Minireview Article

Diagnosis and Current Treatment Strategies for Adult and Juvenile Hereditary Hemochromatosis

ABSTRACT

Hemochromatosis is a common genetic disorder manifesting as an iron overload state requiring complex processes in diagnosis, treatment, and management of both adult and pediatric populations. Iron has a crucial role in major metabolic and homeostatic mechanisms in sustaining the human body with links to genetic factors imperative for normal function. Genetic mutations, as ascribed to hemochromatosis, have significant impact in producing pathophysiology. The basic pathophysiological alterations leading to adult and juvenile hereditary hemochromatosis is explained with details related to the diagnosis and particularly treatment, and management of these disorders while linking scientific advances that may enlighten clinical medicine further in regard to advances in therapy.

Keywords: Adult Hemochromatosis, Juvenile Hemochromatosis, Iron Overloading, Hemochromatosis Management and Therapy

1. INTRODUCTION

Iron plays a crucial role in major metabolic and homeostatic mechanisms for the production of heme and as an important enzymatic co-factor. The majority of iron within the body circulates as a component of hemoglobin proteins delivering oxygen to tissues. The remaining iron is found in the muscles as part of myoglobin or stored in various organs of the reticuloendothelial system. The ingestion of dietary iron is typically matched with the amount of iron that is excreted ensuring the balance of iron in the tissues [1]. These factors are important in understanding the pathophysiological processes when iron is found to be either deficient, or in excess, within the human body. Fundamental processes in iron excess, or overload, where physiologic function and pathological effects is explained, particularly as it relates to the cause and treatment of adult and juvenile hemochromatosis. Concerning iron pathology, iron deficiencies seem to be the leading disruption in iron homeostasis. These pathologies include a wide array of conditions, including anemias that are caused by abnormal iron absorption or excretion. Examples of some etiologies of iron deficiency anemia include pregnancy, malnutrition, or certain chronic diseases [1]. Pathologic states where iron is found to be in excess can be as broad as those causing iron deficiency. Iron overload is considered in diseases such as amyloidosis, sarcoidosis, certain forms of arthritis, or diseases associated with liver cirrhosis. Adult and juvenile hemochromatosis leads to iron overload and has genetic implications causing a myriad of chronic processes.

2. ADULT HEREDITARY HEMOCHROMATOSIS

The first medical description of iron overloading was by Dr. A. Trousseau in 1865, but it was not until 1889 that the term hemochromatosis was used by Dr. von Recklinghausen, a

German pathologist who observed a significant brown pigmentation of skin and tissues of patients with this disorder [2]. He hypothesized this disease was caused by a factor circulating in the patients' blood. The origin of the name hemochromatosis comes from the finding that this is a disease of the blood ("hemo") associated with the presence of brown pigmentation ("chromo") in these patients. Numerous cases of hemochromatosis were identified over succeeding years in a global pattern. In 1935, Dr. Joseph Sheldon was able to identify 311 cases that existed in the scientific literature. Sheldon was one of the first to show that hemochromatosis was a disease that was an inherited disorder in which tissue damage was caused by iron overloading [3]. Initially, the main treatment for hemochromatosis was phlebotomy. Historically, phlebotomy was used as a treatment beginning in 1000 B.C. in Egypt to rid the body of impurities [4]. The use of phlebotomy as a standard treatment was started when Drs. Davis and Arrowsmith first reported that the removal of hemoglobin from the body demonstrated that it was beneficial to patients with hemochromatosis [5]. The first patient that had blood removed as a treatment for hemochromatosis was in 1947. The patient was a 69-year-old woman who had 40 liters of blood drawn over the course of 2 years. This report showed that there was general improvement for this patient during this time. During the mid-1900's, phlebotomy was the only resort for recovering from iron overloading [6].

3. IRON TRANSPORT IN INTESTINAL ENTEROCYTES

Under normal physiologic conditions, the homeostatic balance of iron within the body is mainly controlled via dietary iron. Ingested iron comes in two forms, ferric (Fe^{2+}), which comes from animal sources, and ferrous (Fe^{3+}), which is plant derived. These molecules travel through the upper gastrointestinal tract to the duodenum and proximal portion of the jejunum where iron is absorbed. Ferric iron (Fe^{2+}) is the only form that is able to cross the apical membrane of the enterocyte through a transporter called the Divalent Membrane Transporter-1 (DMT-1) or solute carrier family 11 member 2 (SLC11A2) [7-12]. When ferrous iron enters into the duodenum, it is reduced to ferric iron by a membrane bound protein present in the duodenal brush border called Duodenal Cytochrome b1 (DCYTB1). This allows iron to cross through the DMT-1 transmembrane transporter into the enterocyte where iron is either stored, or transported, to the basolateral surface for transport into the bloodstream where it binds to transferrin. Iron is transported out of the enterocyte by a transmembrane protein called Ferroportin ("iron door" in Latin) which acts in concert with a membrane protein called Hephaestin that returns iron to the ferrous form in preparation for transport.Ferroportin is responsible for transporting iron obtained from the diet to be absorbed through the walls of the small intestine into the bloodstream where iron is carried by the blood to the tissues and organs of the body [1]. Ferroportin also transports iron out of specialized immune system cells (called reticuloendothelial cells) that are found in the liver, spleen, and bone marrow. The amount of iron absorbed during digestion depends on the amount of iron transported from intestinal and reticuloendothelial cells.

