The global burden of iron overload

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Abstract There have been major developments in the field of iron metabolism in the past decade following the identification of the *HFE* gene and the mutation responsible for the C282Y substitution in the HFE protein. While HFE-associated hemochromatosis occurs predominantly in people of northern European extraction, other less-common mutations can lead to the same clinical syndrome and these may occur in other populations in the Asian-Pacific region. The most common of these is the mutation that leads to changes in the ferroportin molecule, the protein responsible for the transport of iron across the basolateral membrane of the enterocyte and from macrophages. Recent research has unraveled the molecular processes of iron transport and regulation of how these are disturbed in hemochromatosis and other iron-loading disorders. At the same time, at least one new oral iron chelating agent has been developed that shows promise in the therapy of hemochromatosis as well as thalassemia and other secondary causes of iron overload.

It is pertinent therefore to examine the developments in the global field of iron overload that have provided insights into the pathogenesis, disease penetrance, comorbid factors, and management.

Keywords Haemochromatosis · Iron metabolism · HFE haemochromatosis · Secondary iron overload

Introduction

The clinical syndrome of hemochromatosis has been recognized in its advanced state for more than 100 years [1], but it is in the last 2 decades that clinical and molecular research into this disease has accelerated. Following identification of the mutation in the *HFE* gene, which is responsible for more than 90% of cases of classic hemochromatosis [2], it was recognized that the genotypic predisposition is common among those of northern European ancestry but that the incidence of biochemical abnormalities and clinical disease is less frequent. The recognition of the HFE mutation has allowed other forms of iron overload to be diagnosed as distinct entities, typically related to mutations in other iron-regulatory molecules. Recent research in the field of iron metabolism has deepened our understanding of the molecular processes of iron transport and regulation and how this is disturbed in hemochromatosis. At the same time, population studies better describe the risk to an individual with a genetic mutation and clinical investigations have improved the tools available for assessment and monitoring. One aspect of this condition that has changed the least is the treatment, with the ancient practice of bloodletting still the main therapy available. With new therapeutic agents under trial, this too may soon be changing. This review focuses on the recent

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developments in the field of genetic hemochromatosis, including the molecular basis of iron metabolism, relevant genetic mutations, and advances in investigations and therapy, and places these in a global perspective.

Molecular basis of iron overload

Knowledge regarding the complexities of human iron metabolism has increased significantly in the last 2 decades and the classification of iron overload diseases has become more detailed (Table 1). The mutation accounting for most of the iron overload in populations of northern European ancestry results in an amino acid substitution at position 282 of the HFE protein. The C282Y substitution is rare outside those of white ethnicity [3–5], although case reports of other mutations exist [6]. Iron overload in Asian, African, and Pacific Islander populations has been well-recognized and is typically due to abnormalities in non-HFE iron-related molecules.

The number of molecular players recognized in the field of iron homeostasis has grown, and it is now recognized that there are complex interactions between the enterocyte, iron regulatory molecules, and iron stores (reviewed in Ganz [7]). Hepcidin is known to be the central controller acting to decrease iron absorption by binding to ferroportin

and causing its internalization and degradation [8]. Ferroportin functions to export iron across the cell membrane of enterocytes and macrophages into the extracellular space, thus the net effect is to reduce iron availability. The regulation of hepcidin is tightly controlled in response to both physiological and pathological processes.

Hepcidin expression is reduced when the demand for iron increases, such as in states of iron deficiency and hypoxia [9]. This produces an increase in the iron absorbed across the duodenal mucosa as well as greater iron release from macrophages, thus providing a continued supply for erythropoiesis. Alcohol consumption also decreases hepcidin transcription, and this effect appears to occur through the induction of oxidative stress [10, 11]. It is possible that this contributes to the increased iron stores commonly seen in alcoholic liver disease. Both iron loading and inflammation have been shown to increase hepcidin transcription and reduce iron availability [12]. Prolonged inflammation causing persistently elevated levels of hepcidin is postulated to be the cause of anemia of chronic disease. The iron accumulation seen in HFE hemochromatosis represents a loss of the negative feedback control with a failure to upregulate hepcidin expression despite excessive and inappropriate duodenal absorption [13].

