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# Are Hemochromatosis Mutations Protective Against Iron-Mediated Atherogenesis?

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## 1. Introduction

Modest levels of stored iron, far less than conventional iron overload, may promote cardiovascular disease, i.e. sustained iron depletion may be protective [1-6]. This so-called “iron hypothesis” was initially presented to explain for the sex difference in cardiovascular disease and the increase in disease following menopause. The idea, although continually debated for more than 25 years, has achieved standing as a plausible and testable hypothesis [7-18] [19].

The hypothesis has not yet been definitively tested. A first randomized clinical trial (FeAST) to address aspects of the hypothesis was recently reported [7]. The FeAST trial [7] had significant limitations as a general test of the idea: 1) it was a trial of secondary prevention, and 2) the iron reduction protocol fell far short of achieving full iron depletion. Zacharski et al [7] reported that reducing iron stores significantly improves survival for patients with symptomatic but stable peripheral arterial disease (PAD), if iron reduction begins at a young age. The FeAST trial provides compelling support for a new trial designed to test the original hypothesis.

Controversial results from multiple epidemiological studies investigating a variety of atherosclerotic events using all kinds of variable parameters of body iron load have presented a confusing picture of the iron hypothesis [20]. Confusion became complete when it appeared that patients with homozygous hemochromatosis who were afflicted with serious, life long iron overload had no increased atherosclerosis and might even be protected against atherosclerosis. In the debate on the hypothesis, the disease pattern in homozygous hemochromatosis has been interpreted as perhaps the most persuasive evidence against the hypothesis [21]. This “hemochromatosis paradox” is seen as an anomaly that makes the hypothesis untenable for some investigators. How can normal stored iron levels be bad for the vascular system, when massive amounts of stored iron in genetic iron overload are not associated with increased atherosclerosis?

## 2. Hemochromatosis and atherosclerosis: More to it than iron load alone

An early corollary to the iron hypothesis was the proposal that heterozygous hemochromatosis might be a significant risk factor for premature myocardial infarction [22]. This was proposed despite the general impression at the time that homozygous hemochromatosis was not prominently associated with increased atherosclerosis. In the

absence of definitive data, this was not seen as necessarily incompatible with the iron hypothesis [22-24]. An impact on cardiovascular event rates in hemochromatosis was not excluded based on available data. In addition, even without promotion of atherosclerosis by genetic iron overload, relevant issues that continue to be unresolved include roles of hemochromatosis mutation-associated iron overload in myocardial reperfusion injury [2;24-26] and endothelial dysfunction [27;28]. Future investigations are needed, as long term exposure to non-transferrin bound iron (NTBI) in genetic iron overload may contribute to life-long progression of atherosclerosis as it promotes monocyte-endothelium interaction and inflammatory pathways.

Mutational effects other than promotion of an increase in total body iron were not considered in the 1990 hypothesis relating heterozygosity to early onset of myocardial infarction [22]. The idea that total body iron load was the only factor that might influence cardiovascular disease expression in hemochromatosis was restated as recently as 2007 in a JAMA editorial on the status of the iron hypothesis by Hu [8]:

*"The 1996 discovery of HFE gene mutations responsible for most cases of hereditary hemochromatosis [[29]] has led to the use of genetic markers of iron stores (ie, heterozygosity for the C282Y mutation in the HFE gene as a marker of lifelong moderate iron overload) in epidemiologic studies. In contrast to biomarkers, genetic markers of iron overload can be measured exactly and are not influenced by such factors as inflammation, recent blood loss, diet, and use of medications (eg, aspirin)."*

The corollary hypothesis that heterozygosity might be associated with myocardial infarction [22] led to a number of investigations, especially after the identification of the disease-causing mutation in most cases of hemochromatosis in 1996 [29]. Early findings appeared to support some increase in cardiovascular events among heterozygotes [23;30;31]. However, these studies taken together with subsequent investigations [32-36] do not support an increase in myocardial infarction, stroke or atherosclerosis in patients who are heterozygous for hemochromatosis. In fact, the body of relevant work, including some older studies [37;38] does not exclude protection against atherosclerosis in hemochromatosis. In an autopsy series that examined coronary artery disease in heavily iron overloaded individuals, Miller and Hutchins [37] reported an odds ratio of coronary artery disease with iron overload of 0.18. This is suggestive of a significant protective effect in patients presumptively homozygous for hemochromatosis who comprised 80% of the autopsy cases reviewed by Miller and Hutchins [37]. Could some poorly understood feature of homozygous hemochromatosis confound the relationship between iron load and atherosclerosis?