Ferroportin is the key iron transporter in intestinal enterocytes and is controlled by a regulator called Hepcidin, a 25 kDa protein released by the liver acting as a key hormone that, when present, allows for the internalization and destruction of Ferroportin which diminishes the amount of iron absorbed into the bloodstream. The lack of Ferroportin does not allow any iron to be released into the bloodstream but instead, promotes excretion by the body (Figure 1). Under iron deficient conditions, increased Ferroportin will allow more iron absorption to adjust iron levels. Alternatively, when iron levels are high, lowered Ferroportin leads to lower iron absorption to adjust iron levels. Therefore, Hepcidin is the key regulator of iron absorption as it controls the amount of active Ferroportin protein in the enterocyte apical membrane. The expression of Hepcidin is controlled by iron levels detected in liver

which derived from a mechanism involving proteins that are mutatedor absent in adult Hereditary Hemochromatosis and Juvenile Hemochromatosis.

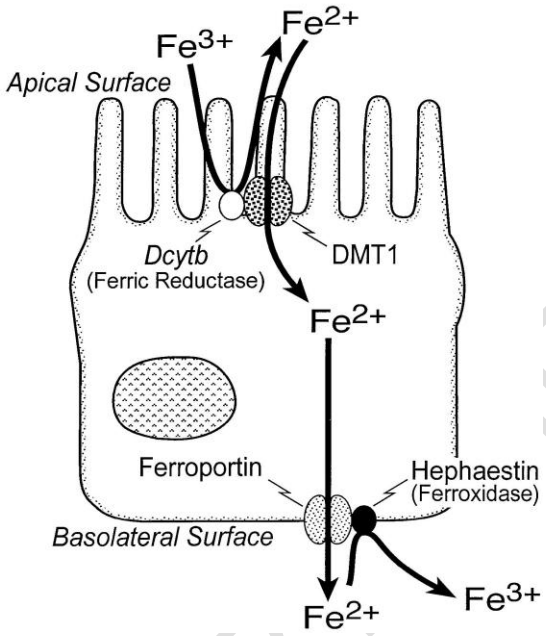

Fig. 1. Iron Transport in Intestinal Enterocytes: Mechanism and Proteins

Iron is ingested as two forms, ferric (Fe^{2+}) and ferrous (Fe^{3+}) iron. Both forms travel through the gastrointestinal tract until they reach their absorption location, the duodenum and jejunum. Here, the ferrous iron is reduced by a surface ferric reductase (Dcytb) and the ferric form is able to cross into the enterocyte via the DMT-1 transmembrane transporter. Once the iron is inside the enterocyte, the iron can either be stored or is transported across the basolateral surface via Ferroportin. Ferric iron is oxidized back into the ferrous form via an oxidase called Hephaestin. From here the iron can be transported through the body via transferrin or other transporting mechanisms.

4. GENETICS AND MECHANISM OF HEREDITARY HEMOCHROMATOSIS

Hereditary Hemochromatosis (HH) is an autosomal recessive disease and is one of the most common genetic disorders in the world effecting largely Caucasian men [13]. The genetic etiology involves the HFE (Hereditary Iron) gene, which normally functions as a homeostatic iron regulator and is primarily located on the surface of liver and intestinal cells. HFE protein associates with the receptor for the signal transduction pathway controlling the expression of Hepcidin. The HFE protein binds to both Transferrin Receptor-1 (TfR1) and Transferrin Receptor-2 (TfR2) in the mechanism to control Hepcidin expression. Under conditions of being iron replete, when diferric-transferrin levels are high, the binding of differic-transferrin to TfR1 induces the HFE protein to be released and to bind freely to TfR2, which is the receptor for the SMAD-CoSmad signal transduction pathway controlling the expression of Hepcidin. The binding of HFE protein to TfR2 induces the signal transduction pathway to increase the Hepcidin gene (HAMP) RNA expression. This generates more Hepcidin protein that can be released to the bloodstream to be bound to Ferroportin and cause its destruction thus lowering iron absorption in response to the iron replete condition. When diferric-transferrin levels are low, under conditions of low iron, the HFE protein remains bound to Transferrin Receptor-1 on liver cells and does not bind to the Hepcidin signaling complex involving TfR2, resulting in lower Hepcidin expression concomitant with higher Ferroportin levels and activity which brings more iron into the body to assist with iron homeostasis.

Figure 2 illustrates this process in the presence of both apotransferrin and diferric-transferrin. However, this intricate mechanism of controlling iron absorption fails when mutations occur in the genes mutated in Hereditary Hemochromatosis.

Patients with Hereditary Hemochromatosis commonly have a mutation in the HFE gene which results in an amino acid substitution that critically affects its function. The C282Y mutation, associated with Hereditary Hemochromatosis, replaces a cytosine residue with a tyrosine at the 282 amino acid position in the protein. Patients with hemochromatosis are homozygous for the more common C282Y mutation (C282Y/C282Y) but there is a rare mutation (H63D) in which a Histidine is replaced by an Aspartic Acid at the number 63 position in the HFE protein [3].