The exact role of the HFE protein and the mechanism by which a common mutation can lead to iron loading are yet to be completely elucidated, but elegant animal models have provided valuable insights into this complex cross-talk. HFE is predominantly expressed on hepatocytes, known to be the site of production of hepcidin [14], although immunohistochemical studies have also demonstrated the presence of HFE in the intestinal crypts [15]. Mice with tissue-specific HFE ablation have provided evidence that disturbed HFE expression in the intestine or macrophage does not alter iron homeostasis [16, 17]. In contrast, mice lacking normal hepatic HFE expression will develop a hemochromatosis phenotype, suggesting that it is the liver that remains the central site of iron control [17].

HFE has been shown to interact with transferrin receptors (TfR) 1 and 2 [18, 19]. Again, genetically altered mice have provided insights into the nature of this interaction and suggest that HFE competes with transferrin in binding to TfR1 and that if HFE–TfR1 binding is experimentally altered to become constitutively active, iron overload develops [20]. Conversely, an interruption in the association between TfR1 and HFE leads to elevations in hepcidin and subsequent iron deficiency. A model is therefore postulated whereby HFE unbound by TfR1 in the setting of iron sufficiency stimulates hepcidin, thus reducing iron release by enterocytes and macrophages (Fig. 1). The interaction of HFE with TfR2 does not compete with transferrin and leads to an increase in hepatic TfR2 [21]. This iron-sensing HFE–TfR2 complex may then interact

Table 1 Classification of iron overload and hemochromatosis

Genetic iron overload (primary)

Type 1 HFE-associated hemochromatosis

C282Y homozygosity

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” (macrophages) phenotype

Hepcidin resistance mutations, also called type 4B or “H” (hepatocyte) phenotype

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)

Fig. 1 A proposed schema of hepcidin regulation in hepatocytes. Functional HFE expression is associated with increased transcription of the *HAMP* gene and synthesis of hepcidin, which appears to be the key regulator limiting inappropriate absorption of iron. HFE and diferric holo-transferrin compete for binding sites in the same region on Tfr1. The higher binding affinity of diferric holo-transferrin “frees up” HFE to interact with Tfr2 and then exert a positive influence on downstream hepcidin production. Whether HFE actually binds to Tfr2 remains unproven. It is proposed that HFE–Tfr2 functions as a complex and may interact with another complex of BMPR-I, BMPR-II, and HJV, which, when stimulated by BMPs (2, 4, and 9), activates SMAD-dependent intracellular pathways. The final common step of this cascade is the synthesis of hepcidin. Defects in any of the key players, including HFE, Tfr2, and HJV, have been shown to lead to iron-loading states associated with inappropriately low hepcidin levels. There has also been interest in other circulating factors (e.g., GDF15 and sHJV), which can negatively affect the production of hepcidin. *Tfr1* type 1 transferrin receptor, *Tfr2* type 2 transferrin receptor, *BMPR-I* type I BMP receptor, *BMPR-II* type II BMP receptor, *BMPs* bone morphogenetic proteins, *HJV* hemojuvelin, *GDF15* growth differentiation factor 15, *sHJV* secreted hemojuvelin

with both hemojuvelin and bone morphogenetic protein (BMP) to bind hepatocyte BMP receptors and activate hepcidin expression via SMAD-dependent pathways [7, 22–24]. It is clear that mutations in hemojuvelin and Tfr2 lead to an iron overload phenotype and that the final common pathway is inappropriately impaired hepcidin activity. It has recently also been recognized that common polymorphisms in BMP genes may influence the severity of iron loading in HFE hemochromatosis [25]. Clearly, this is an exciting and rapidly progressing field, though further research is needed to confirm the molecular basis of a postulated model of impaired iron metabolism.

