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MINIREVIEWS

Management of human factors engineering-associated hemochromatosis: A 2015 update

Menaka Sivakumar, Lawrie W Powell

Menaka Sivakumar, School of Medicine, the University of Queensland, Brisbane QLD 4029, Australia

Lawrie W Powell, Centre for the Advancement of Clinical Research, Royal Brisbane and Women's Hospital Campus, Brisbane QLD 4029, Australia

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Correspondence to: Lawrie W Powell, MD, PhD, Director, Professor, Centre for the Advancement of Clinical Research, Royal Brisbane and Women's Hospital Campus, Level 4, UQ Centre for Clinical Research, Building 71/918, Brisbane QLD 4029, Australia. lawrie.powell@qimrberghofer.edu.au
Telephone: +61-7-36462352
Fax: +61-7-36462355

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Abstract

This review focuses on the management of iron metabolism and iron overload experienced in the hereditary condition, human factors engineering (HFE)-associated hemochromatosis. Hemochromatosis refers to a group of genetic diseases that result in iron overload; the major one globally is HFE-associated hemochromatosis. The evolution in understanding of the most common form of hereditary hemochromatosis, being the substation of cysteine to a tyrosine at position 282 in the *HFE* gene, has been extensively studied Novel mutations in both *HFE* and non-*HFE* genes have been indicated in this disease which hold significance in its application for the Asia-Pacific region. In conditions with iron overload, the storage of excess iron in various body tissues leads to complications and toxic damage. The most common presenting complaint for this disease is malaise, lethargy and other non-specific symptoms. In order to diagnose hereditary hemochromatosis, there are biochemical, imaging and genetic testing options. Currently, cascade screening of affected families is preferred over population-level screening. The mainstay of treatment is venesection and the appropriate approach to treatment has been consolidated over the years. Recently, the indications for venesection therapy of hemochromatosis have been challenged and are the subject of ongoing research.

Key words: Human factors engineering; Iron storage diseases; Genetics; Venesections; Hemochromatosis

Core tip: The concept of hemochromatosis as a single disease entity has changed to an iron storage disease resulting from several genetic disorders although the final common metabolic pathway is inappropriate iron absorption from the intestine and progressive tissue iron loading. The most common form of the disease is due to a mutation in the human factors engineering gene resulting in cysteine tyrosine substitution at position 282 in the molecule. This mutation is relatively common in populations of northern European extraction but is rare

in other populations. In contrast other rarer forms of hemochromatosis resulting from other mutations in the hepcidin pathway are quite ubiquitous. The main stay of treatment remains venesection although new oral iron-chelating agents show promise.

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INTRODUCTION

The clinical and molecular research surrounding the clinical syndrome of hemochromatosis has been substantial in the last two decades even though it has been recognized in its advanced state for more than 100 years[1]. A mutation in the human factors engineering (*HFE*) gene was identified as the cause for more than 90% of cases of classic hemochromatosis[2] in most countries except for the Mediterranean region where it is responsible for around 65% of the cases. The genetic cause for hemochromatosis is more common in individuals with a northern European ancestry; however, the clinical manifestation, or incidence of biochemical abnormalities and clinical disease, is not as common in these populations. Although mutations in the *HFE* gene are most common, there are other forms of iron overload caused by mutations in other iron regulatory molecules that present as distinct clinical diseases. Over time, population studies have served the purpose of outlining the risk to an individual with a genetic mutation and the clinical investigations available for assessment and monitoring have improved. The treatment of hemochromatosis is the one aspect of this condition that has evolved the least over the years with phlebotomy still being the main therapy available. However, the treatment has potential for change with increased research on new therapeutic agents under trial. Although the European Association of the Study of Liver (EASL) and the American Association for the Study of Liver Disease have outlined appropriate treatment regimens, recent research have challenged these guidelines suggesting there is a benefit in beginning treatment early for patients with even mildly elevated iron levels but with or without clinical manifestation. According to current guidelines, the threshold of serum ferritin at which to start treatment is currently taken as above the normal range where the normal range for serum ferritin in men is 24-336 μg/L and in women is 11-307 μg/L. The current clinical standard is to maintain the serum ferritin at 50-100 μg/L[3].

PATHOPHYSIOLOGY

Iron homeostasis

The role of iron in the body is a crucial one from oxygen transport in hemoglobin and oxidative phosphorylation to the production of red blood cells and other functions[4,5]. In situations with overload, there are consequences in disease and mortality to be discussed later in this paper however the extent of this risk is still debated[6-9]. Beginning with iron, when it is consumed, it can enter the body in two forms: Either heme or non-heme[10,11]. Heme is mostly commonly ingested as animal protein and non-heme is *via* vegetables. However, there is no mechanism for the excretion of iron which is toxic in overload. Uncontrolled loss (1-2 mg) in menses, bleeding and the sloughing of skin are the only methods for iron removal.