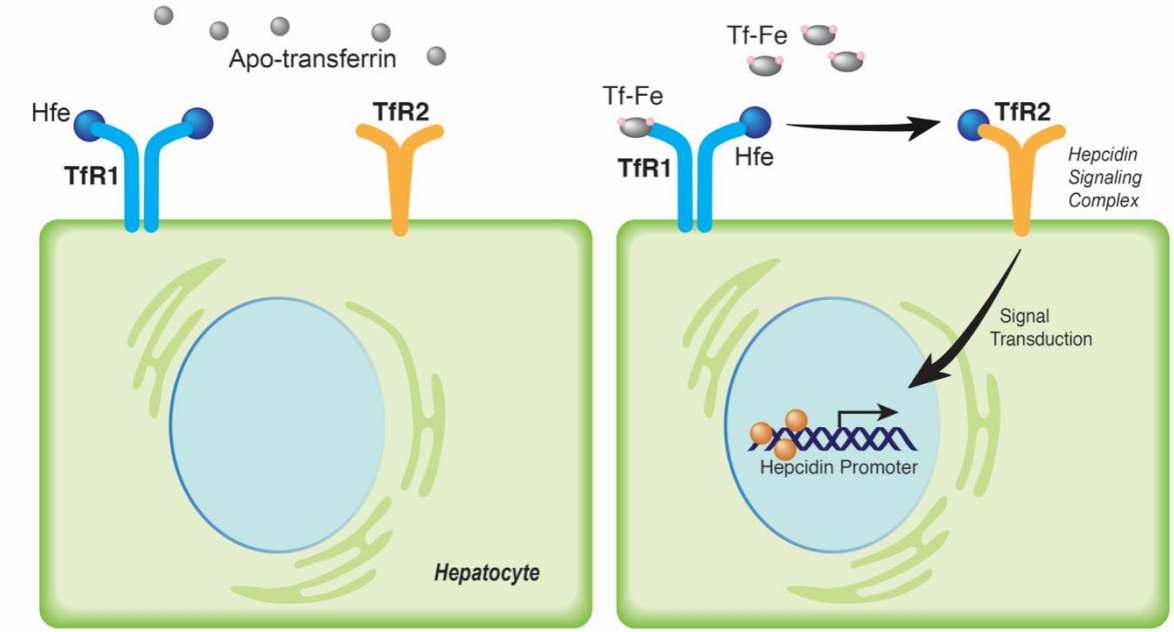

Fig. 2. Normal HFE activity

When apo-transferrin is present, as seen on the hepatocyte in the left, the HFE that is bound to the TfR1 complex is not activated and therefore does not interact with the TfR2 complex to increase Hepcidin production. In the hepatocyte that is on the right, the di-ferric protein seen in the photo is able to activate HFE by also binding to the TfR1 complex, allowing HFE to travel to the TfR2 complex to initiate the SMAD-CoSmad signal transduction pathway and activate the Hepcidin promoter.

Adult hereditary hemochromatosis leads to iron overload over time due to mutations bringing about a decrease in Hepcidin produced by the HAMP gene to control iron levels. Hepcidin controls the amount of Ferroportin available to transport iron. Hepcidin binds to Ferroportin and causes it to be broken down when the body's iron supplies are normal. When the body is low on iron, Hepcidin levels decrease and more Ferroportin is available to transport iron into the bloodstream so it can be delivered to tissues throughout the body.

Normally, high iron levels induce the binding of HFE protein to the Hepcidin signal transduction complex, which includes TfR2, activating the signal and causing increased expression of the Hepcidin gene as seen in Figure 2. Hepcidin protein levels increase and are released from the liver from which the protein migrates to the enterocyte where it binds

to Ferroportin thus facilitating the movement of Ferroportin into the cell for its destruction. This leads to the lowering of iron levels being released into the circulation. However, when this system is aberrant due to a mutation in the HFE gene, iron overloading will result.

The HFE gene was discovered in 1996 by Feder and colleagues as the gene with the most common mutation for Hereditary Hemochromatosis at the C282Y location where a cytosine is replaced by the tyrosine at the number 282 position in the protein [3]. This alteration in the protein sequence results in the inability of HFE protein to bind to β2-microglobulin which serves as a chaperone/transport to assist in binding to TfR1 [14]. The mutation leads to an aggregation of HFE extracellularly. Ultimately, there is no binding of HFE protein to TfR2, the receptor for the Hepcidin signaling complex as seen in Figure 3. Therefore, patients homozygous for the C282Y HFE mutation have a decrease in Hepcidin levels resulting in the Ferroportin transporter not being regulated and resulting in increased iron levels in the body. Excess iron present in the body is toxic secondary to free radical production and the Fenton reaction, which combines iron with hydrogen peroxide to form more free radicals [15]. The presence of these free radicals can travel to organs and cause direct damage. In adult hemochromatosis patients, the organ primarily affected is the liver. The free iron will go to the surface of the hepatocytes and cause damage, resulting in liver cirrhosis, fibrosis, and in rare cases, hepatocellular carcinoma.