### 3. Hepcidin and a resolution of the hemochromatosis paradox

An iron loading mutation is not just "a marker of lifelong moderate iron overload" as indicated by Hu [8]. Hemochromatosis mutations also radically alter the distribution of body iron [39]. Iron-poor Kupffer cells adjacent to iron-loaded hepatocytes are a classic finding in hereditary hemochromatosis [39]. Another classic finding in homozygotes is a relative scarcity of coronary artery iron deposition despite extensive iron deposits in myocardial tissue [39;40].

In 1998, Moura et al [41] reported that monocytes from hereditary hemochromatosis patients released twice as much iron in the low molecular weight form as normal human monocytes after erythrocyte phagocytosis. Thus, even before the discovery and understanding of the iron regulatory hormone, hepcidin [42-44], there was an understanding of "a macrophage

*defect in hemochromatosis leading to a constriction. of the macrophage/reticuloendothelial iron pool" [24]. This macrophage defect [41] in hereditary hemochromatosis was suggested as a factor that might "protect homozygotes from foam cell formation and thus, to a degree, gives some specific protection against atherosclerosis," [24] with a partial protective effect in heterozygotes.*

The discovery of hepcidin [42-44] and the details of its influence on iron metabolism [45-49] illuminated patterns of macrophage iron retention and led to a conceptual *volte-face* on the possibility of diminished atherosclerosis in homozygotes [4;6].

Hepcidin is the major regulator for the amount of iron retained within macrophages. Production of hepcidin is regulated by iron intake and a number of interrelated factors. Elevated levels, favoring macrophage iron retention, are seen with increased iron intake, infection and inflammation. Iron loading in secondary iron overload in wild type individuals is associated with increased hepcidin expression. Reduced hepcidin levels and iron-poor macrophages accompany iron deficiency, hypoxia, anemia and hereditary hemochromatosis. Hepcidin binds to the iron exporter protein ferroportin, leading to the internalization, and intracellular degradation of ferroportin. Loss of the iron exporter function of ferroportin from macrophages leads to intracellular retention of iron and to reduced serum iron levels. In intestinal epithelial cells, hepcidin-induced loss of ferroportin results in reduced iron internalization into the systemic circulation.

Remarkably, the most extreme reductions in hepcidin level are associated with the opposite extremes of total body iron load, i.e. in iron deficiency anemia and in homozygous hemochromatosis [50]. Loss of hepcidin expression can be produced by mutations in hepcidin, hemojuvelin, *TFR2*, and *HFE* [51]. Mutations at these sites leads to hereditary iron overload. In this discussion, the term "hemochromatosis" indicates hereditary iron overload associated with one of the mutations causing lower hepcidin expression. The homozygous *HFE* C282Y mutation is the most common cause of hereditary iron overload and is associated with lower liver expression of hepcidin mRNA [51].

