transferrin saturation <45%.[2,3]

Other aspects of the hepcidin-*ferroportin* interaction are also being investigated. *Ferroportin* is not only a protein that functions to export iron but also a protein that functions as a membrane receptor for plasma hepcidin. So in several genetic disorders where there is impaired function of *ferroportin* as a receptor, even though plasma hepcidin levels are normal, hepcidin is unable to bind to *ferroportin* receptors. This condition is known as hepcidin resistance. Hepcidin resistance has a similar effect to a decrease in plasma hepcidin concentrations, namely an increase in iron export by *ferroportin*. Although the function of *ferroportin* as a receptor is disturbed, the function of *ferroportin* as an iron exporter is not disturbed by genetic mutations.[3,11]

This excess plasma iron is transported by plasma transferrin, increasing TS. When the TS exceeds 45%, Non-Transferrin Bound Iron (NTBI) will be formed which does not bind to transferrin. NTBI will be taken up by parenchymal cells, especially hepatocytes. On the other hand, iron bound to transferrin is mostly carried to the bone marrow to produce erythrocytes. When the TS saturation is > 75%, a new form of NTBI will be formed, which is called Reactive Plasma Iron (RPI) or labile plasma iron. RPI is a form of iron that tends to form Reactive Oxygen Species (ROS) which can damage plasma membranes and intracellular organelles. Therefore, RPI is considered a toxic form of plasma iron which is responsible for cell death that leads to damage to various organs.[3]

In Hereditary Hemochromatosis, excess iron is mainly deposited in parenchymal cells, while in Transfusional Hemochromatosis, excess iron is mainly stored in reticuloendothelial cells. Excess iron is stored in the cells in the form of hemosiderin. This ultimately leads to cell death which is eventually replaced by fibrous deposition leading to destruction and/or impaired organ function. The cascade of mechanisms for the formation of hemochromatosis can be seen in Figures 2. [3,9,12]
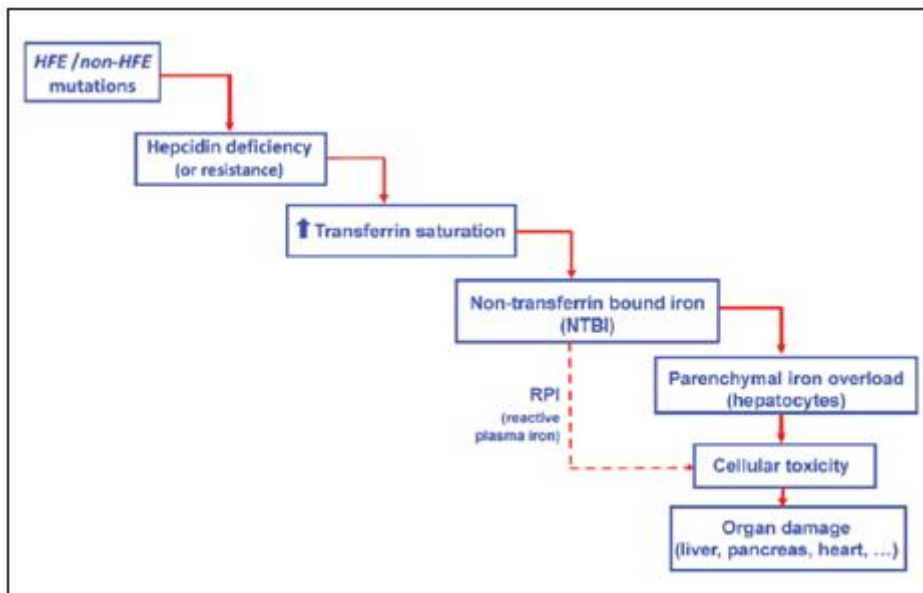
Figure 2. The cascade of mechanisms for the formation of hemochromatosis from mutation to organ damage.[3]

4. DIAGNOSIS

A. Clinical Manifestations

The clinical manifestations of hemochromatosis are very diverse and depend on the organ affected, making diagnosis difficult. The main clinical manifestations are hepatomegaly, skin pigmentation (especially in sun-exposed areas), impaired glucose homeostasis or diabetes mellitus due to destruction of the islets of Langerhans, cardiac dysfunction (arrhythmias, cardiomyopathy), and atypical arthritis. Several patients also experience decreased libido and impotence.[2,9]