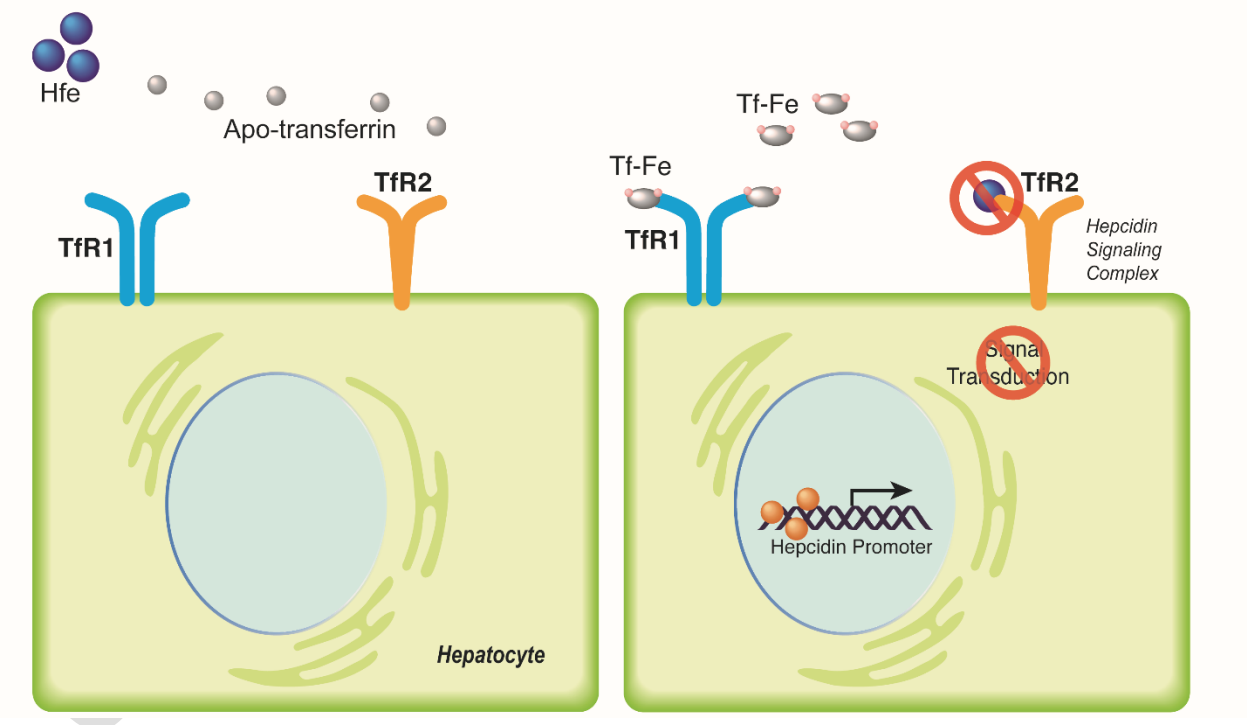

Fig. 3. Defective Mechanism in Hereditary Hemochromatosis

In Hemochromatosis, there is a mutation in the HFE protein that inhibits it from binding to the TfR2 signaling complex as it would in a normal physiological process. This does not allow for the SMAD-CoSmad pathway to be initiated and does not result in any changes in the Hepcidin levels, allowing the Ferroportin protein to continue functioning unchecked, leading to increased serum iron.

The TMPRSS6 gene encodes matriptase-2, which is part of the Hepcidin signaling complex. It is an essential factor that detects iron deficiency and blocks HAMP gene expression [16]. Matriptase-2 is a trans-membrane protein negatively regulating Hepcidin expression by presumably cleaving Hemojuvelin in the Hepcidin signal transduction complex [17].

Mutations in TMPRSS6 lead to iron-refractory iron deficiency anemia in which excess hepcidin is expressed [18].

There are four types of Hereditary Hemochromatosis [19,20]. Type I is the most common form of adult hereditary hemochromatosis and is caused by an autosomal recessive mutation in the HFE gene. The onset of disease occurs in men between the ages of 40-60 years and post-menopausal women (55 years and older). Hemochromatosis Type II is known as Juvenile Hemochromatosis with onset commonly in the second or third decades of life. These patients have autosomal recessive mutation in either the Hemojuvelin (HJV) gene or the Hepcidin (HAMP) gene, both involved in the control of iron homeostasis. Other mutations in iron transport and regulatory genes cause hemochromatosis including gene defects in Ferroportin, TFR2, and Ceruloplasmin. Hemochromatosis Type III is an earlier onset form of adult hemochromatosis caused by a mutation in TFR2, which allows iron to get into the liver cells subsequently affecting Hepcidin expression [19,20]. The onset of type III hemochromatosis occurs in the third or fourth decades of life [19]. Lastly, Type IV hemochromatosis is an autosomal dominant mutation in the SLC40A1 gene, which produces Ferroportin.