The very low hepcidin levels seen in homozygous hemochromatosis are associated with systemic iron loading because reduced hepcidin levels permit unregulated ferroportin-mediated transfer of iron from intestinal epithelial cells into the systemic iron pool. The more extreme the degree of hepcidin deficiency, the more severe the level of parenchymal iron load, but also the more extreme the macrophage iron retention deficit. These patterns offer a potential resolution of the paradox of the proposed protection by iron depletion in wild type subjects against cardiovascular disease despite of the lack of increased atherosclerosis in genetic iron overload [4;6]. Hepcidin may act as an iron-dependent risk factor for atherosclerosis by causing iron loading of plaque macrophages with promotion of foam cell formation. According to this proposal, hepcidin amplifies the plaque iron loading effects of an increased iron load as iron itself upregulates hepcidin concentration. At the other end of the iron status spectrum, iron deficiency downregulates hepcidin and promotes removal of iron from plaque macrophages. In hemochromatosis, the associated hepcidin deficiency is hypothesized to reduce progressive iron accumulation within arterial walls and foam cell formation. Hemochromatosis patients may thus enjoy a specific protection against plaque progression in proportion to the severity of hepcidin deficiency. Hepcidin deficiency would not protect these patients from direct iron-mediated injury to heart muscle from parenchymal iron accumulation in myocardial tissue. The corollary hypothesis that identifies hepcidin as a risk factor for atherogenesis [4] may explain the conundrum of decreased atherosclerosis in the face of massive iron loading and provide additional justification for the contention that the macrophage has a key role in atherogenesis.

Previous studies, especially the work of Miller and Hutchins [37] and Pirart and Barbier [38], raised the possibility of a protective effect of hereditary hemochromatosis against atherosclerosis. An unknown “*facteur constitutionnel*” [38] linked to hemochromatosis that enhances resistance to vascular lesions was proposed. A mechanistic hypothesis to explain the findings [37;38] was not proposed as the studies were done prior to identification of either the principal iron overloading genotypes or the iron regulatory hormone hepcidin. More recent evidence supporting the hypothesis that hemochromatosis-associated hepcidin deficiency is protective against atherosclerosis has been reported [52]. Valenti et al [52] studied vascular disease, iron status, hepcidin levels and *HFE* mutations in 506 consecutive patients with nonalcoholic fatty liver disease (NAFLD). None were homozygous for hereditary hemochromatosis. Serum ferritin was associated with common carotid intima-media thickness (CC-IMT) ( $p = 0.048$ ) and with prevalence of atherosclerotic carotid plaques ( $p = 0.0004$ ), except in patients whose heterozygous *HFE* mutations lower hepcidin levels. Hyperferritinemia was associated with vascular damage only in patients with wild type *HFE* genotypes ( $p < 0.0001$ ). Hepcidin was elevated in those without such an *HFE* mutation and was found to be an independent predictor of the presence of carotid atherosclerosis.

#### 4. Iron, hepcidin, inflammation and vascular disease

Inflammation accelerates atherogenesis [53]. The mechanism may involve iron- and hepcidin-mediated mechanisms [4;6]. Hepcidin is upregulated by interleukin-6 (IL-6), a cytokine induced by inflammatory processes. IL-6 has also been found to be a cardiovascular disease risk factor [54]. An important end result of any process that induces IL-6 is increased deposition of iron within reticuloendothelial cells, including atherosclerotic plaque macrophages, because of hepcidin upregulation. Continued inflammation-mediated hepcidin synthesis maintains iron in storage sites even in the face of a low hematocrit as in the anemia of inflammation (i.e. the “anemia of chronic disorders”).

Hepatic hepcidin may be normally upregulated in inflammation even in hemochromatosis homozygotes who usually have markedly low hepcidin levels [55]. The effects of inflammatory processes in hemochromatosis patients on possible redistribution of iron from parenchymal cells to the reticuloendothelial compartment, including arterial plaque macrophages, are not currently known. Interactions between mutational effects and inflammation-induced effects on hepcidin level may result in complex epidemiological patterns in studies of cardiovascular disease expression in hemochromatosis patients.

#### 5. Blunted inflammatory responses in macrophages in hemochromatosis or induced iron depletion

A recent study of macrophages in the *Hfe* knockout (*Hfe*  $-/-$ ) mouse [56] is pertinent to the present discussion of iron, inflammation and atherosclerosis. Wang et al [56] found attenuated inflammatory responses in a mouse model of human hemochromatosis and reduced translation of cytokine mRNAs in *Hfe*  $-/-$  macrophages in response to *Salmonella* and LPS exposure. Intramacrophage iron levels were decreased in the *Hfe*  $-/-$  mice in association with upregulation of macrophage iron exporter ferroportin (FPN). *Salmonella*- and LPS-induced inflammatory responses were diminished in the *Hfe* knockout animals. Less severe enterocolitis was observed in vivo and reduced macrophage TNF- and IL-6 secretion was observed in vitro.