The classic clinical triad of hemochromatosis is liver cirrhosis, skin pigmentation, and diabetes mellitus. However, this triad is often not observed early in the course of the disease because most patients are asymptomatic until they reach adulthood. Symptoms that patients most often complain about early in the course of the disease include chronic fatigue, arthralgia, and lethargy. Fatigue is often interpreted as a psychological manifestation. Later manifestations of hemochromatosis occur when iron begins to be deposited in various tissues, as shown in Table 2.[2,3,6,9]

Table 2: Clinical Manifestations of Hereditary Hemochromatosis.[2,6,9]

Organ	Clinical Manifestations	Pathophysiology	Prevalence
Skin	Hyper-melanotic pigmentation (diffuse hyperpigmentation/bronze skin)	Increased melanin production and deposition	
Joint	Arthralgia Arthritis Chondrocalcinosis Joint swelling	Iron accumulation in joints (metacarpophalangeal joints, proximal interphalangeal joints, knees, wrists, hips, back, neck)	

Liver	Increased liver enzymes Hepatomegaly Fibrosis Cirrhosis Portal hypertension Hepatocellular carcinoma (HCC)	Oxidative stress	30% overall; 18% of men, 5% of women have hepatic manifestations without other symptoms
Heart	Cardiomyopathy Arrhythmia Heart failure	Endothelial dysfunction, thickening of the tunica intima-media, oxidative stress due to iron deposition in cardiomyocytes	Very low: 0.9%; 3.1% The second cause of death in HH
Endocrine	Hyperglycemia Diabetes mellitus (DM) Hypogonadism (which causes decreased libido, impotence, amenorrhea) Testicular atrophy Hypopituitarism Thyroid dysfunction Adrenal dysfunction Parathyroid defect Osteoporosis	The accumulation of iron in endocrine organs such as the pancreas, pituitary gland, thyroid causes a decrease in hormone secretion	DM 13-23% Osteoporosis 25%

B. Laboratory and other Supporting Examinations

a. Iron Status Check

Initial evaluation in patients suspected of having iron overload is transferrin saturation (TS), Serum Ferritin (SF), and Unsaturated Iron-Binding Capacity (UIBC) or Total-Iron Binding Capacity (TIBC). TS is the preferred initial screening examination and patients do not need to fast before the examination.[2,6,8]

TS abnormality is the earliest detectable biochemical abnormality. A normal TS level can rule out a diagnosis of hemochromatosis. TS levels in hemochromatosis are >60% in men and >50% in women. TS levels should be measured twice because TS levels can fluctuate. A persistent TS value of more than 75% can be used to indicate the presence of RPI in plasma. TS >45% can identify 97.9%-100% homozygous C282Y. However, a small number of HH patients, such as younger patients, may show lower TS, ie < 45%.[2]

Examination of SF levels can also be used to help diagnose hemochromatosis. In hemochromatosis, the ferritin value in men is >300 ng/mL while in women it is >200 ng/mL. High ferritin levels indicate an increase in body iron load. Iron overload conditions can manifest as an increase in SF even though TS levels are still normal, especially in non-HFE-related iron overload. SF is also an accurate predictor of advanced fibrosis, although it does not have high specificity for use as a screening method. This is because SF is also an acute phase reactant so *hyperferritinemia* can also be caused by other conditions such as alcoholic liver disease, HCV infection, NAFLD, metabolic syndrome, infections, and neoplasms. In the C282Y homozygote, an SF level >1000 ng/mL combined with elevated aminotransferase levels and a low platelet count predicts cirrhosis in >80% of patients. Normal SF levels, defined as SF < 200 ng/mL in premenopausal women or 300 ng/mL in men and post-menopausal women when combined with TS levels < 45% have a negative predictive value (NPV) of 97% to exclude the presence of an iron overload condition. Iron overload based on ferritin can be classified into moderate (levels <500 ng/mL), important (500-1000 ng/mL), and major (>1000 ng/mL).[2,3,9,18]