5. DIAGNOSIS OF HEREDITARY HEMOCHROMATOSIS

Diagnosis of Hereditary Hemochromatosis is based on a clinical suspicion of iron overload given a patient's presentation. Situations that lead to this concern are unexplained fatigue in the face of conditions that suggest iron overload such as chronic liver disease or cirrhosis, cardiac enlargement, heart failure, or conduction defects. Type II diabetes, hypogonadism, decreased libido, or male sexual dysfunction can also be recognized in iron overload states secondary to HH. Furthermore, skin pigmentation and arthropathy of the second and third metacarpophalangeal joints are suggestive in considering the need for further diagnostic work-up [13]. Given that the liver is the metabolic epicenter of the body, decreased liver function likely contributes to fatigue. Iron overload impacts glucose control leading to the potential diagnosis of type II diabetes in that iron is able to bind to the pancreas and damage the Beta-cells responsible for insulin metabolism. Liver cirrhosis can cause damage to the biliary system, thus impeding the activity of the pancreas. Abdominal pain can result secondary to liver inflammation whereby circulating iron is able to release free radicals causing pain. Another result of iron overload is the pituitary gland where altered androgen production subsequent decreased libido, specifically in men, can occur. In women, a common finding is increased post-menopausal osteoporosis [21]. These processes create the complexity in clinical reasoning and medical decision making when dealing with the diagnosis of HH.

The initial recommendations for laboratory testing in the diagnosis of HH is to obtain serum iron panels. Many patients homozygous for the HFE mutation will have an increase in the serum ferritin levels. However, it has been shown that 50% of females and 20% of males that are C282Y HFE homozygotes have normal serum ferritin levels and may never need treatment [21]. In order to diagnose a patient with Hereditary Hemochromatosis and determine whether treatment is necessary, the patient must undergo evaluation of total iron, iron binding capacity, serum transferrin, and serum ferritin. Serum transferrin levels reflect the amount of iron that is bound to transferrin circulating through the body. Laboratory results that may be associated with HH include unexplained liver function test abnormalities, high serum ferritin levels (e.g. >300 ng/mL in men or postmenopausal women; >200 ng/mL in premenopausal women), High transferrin saturation (TSAT; >45 percent for men or >55 percent for women), along with HFE gene mutation [8]. A liver biopsy can also be performed to look for the presence of iron, cirrhosis, fibrosis, or scarring due to liver damage. Given the strong genetic etiology, genetic profiling is available which will test for the various genes that

can cause hemochromatosis. Lastly, imaging, such as a CT or an MRI, can be utilized to degrees of pathology and the effects of iron overload [13].

6. TREATMENT OF ADULT HEREDITARY HEMOCHROMATOSIS

Once a diagnosis of Hereditary Hemochromatosis is obtained, a treatment plan is constructed. The current available treatments for adult hereditary hemochromatosis are phlebotomy and iron chelating drugs. Phlebotomies are the most commonly used treatment because they have less side effects than the iron chelating drugs and tend to be more effective in treatment. The frequency of the therapeutic phlebotomies and the dosage of medications are case dependent and primarily based on serum transferrin and ferritin levels [13,19,20,22]. For more severe cases (serum ferritin levels that are >1000 ng/mL), the initial stage of treatment may consist of frequent phlebotomies one to two times weekly [13]. With each unit of blood that is removed from the body, it is estimated that there will be a 30 ng/mL decrease in the serum ferritin level [22]. Given that the normal range is from 50-150 ng/mL that is approximately 28 phlebotomies for the patient (given that their level is 1000 ng/mL) in order to reach a normal level. Once serum ferritin levels are within a normal range, the phlebotomies can decrease in frequency but continued monitoring of serum ferritin levels is common.

Several studies have shown patients report feeling better immediately following their phlebotomy treatment with symptomatic changes including decreased fatigue, better glucose management, and an improvement in hyperpigmentation [19,20]. However, the necessary frequency required for phlebotomy can lead to social determinants of health mainly encompassing compliance. The procedure itself can be time consuming in multiple respects. Patients may have limitations due to their employment, transportation, and access to appropriate facilities. Additionally, financial constraints may limit the amount of procedures that can be done in managing their hemochromatosis. Even though phlebotomies have been a common medical practice for hundreds of years, there are complications that can occur immediately following the procedure. Some patients will experience dizziness and hypotension following treatment and are required to increase the amount of post-phlebotomy salt solution in their diet. In severe cases of post-procedure hypotension, the treatments may have to be decreased. This decrease in treatments means that the time that it takes to get the patients iron levels stable will increase. Other complications with phlebotomy are infection at injection sites or inflammatory eruptions, called phlebitis. Problems with venous access will add to the complexity of patient management and may have the potential for medical emergencies if left unmonitored.