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. Mutations within the ferroportin gene produce differing disease patterns depending on the nature of the alteration. Type B ferroportin disease produces a disease similar to HFE hemochromatosis due to mutated ferroportin, which is resistant to the action of hepcidin [26]. Reduced ferroportin degradation leads to iron loading in hepatocytes and elevated transferrin saturation. The disease resulting from loss-of-function mutations results in a distinctly different phenotype with iron retention predominantly within macrophages, little elevation in the transferrin saturation, and a milder pattern of liver disease [27]. Several different mutations have now been reported in families of varying ethnicity [28–31] and considerable phenotypic variability has been noted. It is likely that this classification will be proved an oversimplification as our understanding of this field increases. It should be noted that ferroportin disease is considered the only form of genetic hemochromatosis following a dominant pattern of inheritance and that this form of hemochromatosis occurs in nonwhite populations [29].

Secondary iron overload with deposition of iron in parenchymal cells occurs in chronic disorders of erythropoiesis, particularly in those due to defects in hemoglobin synthesis or ineffective erythropoiesis such as sideroblastic anemia and thalassemia. In these disorders, iron absorption is increased via downregulation of hepcidin [32]. In addition, these patients require blood transfusions and thus accumulate more iron. A detailed discussion of secondary iron overload is beyond the scope of this article.

Clinical manifestations

Although most equate genetic hemochromatosis with liver disease, including cirrhosis, iron loading produces dysfunction in other organs. Cardiac arrhythmias and cardiomyopathy occur in 3–10% of symptomatic patients and are related to iron deposition in the conducting bundles and parenchyma, respectively [33, 34]. The incidence of diabetes mellitus has been variably reported in the literature (12–48% of symptomatic C282Y homozygotes [35]), although its incidence in asymptomatic patients is similar to controls [36, 37]. Iron may also be deposited in other glands, such as the pituitary and parathyroids and less commonly the thyroid, with consequent endocrine dysfunction [33, 38]. Importantly, arthropathy occurs in patients both asymptomatic and symptomatic for liver disease and appears to be unrelated to serum ferritin levels in homozygotes [37]. Frank arthritis is due to the

deposition of calcium pyrophosphate in the articular cartilage, and this manifestation is not affected by phlebotomy.

Penetrance

Until the cloning of the *HFE* gene and the description of the 2 common mutations (C282Y and H63D), the diagnosis of hemochromatosis was made following a liver biopsy and liver iron quantification in a patient with elevated iron indices or clinical signs of iron loading. With the advent of genetic testing, it became clear that the mutation leading to the C282Y substitution is a commonly inherited trait in those of northern European extraction [39]. Most C282Y homozygote males will develop biochemical indices of iron loading [36, 37, 40–43], but often this is not enough to lead to disease without comorbid factors [40] (Fig. 2). Active research in 2009 now centers on describing the risk of iron loading and disease in those with the genetic predisposition, and 2 recent articles inform this discussion.

One of the most significant recent developments in this regard come from a large, Australian population-based longitudinal study of 31,000 adults [37]. Genotyping identified 203 C282Y homozygotes and a clinical assessment of these subjects and appropriately matched controls were performed to define disease presence. Importantly, clinicians were blinded to HFE genotype results. Liver biopsies were recommended for standard indications. The present study demonstrated the presence of iron overload-related disease in 28% of males but only 1% of women

homozygous for the C282Y mutation. A serum ferritin level of more than 1,000 ng/ml was shown to be a risk factor for liver disease. Hepatic fibrosis and cirrhosis were present in 14 and 3%, respectively, of male C282Y homozygotes. This may be an underestimate because not all with clinical indications underwent biopsy and also subjects previously diagnosed with hemochromatosis were excluded from analysis. The presence of a clinically diagnosed arthropathy was unrelated to the serum ferritin level in C282Y homozygous subjects. The strengths of this study are its size, strictly defined disease definitions as assessed by clinicians blinded to genotype, and the long follow-up period averaging 12 years. It therefore provides robust data on disease penetrance in the general white population.