The UIBC value has an inverse relationship with TS. The UIBC has a diagnostic accuracy similar to that of TS and is considered to be an alternative screening test to detect HH. A UIBC level <26 mmol/L has a sensitivity of 90% for detecting the homozygosity of C282Y.[7] Total iron-binding capacity (TIBC) is also a useful parameter for diagnosing pathological iron accumulation. In hemochromatosis, TIBC values are usually > 450 mcg/dL or > 80.55 mmol/L.[6,8]

b. Liver Biopsy

Liver biopsy is the most sensitive and specific examination for assessing iron levels in the liver and assessing liver damage. However, with the widespread availability of genetic testing to establish the diagnosis of HH, the utility of liver biopsy in HH is now primarily for assessing the stage of fibrosis. If the patient does show clinically advanced fibrosis based on physical examination, laboratory, or imaging, then a liver biopsy may be considered.[2,9]

A routine histopathological examination should be included at the time of liver biopsy, Perls' Prussian Blue staining is used to identify and evaluate the cellular distribution of iron stores in the liver. The principle of Perls' Prussian Blue staining is the release of ferric ions (Fe^{3+}) from protein bonds by hydrochloric acid which then binds to potassium ferrocyanide to produce ferric ferrocyanide in the form of an insoluble bright blue component called Prussian Blue.[2,10,19]
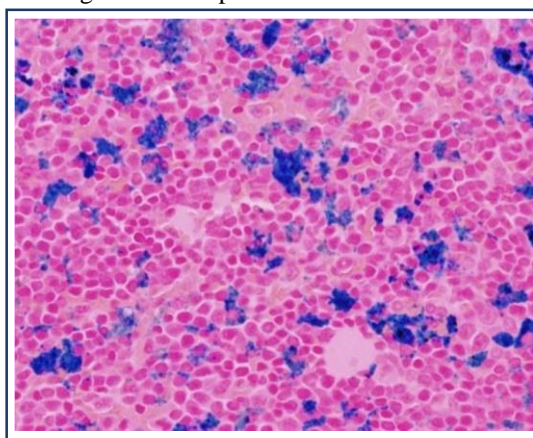

Figure 3: Fe accumulation in hepatocytes by Perl's Prussian Blue staining.[19]

A liver biopsy can be used to assess the Hepatic Iron Concentration (HIC) or Hepatic Iron Index (HII).[2] The Hepatic Iron Index was first introduced in 1986 and is often used to support the diagnosis of HH.[20]

c. Imaging

Iron-Magnetic Resonance Imaging (MRI) is a modality that can be used to help diagnose HH and assess HIC non-invasively. Three main things can be assessed through iron-MRI, namely visualizing iron overload in the liver (iron lowers the MRI signal), quantifying iron overload (the darker the liver looks, the higher the iron concentration in the liver), and providing clues regarding the mechanism of iron overload by assessing liver/spleen iron overload. An example of an MRI in a hemochromatosis patient can be seen in Figure 4, where the liver looks black if there is massive iron overload, and the spleen looks white.[2,3,9]
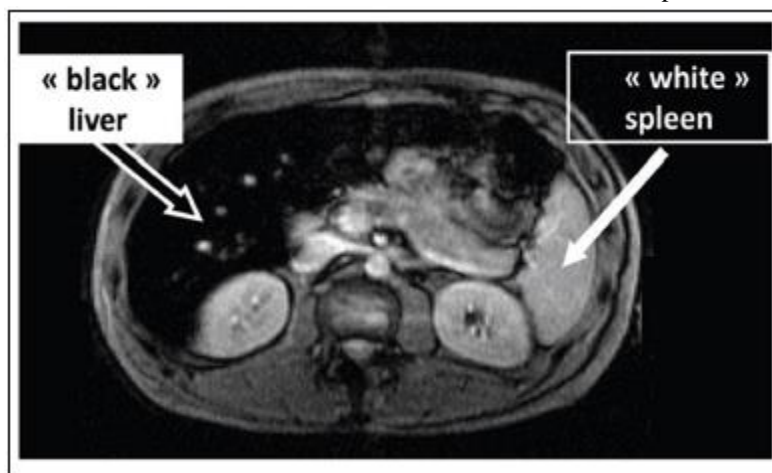
Figure 4: Typical MRI of hemochromatosis. Massive iron loading in the liver (black liver) and non-overloaded spleen (white spleen).[3]