Some patients require dual treatment with phlebotomies and iron chelating drugs secondary to the severity of the iron overloading. The main iron chelating drugs that are used in adult Hereditary Hemochromatosis patients are deferoxamine and deferasirox.Deferirpone is another iron chelating drug that is in the same class but is not tolerable in patients with hereditary hemochromatosis [23]. Deferoxamine (DFO) has been approved for long term iron chelation use as it is non-toxic and effective in decreasing the serum ferritin levels. Pharmacokinetically, DFO is able to bind to iron in a 1:1 ratio and is able to release old iron from the reticuloendothelial system, precipitate it, and cause it to be excreted in the urine [23]. If the DFO does not bind, it travels to the parenchymal cells and releases some of the hepatic iron into the bile. In regard to cardiac muscle cells, the DFO is able to directly absorb iron accumulations in myocytes [24]. Oral deferoxamine is not optimal as it is not fully absorbed [23]. It is recommended that the drug be administered via an intravenous or subcutaneous route making home administration difficult. DFO has a short plasma half-life which requires continuous administration which is mandatory in order to keep the iron excretion rate elevated. This treatment is time consuming and expensive for patients. Acute

side effects of the medication include abdominal pain, nausea, vomiting, diarrhea, and hypotension. Chronic treatment can have side effects of visual and auditory neurotoxicity. High doses of DFO can cause pulmonary hypertension and leave the patient susceptible to several pulmonary bacterial and viral infections. Deferasirox (DFX) has a high affinity for iron and binds in a 2:1 ratio. A low affinity to other metals allows the drug to target only the iron present in the body. This medication can be taken orally and is soluble in water, juice, and can be administered on an empty stomach [23]. The common dosage of the medication is about 30 mg/kg/day but typically is calculated based on ferritin levels. Common side effects of DFX include abdominal pain, nausea, vomiting, diarrhea, rash, and eye problems. These side effects are more commonly seen in elderly patients with prior renal or hepatic diseases and low platelet counts. DFX is able to cause proximal renal tubular dysfunction and therefore the patient's serum creatinine levels, serum transaminase levels, and bilirubin should be monitored throughout course of treatment. Severe complications include metabolic acidosis, hypokalemia, and hypophosphatemia; therefore, complete blood counts (CBCs) should be monitored regularly as well. A growing concern amongst medical practitioners is potential drug withdrawal effects seen after ending therapy secondary to electrolyte abnormalities [23].

7. JUVENILE HEMOCHROMATOSIS

Type II hemochromatosis, also known as Juvenile Hemochromatosis (JH), is a form of iron overloading that has an earlier onset than adult hemochromatosis with an ancestral European inheritance pattern [25]. Mutations of the Hemojuvelin gene (HJV) that is located on the long arm of chromosome 1 at the 21.2 position (1q21.1) are the primary genetic etiology that is found in cases of Juvenile Hemochromatosis [26]. HJV gene mutations are the cause of the more severe iron overloading presentation at such a young age. There are over 30 possible mutations of the HJV gene causing Juvenile Hemochromatosis with the most common being a missense mutation resulting in a valine residue replacing a glycine at the 320th amino acid position (Gly320Val) [27]. Similar to HFE protein, HJV protein is responsible for maintaining proper levels of Hepcidin that function in regulating iron. The TfR1 and TfR2 complexes, HJV protein, and BMP receptor and protein work together to increase the Hepcidin expression within the body. Figure 4A represents the hepatocyte membrane without di-ferric iron present. HFE is bound to TfR1, and all of the involved proteins are solitary without induction of signaling pathways in the presence of apo-transferrin. In a normal physiologic response to di-ferric iron, the mechanism is similar to what is seen in Hemochromatosis. HFE is bound to TfR1 and is activated by the di-ferric protein, allowing the HFE to detach and travel to the TfR2 complex. When operational, the HJV protein is able to act as a co-receptor for the bone morphogenic protein (BMP) alongside the BMP receptor [20]. Following the activation of both complexes, the HJV/BMP and the TfR2/HFE join together to initiate the Hepcidin SMAD signaling pathway and regulating the hepatic levels of Hepcidin protein expression [25]. Ferroportin is internalized upon binding to Hepcidin and broken down and the excess iron can be excreted from the body. However, as a result of an HJV gene mutation leading to absence of Hemojuvelin, there is a decrease in the levels of Hepcidin which leads to unregulated activity of Ferroportin, increasing serum iron as shown in Figure 4B. Juvenile Hemochromatosis can also be caused by a mutation in the HAMP Hepcidin gene itself. The HAMP gene is located on Chromosome 19p13 which, when mutated, will lead to low levels of Hepcidin and subsequent iron overloading [25].

A common presentation of patients with Juvenile Hemochromatosis includes fatigue, hypogonadotropic hypogonadism, diabetes, and cardiomyopathy without a clear cause [28]. Similar to adults with HH, these symptoms can be vague for diagnosticians in JH in reaching appropriate conclusions. Fatigue, as seen in the adult form, is primarily due to the slowing

activity of excess iron on the body's metabolic and energy supplying pathways. When there is an excess in iron, accumulation is noted within associated organ sites thus affecting metabolic efficiency. Specific to these processes, patients developing hemochromatosis at a younger age may demonstrate more dramatic effects of iron overloading, for example, the effect of the pituitary iron accumulation tends to be more prevalent than in adult hemochromatosis patients.