In order to understand iron homeostasis, a discussion regarding the pathway of iron is necessary. Iron is absorbed on the apical surface of enterocytes in the duodenum and proximal small bowel. Non-heme iron can be either ferrous (Fe^{2+}) or ferric (Fe^{3+})[4]. It is important to note that since ferrous iron is more soluble, it is necessary for ferric iron to be reduced to ferrous iron prior to absorption[12]. In order to reduce ferric iron found in non-heme iron to the ferrous state both gastric acidity and duodenal cytochrome B (DCytB1) have been identified as well as other non-enzymatic pathways[13,14]. On the apical surface of enterocytes, the divalent metal transport 1 (DMT1) protein takes in ferrous iron[14]. The DMT1 protein also serves to transport manganese and copper (Figure 1).

From the enterocyte, iron uptake into tissue is mediated by transferrin receptors (TfR1 and TfR2). In transportation, iron is consistently bound to a molecule due to its ability to form free radicals. Transferrin, the carrier protein for iron binds to the TfR1 and is taken up by endosomes, where transferrin is cleaved and the receptor recycled back to the cell surface[15]. In the case of iron overload, excess iron is stored in complexes of hemosiderin or ferritin. Another form of iron storage is hemosiderin which is a by-product of ferritin degradation[13].

On the basal surface of enterocytes, ferroportin (FPN1) is the sole expressed exporter in cells. Iron is released into circulation when FPN1 interacts with ferroxidase and hephestin. Hephestin next acts to oxidize the iron and the iron is then immediately bound to the transport molecule transferrin (Tf)[4]. Another important regulator of iron homeostasis is ferroportin, a protein which acts to export stored iron from enterocytes and other intracellular stores. A small hepatic peptide, hepcidin, negatively regulates ferroportin[12] by causing the internalization and degradation of this protein thereby affecting the export of iron. In summary, hepcidin reduces iron uptake and serum iron[12,16]. There have been certain factors such as iron, inflammation and oxidative stress that have been demonstrated to have an inhibitory effect on the expression hepcidin. However, hepcidin regulation is not a topic that is completely understood.