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An echocardiogram can be performed to assess heart problems due to iron accumulation, especially in advanced stages of hemochromatosis. Changes that can be seen through echocardiography can be in the form of cardiac hypertrophy and impaired diastolic function.[6,9]

d. Genetic Test

Genotyping for the HFE mutation (C282Y) became part of the standard evaluation in patients with clinical or laboratory suspicion of iron overload. Most commercial laboratories usually report the results of the three most common types of mutations, namely C282Y, H63D, and S65C.

e. Other Laboratory Parameters

Patients may have elevated liver enzyme levels, particularly elevated aminotransferase levels. However, this increase in liver enzyme levels is usually no more than twice the normal value. Fasting blood sugar checks also need to be done to assess the presence of diabetes mellitus. Examination of glycosylated hemoglobin (HbA1c) is less reliable because of the high red cell turnover in hemochromatosis patients. Hormone levels should also be checked to assess endocrine disorders such as hypogonadism.[9]

5. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of hemochromatosis is extensive, due to the involvement of multiple organ systems.[21] There are many other diseases associated with iron overload (table 3).

Table 3: Differential diagnosis of iron overload.[22]

Hemochromatosis associated with HFE
1. Homozygote C282Y (95%)
2. Heterozygote compounds C282Y/H63D (4%)
3. Homozygote H63D (1%)
Hemochromatosis unassociated with HFE
1. *Ferroportin* disease
2. Transferrin receptor 2 mutation
3. Juvenile hemochromatosis (young adults with heart disease and endocrine dysfunction)
4. Other excesses of iron
5. African-American iron overload
6. African iron overload
7. Excess iron transfusion
8. Iron overload linked to insulin resistance
9. Aceruloplasminemia
10. Alcoholic siderosis
11. Iron overload due to end-stage cirrhosis
12. Porphyria cutanea *tarda*
13. *Postportaval* shunt

6. MANAGEMENT AND THERAPY

A. Phlebotomy

Phlebotomy is a conventional treatment for hereditary hemochromatosis, which has been known for more than 70 years and remains the mainstay of treatment for hemochromatosis. Phlebotomy is a hemochromatosis therapy that is well tolerated by the patient, quite simple, requires less cost, and is effective. Reducing the number of red blood cells as the main iron carrier in the body can minimize iron toxicity. Patients need about 50-100 phlebotomy with a volume of ~7 mL/kg BW (approximately 500 mL) to lower blood iron

levels to normal. Phlebotomy in the initiation phase is usually performed 1-2 times per week with a blood volume removed of 500 mL. Every time phlebotomy removes 450 mL of blood, it is estimated that it can reduce 225 mg of iron in the body. Higher blood volumes, usually 1000 mL, can be removed to speed up the removal of excess iron if well tolerated by the patient. If the patient cannot tolerate weekly phlebotomy, the volume of blood removed can be decreased or the interval between sessions may be increased. When iron levels have returned to normal (target serum ferritin has been reached), the initiation phase is complete and the maintenance phase can be performed with less frequent phlebotomy (3-4 times per year). Before and during the phlebotomy, the patient's Hb level should always be checked and ensured that it is > 11 g/dL.[2,3,5,9,10,23]

The evaluation of phlebotomy therapy was assessed based on *ferritinemia*, with the goal of initiation of phlebotomy therapy to achieve a serum ferritin level of 50-100 ng/mL, and the goal of maintenance phlebotomy therapy was to maintain a serum ferritin level of approximately 50 ng/mL.[2,3,9]