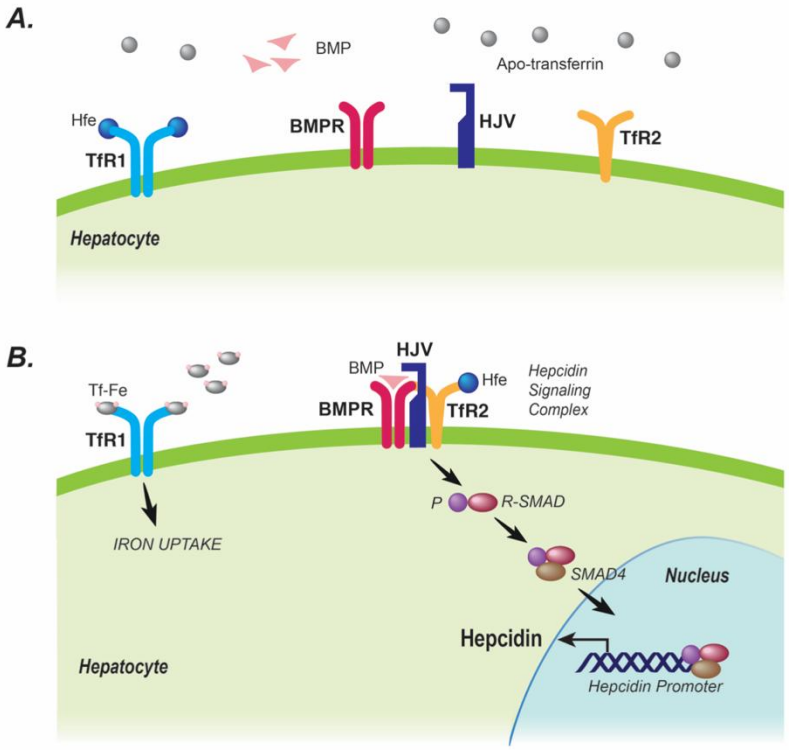

Fig. 4. Role of HJV in Mechanism Causing Juvenile Hemochromatosis

(A) *In the presence of apo-transferrin, TfR1, TfR2, HJV, and BMPR are separate and the HFE remains on the TfR1. (**B**) Di-ferric iron activates the HFE, and allows it attach to TfR2. BMP is able to bind to BMPR and HJV and this complex merges with TfR2/HFE to activate the SMAD SMAD/CoSmad pathway, increasing Hepcidin production.*

This leads to hypogonadotropic hypogonadism and, in males, this presents as a decreased libido and testosterone levels, resulting in problems for pre-pubescent patients. In females, amenorrhea is the common result of the hypogonadism [28]. The pancreas is another major target of iron accumulation whereby destruction of the beta-cells is noted much as that discussed in the adult form of HH. The most common pathologic change in Juvenile Hemochromatosis patients is cardiomyopathy secondary to iron accumulation in cardiac myocytes. Eventually the excess strain that is caused on the heart can lead to heart enlargement, failure, and conduction abnormalities to the point where heart transplantation is considered in certain cases. In terms of prognosis, cardiac complications are the number one cause of death in patients with juvenile hemochromatosis [25].

8. DIAGNOSIS OF JUVENILE HEMOCHROMATOSIS

Diagnosis of Juvenile Hemochromatosis is similar to the adult form. For pediatric and young adult patients, the normal transferrin saturations fall between 16% and 45% of transferrin

that is saturated with iron [27]. In a patient with Juvenile Hemochromatosis, these values can be close to 100%. The normal range of serum ferritin levels for male and female children and adolescents is 100-125 ng/mL, with JH patients exhibiting levels over 1000 ng/mL.These values are important in that they are able to be used as a prognostic tool for both liver and heart complications. Other diagnostic laboratory tests include complete blood counts, fasting blood glucose, hemoglobin A1C, FSH/LH panels, liver function testing, and specific iron panels as clinically indicated [27]. For cases involving iron overload in adult hemochromatosis, liver biopsy is considered more frequently. However, this procedure has increased risk in pediatric cases, including the risk of bleeding or bile leakage, and as such, is typically avoided if possible. Targeted gene sequencing is used to confirm the diagnosis following serum testing. A frequent finding is a H63D heterozygosity for the HFE gene, leading to decreased Hepcidin expression. Multigene sequences are able to test for all three iron related genes; HFE, HJV, and HAMP whereas single gene sequencing can test for HJV and HAMP mutations [20,29].

Prognosis for Juvenile Hemochromatosis is primarily linked to cardiac function as it is the main cause of death in these patients. This can be obtained by a number of tests including CT and MRI. Other cardiac studies include a transthoracic echocardiogram or an electrocardiogram (ECG) in order to monitor any changes in cardiac function [28]. Common abnormalities that are seen with these tests include left ventricular diastolic dysfunction secondary to heart failure. If there are arrhythmia changes noted on the ECG, a Holter monitor may be prescribed for the patient to assess for cardiac conduction abnormalities in an ambulatory fashion [28].

9. TREATMENT OF JUVENILE HEMOCHROMATOSIS

Phlebotomy is the primary form of treatment in patients with Juvenile Hemochromatosis. The frequency of the treatment is based on the serum ferritin with a target of 50-150 ng/mL. With each phlebotomy, up to 200 mg of iron can be removed from the blood [28] Since the progression of the juvenile form of the disease is so rapid, the iron levels reach higher levels at a quicker rate than in adult hemochromatosis [26]. This expedited rate of accumulation, and the fact that the iron mainly affects the heart in these patients, creates a time sensitive element in the course of treatment. For children and adolescents with the condition, the procedure can be difficult secondary to problems with venous access and treatment frequency.