Crooks et al. [35] provided complementary information regarding disease associations of clinically diagnosed hemochromatosis in a primary care cohort of patients and sex/age-matched controls. Again, this work was conducted on a large scale (501 patients with hemochromatosis and 4,950 controls) identified through a United Kingdom-based general practice database over 15 years. There is a clear selection bias in these patients as they presented to medical care and were diagnosed during the follow-up period. As the authors describe, the cohort is placed between a “healthy population and a tertiary care cohort.” It must also be acknowledged that the patients’ mode of diagnosis cannot be confirmed to be based on genotyping or iron studies. Nonetheless, valuable information is available that clearly demonstrates a rising incidence in the diagnosis of hemochromatosis during the period in which genetic

Fig. 2 The natural history and disease burden of HFE-associated haemochromatosis. Adapted from Pietrangelo [100], Allen et al. [37], and Whitlock et al. [75]

testing became available and guidelines on screening were published. In this cohort of patients, the diagnosis of hemochromatosis was associated with diseases including diabetes, arthritis, impotence, and atrial fibrillation. Liver cancer was also strongly associated and an overall doubling of mortality rates was demonstrated in the patients compared with matched controls. Taken together, the data show that iron overload-related disease in males with hemochromatosis is a common or benign condition; however, greater community awareness may now be leading to earlier diagnosis.

Although these studies have dealt with white populations, analyses of racially diverse groups have also been undertaken [36]. In screening almost 100,000 participants in the HEIRS (Hemochromatosis and Iron Overload Screening) study, the investigators found 299 C282Y homozygotes with most of these ($n = 281$) self-identifying as being of white ethnicity. Thirteen percent of untreated subjects were found to have a serum ferritin level greater than 1,000 $\mu\text{g/l}$ and had higher risks of self-reported liver disease. It is observed in this study that there is a greater proportion of elevated serum ferritin measurements in those subjects of Pacific Islander and Asian ethnicity than whites. This is not due to HFE mutations and is more frequently accompanied by elevated transferrin saturation in Asian subjects. Further data would suggest that these differences are unlikely to be accounted for by the presence of self-reported diabetes, liver disease, excessive alcohol, body mass index (BMI), or hemoglobinopathies [44]. Information regarding iron loading as assessed by liver biopsy or quantitative phlebotomy suggests that the higher transferrin saturation and serum ferritin level may not reflect iron overload in these populations and may indicate biological differences among difference races.

Factors affecting clinical expression

Environmental

A number of studies have sought to explore the genetic and environmental factors affecting the penetrance of C282Y homozygosity. The higher risk of iron accumulation and liver damage associated with male sex [36, 37, 40, 41, 43, 45, 46] and excess alcohol consumption [47–49] is now accepted and these 2 factors are likely to have the greatest influence on the progression of liver fibrosis. Lesser effects have been suggested by other factors including dietary heme consumption [50] and the protective effect of habitual tea drinking [51]. Recently, the suppression of gastric acid with proton pump inhibitors has been shown to reduce venesection requirements in C282Y homozygote subjects, potentially by reducing iron bioavailability and absorption

[52]. In vitro research suggests that calcium channel blockers may also modify iron loading, although this remains to be shown in clinical practice [53]. The consumption of noncitrus fruit is thought to be protective, although it is unclear whether this occurs by the inhibition of iron absorption or as a confounder for other behavior [54].

Genetic

Jacobs et al. [55] investigated determinants of iron overload in a detailed study of 224 probands and 735 of their first-degree family members. Not surprisingly, the HFE genotype of the relatives strongly predicted likelihood of iron overload, with the highest risk seen in C282Y homozygotes. In multivariate analysis, the age at testing, use of iron supplementation, and familial iron severity were predictive of the risk of iron overload. Interestingly, gender and alcohol use did not produce a statistically significant effect. The effect of BMI was complex. Lower BMI appeared protective against iron overload, but the highest BMI ($>30 \text{ kg/m}^2$) was associated with a lower transferrin saturation and higher serum ferritin levels. The present study confirmed previous work [56], suggesting that the severity of iron overload in a proband predicts phenotypic expression in affected relatives. The factors modifying this familial tendency to biochemical penetrance remain to be elucidated, but the possibility of coinherited genetic factors is a distinct possibility.