Genetics

Hereditary Hemochromatosis is caused by different

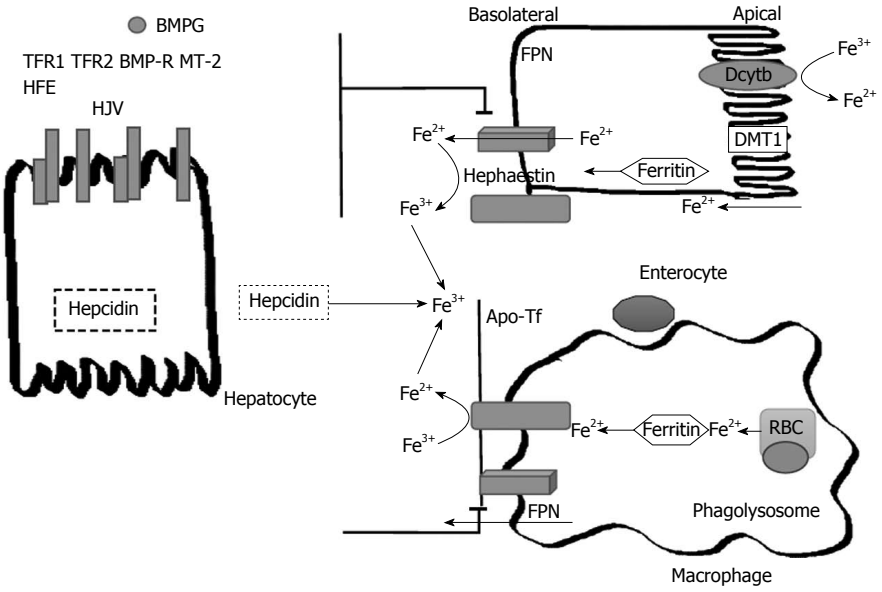

Figure 1 Pathways of Iron transport and metabolism. The pathway of iron in enterocytes and macrophages as effected by hepcidin. Dietary non-heme iron is taken into the enterocyte *via* the DMT1. In order for iron to move across the brush border of the enterocyte *via* DMT1, it must first be reduced from Fe^{3+} to Fe^{2+} by DcytB. Once inside of the cell, iron can be sequestered into storage as ferritin or continue along the pathway into circulation. In this process, the iron exporter FPN located on the basolateral surface of enterocytes is responsible for the transport of ferrous iron into circulation. Once iron is in circulation, hephaestin oxidizes the ferrous iron back into the ferric state and then it immediately binds to plasma transferrin. The iron is now able to travel to sites of iron storage or where iron is required. In macrophages, phagolysosomes containing senescent RBC release iron which is also then exported into circulation *via* ferroportin. Hepcidin, a protein derived from the liver, regulates iron transport in the body by causing the internalization and degradation of FPN transporters on macrophages and the basolateral surface of enterocytes. Hepcidin is regulated based on body iron requirements by signals produced from the interaction between different proteins on hepatocytes. The interaction of the HFE protein and transferrin receptors 1 and 2 (TFR1 and TFR2) and the interaction between bone morphogenic protein (BMP6), hemojuvelin (HJV) and the bone morphogenic protein receptor (BMP-R) and matriptase 2 (MT-2). RBC: Red blood cells; FPN: Ferroportin; DMT1: Divalent metal-ion transporter 1; DcytB: Duodenal cytochrome B; HFE: Human factors engineering.

Table 1 Classification of iron overload and hemochromatosis

Genetic iron overload (primary)
Type 1 HFE-associated hemochromatosis
C282Y homoyzygosity
C282Y/H63D compound heterozygosity
Type 2 juvenile hemochromatosis
2A hemojuvelin mutations
2B hepcidin mutations
Type 3 TfR2-related hemochromatosis
Transferrin receptor 2
Type 4 ferroportin disease
Loss of function mutations, also called type 4A or "M"
Hepcidin resistance mutations, also called type 4B or "H"
Aceruloplasminemia
Ceruloplasmin mutations
A(hypo)transferrinemia
Acquired iron overload (secondary)
Ineffective erythropoiesis
Thalassemia major
Sideroblastic anemia
Chronic hemolytic anemia
Dietary iron overload (African)
Parenteral iron overload (including transfusional overload)

HFE: Human factors engineering.

mutations that alter the regulatory proteins involved in iron homeostasis and hepcidin pathways. The genetic causes for hemochromatosis can be categorized into *HFE* gene mutations and non-*HFE* gene mutations (FPN, TFR HJV)[2]. While non-*HFE* gene mutations are not as common as *HFE* gene mutations, there is an increased proportion of these mutations in non-Northern European populations[4]. Therefore, this information is of significance in Asia-Pacific populations[4].

The knowledge and classification of hemochromatosis and other iron overload diseases has become more detailed in the last 2 decades (Table 1). Mutations in the genes encoding HFE, TfR2, hemojuvelin and hepcidin all lead to decreased hepcidin activity and increased iron absorption, resulting in the syndrome of hemochromatosis[5]. Mutations in *HFE, HJV, HAMP, TFR2* and *SLC40A1* have been linked to the various types of hemochromatosis[2,5].

HFE-associated hereditary hemochromatosis

In Northern European ancestry, an amino acid substitution specifically at position 282 of the HFE protein is the mutation most responsible for iron overload in this population[5]. The C282Y substitution is rare outside those of white ethnicity[17-19]. *HFE* is tightly linked to the HLA-A locus on chromosome 6p. Persons who are homozygous for the mutation are at increased risk of iron overload and account for 80% to 90% of clinical hereditary hemochromatosis in persons of northern European descent[6-9]. Pietrangelo suggest that between 10% and 33% of homozygous patients develop hereditary hemochromatosis[4,20]. This suggests that there are other genetic and non-genetic factors in the disease[21].

There have been alternative mutations of HFE identified, primarily H63D and S65C; however, these mutations have not been proven to cause substantial iron overload[4]. In order to produce symptomatic disease, a heterozygous mutation is necessary. Since there is an increased prevalence of C282Y, and H63D is more relevant clinically, compound heterozygotes with symptomatic disease are usually C282Y/H63D[2,22-24].

Non-HFE associated hereditary hemochromatosis

Discussion regarding non-HFE associated hemochromatosis is beyond the scope of this paper.