The use of iron chelating drugs in children tends to have increased side effects associated with the treatment. Deferoxamine (DFO) causes severe generalized pain when administered to children which is likely secondary to its intense pharmacokinetic pathway and its specific effects in children. For this reason, Deferasirox (DFX) is the main drug that is used in juvenile cases as it is the most tolerated [24,25]. DFX is able to target the cardiac iron accumulation directly which can help alleviate complications due to iron-induced heart failure. The dual treatment of phlebotomy and iron chelating drugs is only used in extreme cases of iron overloading. If FSH/LH levels are low, or there are physiological related changes secondary to hypogonadism, the patient can be administered testosterone or estrogen as needed [28].

10. ADVANCES IN TREATMENT OF HEMOCHROMATOSIS

Advances in treatment are continually being sought given the complexity and side effect profiles of current therapy. Scientists and physicians are working together to establish alternative treatments. A relatively new treatment, called erythrocytophoresis, has surfaced and proves to be effective in lowering serum iron levels. Erythrocytophoresis allows for iron

containing red blood cells to be removed from the body while preserving the platelet and plasma levels in the blood. Erythrocytophoresis, while very effective at lowering the serum iron levels, is expensive and requires special personnel trained in its administration [28]. If this technology is able to expand, it is likely to be incorporated into treatment plans worldwide. In addition, a novel pharmaceutical approach of using matriptase-2 inhibitors to prevent cleavage of HJV to treat iron overloading is being examined [30,31]. Matripase-2 inhibitors will increase the therapeutic levels of Hepcidin to treat iron overloading.

Patient compliance with treatment for iron overloading is a challenge to clinicians treating Hereditary Hemochromatosis. A study was conducted to evaluate patient compliance with phlebotomy therapy for iron overload in hemochromatosis patients which included a total of 118 patients treated for iron depletion and 142 for maintenance therapy. The results for maintenance therapy indicated that 96.6% achieved iron depletion in the first year. However, compliance with maintenance therapy decreased 6.8% annually. Therefore, there is a constant decline in the percentage of patients who comply with maintenance therapy [32]. However, alternative strategies for treatment may be uncovered by studying mouse models. Animal studies are able to help scientists understand more about physiologic conditions, pharmacologic targets, and possible new treatments that could be used for a number of diseases and conditions. Hereditary Hemochromatosis has been studied for years in terms of iron metabolism and homeostasis. Mouse models have been used in several studies to help scientists understand iron metabolism and transport as well as for developing advances toward identifying a pharmacological target for iron overload disorders [33,34]. The hereditary erythroblastic anemia mouse mutant (gene symbol hea) and iron deficient flaky skin mouse mutant (gene symbol fsn) have been used in studies to address iron overloading. Mapping the locations of these mutations on the mouse genome led to the realization that the hea and fsn are allelic mutations of the same gene, Ttc7 (tetratricopeptide repeat domain 7) and lead to an iron metabolism disorder [34]. Previously, Beamer et. al. demonstrated that fsn mice excrete 100X more non-heme iron in their urine than normal mice after injection of radioactive iron [35]. Whereas fsn mice produce an abnormal TTC7 protein from their Ttc7 mutation, the mutation in hea mice have a null mutation with most of the Ttc7 gene being deleted and no TTC7 protein made. In humans, the gene homolog (TTC7A) has been noted to cause gastrointestinal defects in the form of irritable bowel syndrome and immune deficiency syndrome in homozygote or compound heterozygote genotypes. However, there are no deleterious effects for genotypes in the heterozygous state in mouse and man [36]. Therefore, these data on mouse mutants have yielded important findings on potential treatment impacting hemochromatosis and suggests that inhibition of the TTC7 protein may be able to overcome iron overloading by excreting the excess iron in their urine [33]. These studies may have led to the identification of a new potential pharmacological target which will be an alternative treatment to phlebotomy for iron overloading diseases [34].

For any patient with an iron overloading condition, preventative measures should be taken to avoid adding excess iron through the diet. It is important that patients avoid alcohol consumption, supplements containing iron or vitamin C, or eating uncooked shellfish. Limiting red meat is imperative in keeping iron levels as low as possible [28]. Finally, a regimen of routine monitoring through symptom surveillance, preventive maintenance, and laboratory testing should be the mainstay of management in all forms of hemochromatosis.

11. CONCLUSION

The metabolism of iron in the human body is a complex mechanism associated with many genetic factors. Mutations in the function of genes controlling iron management lead to significant disorders such as hemochromatosis in the adult and juvenile forms. Diagnostic

processes are related to the clinical presentations of patients and lead to concerns for iron overload states which require clinicians to embark on specific processes in accurately diagnosing these disorders so that effective treatment can be applied. It is hoped that further advances in medicine and clinical science can lead to more effective and safe treatments to manage these chronic disorders decreasing the burden of hemochromatosis on the adult and pediatric populations alike.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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