Previous investigations into genes modifying the iron loading in HFE hemochromatosis have identified mutations in iron-related molecules (HAMP, HJV, Cp, TfR2), which may accelerate iron loading in HFE hemochromatosis [57–61]. The rarity of these mutations means that they are unlikely to account for a significant proportion of disease variability. Common polymorphisms in the BMP signaling pathway are an alternative explanation, with the mechanism occurring via effects on hepcidin expression [25]. Ferroportin has been considered another candidate gene by Altes et al. [62], who studied a cohort of 100 Spanish HFE hemochromatosis patients. Automated sequencing was used to identify 5 polymorphisms in the *SLC40A1* gene, and a single-nucleotide polymorphism in intron 1 was shown to be associated iron loading as assessed by quantitative phlebotomy. These results clearly warrant further investigation in larger sample sizes for validation.

Hepatic iron and steatosis—an injurious partnership

Hepatic steatosis is purported to be a cofactor in the development of fibrosis in the setting of chronic hepatitis C [63]. It has also been implicated as a risk factor for the

progression of liver injury in hemochromatosis [64]. A significant correlation between steatosis and fibrosis was seen in a study of 214 C282Y homozygotes and this remained significant even after the adjustment for other factors such as the degree of hepatic iron loading and alcohol use. The rising global incidences of obesity and the metabolic syndrome and the related conditions of hepatic steatosis and steatohepatitis have enormous implications for liver disease. There appears to be a tantalizing relationship between iron, insulin, steatosis, and hepatic injury. A clue is provided with the observation that venesection may lead to improved insulin levels in those with nonalcoholic fatty liver disease but without hemochromatosis [65, 66]. It is possible that the mechanism of hepatic injury is mediated through cumulative effects of oxidative injury [64].

Iron also appears to be a significant cofactor in the development of hepatocellular carcinoma (HCC) in the setting of nonalcoholic steatohepatitis [67]. A retrospective study of patients with nonalcoholic steatohepatitis found that the iron score was significantly higher in those who developed HCC than in those free of the complication. A similar finding was reached in a prospective study of patients with alcoholic cirrhosis [68]. Although there is some evidence that venesection improves virological response rates in hepatitis C [69], larger prospective trials are awaited to examine the impact of iron-lowering strategies on the progression of chronic liver disease and complications such as HCC.

Natural history

A high proportion of C282Y homozygotes will develop elevated iron indices during adulthood; however, the risk of progression to a threshold serum ferritin level of more than 1,000 µg/l and its attendant risks of symptomatic disease and cirrhosis have been less clear. Two small longitudinal studies have investigated the natural history of untreated hemochromatosis and shown modest increases in transferrin saturation and serum ferritin levels in most subjects [70, 71].

The probability of iron loading progression was clarified by further data from the *HealthIron* study in Melbourne, Australia [72]. The follow-up period averaged 12 years, with baseline and sequential indices available in 72 untreated C282Y homozygotes allowing a calculation of risks. Statistical modeling shows that a male adult with a serum ferritin levels between 300 and 1,000 µg/l will have up to a 25% probability of a rise in the serum ferritin to levels more than 1,000 µg/l over 12 years. This risk can also be stratified by knowledge of the transferrin saturation at baseline. Most C282Y homozygotes who are destined to

develop serum ferritin levels above the threshold for disease will have done so by the age of 55 years.

By definition, juvenile forms of hemochromatosis resulting from mutations in hemojuvelin and hepcidin produce an accelerated pattern of iron loading and presentation within the second and third decades of life [73]. Endocrine involvement with hypogonadism appears to be frequently reported. Ferroportin disease shows considerable variability in expression, but, in general, Kupffer cell iron accumulation may be less fibrogenic than hepatocytes iron loading [74].

Diagnosis and screening

Although a disease with a common genetic mutation, life-threatening complications, and a safe effective treatment may seem like an ideal prospect for population screening, the incomplete penetrance of hemochromatosis has led to general consensus that this is not appropriate [75, 76]. There is, however, widespread acceptance of the benefit of cascade screening from newly identified probands [77]. It must be recognized that many who might never have developed disease will undergo screening and that the process of undergoing genetic testing and its implications may induce significant anxiety. Relatively few screening studies have specifically assessed the psychological impact of DNA testing in at-risk individuals such as those with a known family history. A recent meta-analysis [78] reviewed only 3 small cohorts and, although the evidence was limited, concluded that there is no demonstrable rise in anxiety levels or decrease in quality-of-life scores following testing. This concurs with population screening studies, which have found both genotypic and phenotypic methods to be acceptable and producing no evidence of psychological disturbance [79, 80].