Blood taken from a phlebotomy procedure can be used for transfusion, although there are no rules regarding the use of blood from HH patients for donation. Many blood banks have regulations not to use blood from HH patients for transfusion, although several other agencies have reported doing so without complications. Several in vitro studies have found that blood from iron-overloaded patients is more susceptible to bacterial growth. However, this still needs to be confirmed by in vivo studies.[2,24]

B. Chelating Agents
Chelating agents are not recommended for use as first-line therapy in HH because of the higher effectiveness of phlebotomy and the many side effects of chelating agents therapy. In addition, until now there is not enough data regarding the effectiveness of therapy.[2]

C. *Erythrocytapharesis*
One alternative therapy for phlebotomy is *erythrocytapharesis* which is a technique to selectively remove erythrocytes and return other blood components such as plasma proteins, clotting factors, and platelets to the patient. This therapy is especially useful for patients with hypoproteinemia or thrombocytopenia. In addition, *erythrocytapharesis* can remove up to 1000 mL of erythrocytes per procedure, much more than the 200-250 mL by phlebotomy.[2,8,23] Several studies have compared *erythrocytapharesis* with phlebotomy.

Erythrocytapharesis is known to reduce serum ferritin levels more than phlebotomy in the initiation phase, although the overall effectiveness of *erythrocytapharesis* and phlebotomy in reducing serum ferritin and transferrin saturation is the same. In the maintenance phase, *erythrocytapharesis* and phlebotomy have the same effectiveness, although *erythrocytapharesis* requires a lower frequency of therapy and costs more.[2]

D. Proton-pump Inhibitor
Stomach acid has an important role in the release of non-heme iron contained in food. Proton-pump inhibitors (PPIs) can inhibit iron absorption in HH patients thereby reducing the number of phlebotomy procedures that must be performed to keep serum ferritin levels below target. Although PPIs have the potential to reduce the frequency of phlebotomy, they are not recommended for routine use in HH patients. PPI should be given if there is a primary indication for PPI only.[2]

E. Therapeutic Innovation
Although phlebotomy is currently the mainstay of treatment for hemochromatosis, phlebotomy is only symptomatic treatment. Thus, therapies that target the basis for the formation of hemochromatosis conditions are currently being developed. Two examples of such therapy are hepcidin supplementation by subcutaneous injection of synthetic hepcidin and oral *ferroportin* antagonists to decrease *ferroportin* activity in the duodenum.[3]

F. Liver Transplant
Liver transplantation may be indicated in HH patients with end-stage liver disease or hepatocellular carcinoma (HCC). Liver transplantation is not only curative for patients with decompensated cirrhosis and HCC but also normalizes hepcidin levels and improves iron metabolism.[2,8]

7. PROGNOSIS

If hemochromatosis is not treated, the patient may develop progressive liver damage leading to cirrhosis and hepatocellular carcinoma. In addition, patients can also experience complications due to damage to various tissues and organs. Liver fibrosis or cirrhosis is the main prognostic indicator of hemochromatosis. Serum ferritin and transferrin saturation are parameters that can be used to assess the prognosis of HH patients where an increase in serum ferritin and transferrin saturation is correlated with an increase in mortality.[2,9,18]

8. SUMMARY

Hereditary Hemochromatosis is an autosomal recessive genetic disease characterized by abnormal iron regulation in the body that causes iron deposition in various organs. Iron deposition causes organ dysfunction and causes various clinical manifestations such as chronic fatigue, arthritis usually involving the II and III metacarpophalangeal joints, skin hyperpigmentation, hepatic cirrhosis, hepatocellular carcinoma, diabetes, arrhythmias, heart failure, decreased libido and impotence. Hemochromatosis must be distinguished from non-genetic conditions that cause secondary elevations in serum iron levels such as multiple transfusions and increased iron supplementation. Clinical manifestations in males appear slightly earlier than in females.

Hemochromatosis can be screened and diagnosed by testing serum ferritin levels, transferrin saturation, liver biopsy, magnetic resonance imaging, and genetic testing in patients with suspected hemochromatosis. The main treatment for hemochromatosis these days is phlebotomy although other therapeutic methods can also be used to help lower iron levels and improve patient clinical outcomes, such as therapy with chelating agents, *erythrocytopharesis*, and liver transplantation.

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