CLINICAL MANIFESTATIONS

Hereditary hemochromatosis is most commonly associated with liver disease including cirrhosis, but the clinical manifestations of iron overload are diverse and involve many other organs. Hemochromatosis is an overall underdiagnosed disease due to the idea that it is a rare condition and also associating diagnosis with clinical features seen in advanced disease such as cirrhosis, diabetes and skin pigmentation[3]. Genetic susceptibility for hemochromatosis is seen in approximately one in 250 Caucasians; however, fully expressed disease with end-organ manifestations is seen in fewer than 10% of these individuals[3]. Hemochromatosis patients mostly present with non-specific symptoms such as lethargy, arthralgia and weakness[25,26]. The other more commonly affected organ systems include liver, heart, pancreas, pituitary, skin and joints. Iron deposition in the conducting bundles and parenchyma of the heart result in cardiac arrhythmias and cardiomyopathy in 2%-19% of symptomatic patients[27,28]. Diabetes mellitus (DM) can be seen in up to 60% of symptomatic homozygotes but the rates of DM in asymptomatic patients are comparable to controls[7,29]. Endocrine dysfunction can occur as a result of iron deposition in pituitary and parathyroid glands[27,30]. Arthropathy is also observed in symptomatic and asymptomatic patients due to calcium pyrophosphate deposition in the articular cartilage, not iron sequestration and primarily involves the 2nd and 3rd metacarpophalangeal joints[25,31].

MANAGEMENT AND TREATMENT

Treatment for hemochromatosis with venesection (phlebotomy) has remained unchanged over the years[5]. Venesection as a treatment has two purposes: Directly reduce serum iron by depleting hemoglobin levels and to replace the depleted circulating serum iron by mobilizing iron stores from tissues. Early intervention, prior to the onset of symptoms, improves patient prognosis[32]. Furthermore, venesection in symptomatic individuals improves certain symptoms, such as skin pigmentation, while not having an effect on others such as cirrhosis and arthropathy[32].

According to EASL clinical practice guidelines, the threshold of serum ferritin at which to start treatment is currently taken as above the normal range. In regards to maintenance, the advocated standard practice is to maintain the serum ferritin at 50-100 μg/L and this is usually achieved with 3-6 mo of venesection[32]. It has been identified that the morbidity and mortality related to hereditary hemochromatosis can be greatly reduced by beginning treatment (phlebotomy) before the development of cirrhosis and/or diabetes. As a result of these findings, it is generally recommended that individuals at risk have prompt identification and pre-emptive treatment[32]. The pre-emptive treatment should be extended to involve those with homozygous HH that are asymptomatic and have markers of iron overload. Also, individuals with indications or evidence of increased level of hepatic iron should be treated. In summary, the American Association for the Study of Liver Disease recommends that in the absence of indicators suggestive of significant liver disease (alanine amiotransferase, aspartate transaminase elevation), C282Y homozygotes who have an elevated ferritin (but < 1000 μg/L) should proceed to prophylactic phlebotomy without a liver biopsy where target levels of phlebotomy should be a ferritin level of 50-100 μg/L[3,23,32].

Traditionally, it was suggested that serum ferritin be maintained below 50 μg/L, but this has been updated to the range stated. Treatment guidelines also suggest yearly follow-up for the patients whose ferritin levels are at the normal range. This treatment strategy works for types 1-3 hereditary hemochromatosis but patients with type 4a may not tolerate venesection due to the irregular iron export from cells therefore treatment must be intermittent and is more complicated[32].

Generally, 1 unit of blood is understood to contain approximately 200-250 mg of iron but the amount of iron that is removed each venesection can be variable[3]. It has been reported that on average, phlebotomy removes around 200-250 mg of iron per session[33]. Therefore, treatment must be provided on a personalized and case by case basis for each patient for appropriate venesection intervals and treatment regiments.

Although the treatment has remained the same for many years, there is still debate regarding the appropriate serum ferritin levels for maintenance of hemochromatosis. A recent study conducted by Bardou-Jacquet *et al*[6] found that early and sustained iron removal is beneficial as patients with serum ferritin levels between normal and 1000 μg/L, when treated, have reduced cardiovascular and extra-hepatic related mortality rates despite normal liver-related mortality rates. This study suggests that patients with even mild iron overload should be treated which builds on current management guidelines. However, this subject remains controversial.

CONCLUSION

There is a continuing need to study the factors contributing to hemochromatosis due to the variable clinical penetrance of HFE mutations and the worldwide

prevalence of hemochromatosis in the absence of HFE mutations. Hemochromatosis has been divided into HFE-associated hemochromatosis related to mutations affection iron transport and absorption and also HFE negative hemochromatosis or disease without HFE mutations. There is an incomplete understanding of the reasons for incomplete penetrance of disease phenotype in those with HFE mutations but recent research has revealed the presence of at least one other significant modifying genetic mutation[34]. Individuals at risk for hemochromatosis with genetic mutations and with or without symptomatic disease are recommended to pursue treatment at the earliest time possible and prior to any disease as this can help prevent further morbidity and mortality associated with hemochromatosis. Research advancement is opening doors for the management and treatment of iron overload as recent research has begun to develop the importance of treating mild iron overload due to its identified relation with reduced cardiovascular and extrahepatic related mortality rates.

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