Allen et al. [81] found no difference in perceived health scores between newly diagnosed C282Y homozygotes and controls in a large workplace-based screening program. At 12-month follow-up, homozygotes had significantly reduced anxiety scores compared with pretesting levels; all had complied with therapeutic venesection and most (95%) correctly recalled their results. At present, there is little evidence of discrimination on the basis of this genetic diagnosis [82].

Investigations

Noninvasive markers of fibrosis

The development of cirrhosis in a patient with hemochromatosis is a crucial time point in terms of the change in

prognosis and management, requiring screening for HCC and portal hypertension [34, 77]. Traditionally, the grading of hepatic fibrosis has occurred via liver biopsy, but concerns about complications and sampling error have spawned a search for noninvasive tests of cirrhosis. Several biochemical markers have been examined for reliable correlation with liver damage. The most obvious of these are the serum transaminase levels (aspartate aminotransferase and alanine aminotransferase), but these are normal in up to half of patients with cirrhosis due to hemochromatosis [38]. In 2002, a combination of serum ferritin level of more than 1,000 µg/l, platelet count of less than $200 \times 10^9/l$, and an abnormally high alanine aminotransferase level was found to predict cirrhosis in more than 77% of the study cohort patients and 90% of the validation group of patients with C282Y homozygosity [83]. A serum type IV collagen level more than 115 ng/ml has been found to be 100% sensitive in the prediction of underlying cirrhosis in homozygous subjects [84]. Interestingly, other markers of advanced fibrosis and cirrhosis with reasonable diagnostic accuracy in alcoholic and chronic viral liver diseases (serum procollagen III N-propeptide and serum laminin) seem to be of little value in iron-loaded livers [84, 85].

In a recent study, 56 untreated patients homozygous for the C282Y mutation were examined for the role of non-invasive markers in combination with elevated ferritin levels ($>1,000$ µg/l). Investigators found that serum hyaluronic acid, a prominent marker of fibrotic activity, had 100% sensitivity in identifying cirrhosis at a cutoff of 46.5 ng/ml [86]. Importantly, hyaluronic acid levels were not significantly raised in early fibrosis, were independent of alcohol consumption, and there was no overlap of values between the cirrhotic and noncirrhotic groups. Although there were only 11 patients with cirrhosis in this cohort and the results need validation in larger studies, this appears as a promising test for the future.

Transient elastography, a noninvasive technique to assess liver stiffness, has now been evaluated in the detection of liver fibrosis due to viral and other chronic liver diseases; however, it has not yet been assessed in hemochromatosis. A study of patients with transfusional iron overload has found that this technique can distinguish between no/mild fibrosis and those with severe fibrosis or cirrhosis, although some overlap does occur [87]. Such results do not necessarily get translated to C282Y homozygotes but may prompt further evaluation in this group.

Magnetic resonance imaging (MRI) has an evolving role in the quantification of hepatic iron content based on the deposition of iron particles causing an alteration in the liver's magnetic milieu. Iron disrupts the normal coherent behavior of hepatic protons and subsequently alters the signal transmitted to the scanner. Application of an algorithm using relaxation time constraints or signal intensity

ratios generates measurements that correlate well with iron content measured on biopsy [88, 89]. Proponents of MRI point to consistent measurements across operators and machines as well as generally high sensitivity and specificity as obvious strengths [89–91]. MRI also allows an assessment of iron loading in other target organs, such as cardiac iron content, which bears less relationship to serum ferritin [91].

The determination of hepatic iron content is likely to be of most use in cases of diagnostic doubt, for example, in the absence of known HFE mutations or elevated serum ferritin levels in association with the metabolic syndrome. However, it may also be of benefit in characterizing the risk of hepatic fibrosis. Using the product of [hepatic iron concentration $\times$ age] has allowed accurate prediction of high-grade fibrosis by MRI [92]. Based on the advances of the last 5 years, the role of liver biopsy in the investigation of hemochromatosis is diminishing.

Management

Investigation of the iron-loaded patient needs to be placed in the context of their ethnic background. In view of the infrequent occurrence of HFE mutations in nonwhite populations, one should consider other genetic mutations, for example, ferroportin in such subjects. The removal of excess iron by venesection in C282Y homozygotes with clinical disease produces well-established benefits on both symptoms and prognosis [34, 45, 93]. It is clear that in those with hepatic fibrosis, de-ironing will lead to a regression in fibrosis scores in most patients [45, 94]. A study of 36 subjects with paired liver biopsies before and after therapeutic venesection suggested simple, available biochemical markers that predict a lack of fibrosis regression [94]. Three of the subjects in this study developed HCC and this complication was seen only in those with cirrhosis and no regression of fibrosis following treatment. It is possible that those with severe, progressive disease were selected out of this study because of suboptimal response to recruitment. Although cirrhosis has generally been thought to be irreversible, appropriate venesection may lead to a reduction in portal pressure thereby reducing the risk of variceal bleeding [95].

The commonly accepted regimen is that of an induction phase of venesection with the aim of removing a typical volume of 400–500 ml of blood weekly until a serum ferritin level of less than 50 µg/l is reached [93]. Overt iron deficiency anemia is not required and may be counterproductive by inducing a negative feedback response to hepcidin, which, in turn, favors iron absorption [96]. Maintenance venesection requirements are typically in the order of phlebotomy every 3–4 months.

Some patients with loss-of-function mutations in the ferroportin gene may be intolerant of aggressive venesection regimens with the rapid development of anemia [97]. This is likely to reflect a limitation in the mobilization of iron stores. A more cautious monitoring approach is necessary and the serum ferritin levels of less than 50 µg/l may not be required. Although the level for C282Y homozygotes is established (50–100 µg/l), the tailoring of treatment according to other specific mutations is an evolving area requiring further research.

Iron chelation has been used in the past typically for patients with iron overload related to hemoglobinopathies. Although effective, the adverse effects and parenteral administration of desferrioxamine limited its use to select cases of HFE hemochromatosis in which venesection was difficult or rapid iron loss was required [98]. The advent of an oral iron chelator with proven efficacy in transfusional iron overload may prove to be a turning point in hemochromatosis management. Deferasirox has been shown to be generally well-tolerated and follow-up of up to 3.5 years indicates an acceptable safety profile [99]. An international clinical trial of this oral agent in subjects with hemochromatosis nears completion and the results are awaited.

A susceptibility to infections with ferrophilic organisms such as *Yersinia* and *Vibrio* has been recognized in iron-overloaded subjects. Therefore, the consumption of uncooked seafood (a source of *Vibrio* infection) is not recommended. In addition, because of the established risk of excess alcohol, the consumption of alcohol should be limited in all patients and avoided in patients with cirrhosis. It is recommended that patients should eat iron-rich foods (such as red and organ meats) in moderation. Likewise, vitamin C, which promotes iron absorption, should be restricted [93].

Conclusion

The physiological control of iron metabolism is tightly regulated in health to allow a supply for the human body's needs in the absence of an effective method for excretion and in the presence of dietary variation. When this system fails, iron accumulation in tissues may occur together with the risk of hepatic fibrosis and cirrhosis, cardiomyopathy, and endocrinopathies. Recent advances have better defined the risks related to mutations in iron-regulatory molecules and unlocked some of the pathology behind early clinical observations. One may speculate on the possible developments that the next 5 years may bring. It is likely that future studies will provide further insights into the exact function of the HFE protein and other iron-related molecules, including hepcidin, as well as further genetic mutations. Genome-wide studies may begin to explain the variability in the penetrance of biochemical and liver

abnormalities in these patients. Further noninvasive investigative and therapeutic tools are likely to be the subject of clinical trials and validation, thus potentially reducing the need for liver biopsy and venesection. An effective oral iron-chelating agent is likely to be widely available in the foreseeable future.

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