Of special significance in the present discussion, the reduced translation of cytokine mRNAs of the mutant macrophages could be reproduced in wild-type cells by reducing the intracellular iron concentration with chelation. Atherosclerotic plaque macrophages in patients with hemochromatosis mutations associated with diminished hepcidin may display similar attenuated inflammatory responses such as those from *Hfe*  $-/-$  mice [56], and thereby a diminished tendency to form atherosclerotic foam cells.

## 6. Iron, hemochromatosis and other cell types in vascular disease

Iron plays a role in vascular disease in other cell types than the macrophage, e.g. endothelial cells [3;9;14;18;57-59] and vascular smooth muscle cells [60-62]. Patients with hemochromatosis have endothelial dysfunction that is improved by iron reduction therapy [63]. This suggests that iron overload itself rather than mutational effects of iron overload genes influences endothelial function. Proliferation of vascular smooth muscle cells [60-62] also requires iron. How hemochromatosis mutations might modify iron-mediated atherogenic processes in these cell types will require additional studies.

## 7. Serum cholesterol level, hemochromatosis, macrophage iron loss, and cardiovascular disease

Adams et al [64] reported that hemochromatosis patients homozygous for C282Y have diminished serum cholesterol and low-density lipoprotein (LDL) levels. Systemically lower cholesterol and LDL could represent an additional mechanism by which hemochromatosis patients are relatively protected from atherosclerosis. This could be associated with the iron retention deficit in mutant macrophages. A role for macrophage iron metabolism in regulation of cellular lipid level has been proposed [65]. As noted above, the most extreme reductions in hepcidin level are seen at the opposite extremes of total body iron load, i.e. in both iron deficiency anemia and in homozygous hemochromatosis. Consistent with a hepcidin level similar to that in hemochromatosis, iron deficiency is also associated with lower systemic levels of serum cholesterol and LDL [12;66;67]. Future studies are needed to determine if lower macrophage iron level in iron deficiency or inherited iron overload negatively regulates systemic cholesterol level.

## 8. Mutational protection against atherogenesis: Epidemiological implications

The literature on the role of iron in cardiovascular disease in the general population is contradictory and inconsistent, as has often been noted [8]. There have been misconceptions regarding the hypothesis leading to inadequate study designs [20;68]. Another key limitation of previous studies that has not been addressed is the possibility of a protective effect of hemochromatosis mutations against iron-mediated atherogenesis. If hemochromatosis mutations confer protection against atherogenesis, previous epidemiological studies of iron and atherosclerosis may be critically flawed. The highest serum ferritin levels in population groups whose hemochromatosis gene status has not been ascertained will select a disproportionate share of subjects who are heterozygous or homozygous for hemochromatosis. These high serum ferritin individuals may have less disease because of mutational protection against atherosclerosis and may confound underlying associations of iron load and atherosclerosis in normal subjects.

## 9. Penetrance and testing the hepcidin hypothesis

This problem of clinical penetrance of the hemochromatosis mutations needs to be considered in the design of a study to test the hepcidin hypothesis. There is undoubtedly a variable impact of genotype on hepcidin expression. Genotype of subjects in a study to test the hypothesis should be determined; however, testing the hypothesis would not rely directly on showing an association of genotype with disease. The hypothesis suggests that protection against atherogenesis is inversely proportional to hepcidin expression. In an epidemiological study, the hypothesis suggests that, among those with any one of a number of iron overloading genotypes, protection against atherogenesis would be seen in proportion to the degree of life long hepcidin downregulation.

It would be inappropriate to simply look at a group of all subjects with hepcidin expression below some prespecified level. It would be necessary to exclude the iron deficient subjects from a group defined by such a criterion, as iron deficiency is associated with quite low hepcidin levels. A future interventional study of the effect of long term iron deficiency-induced reduction in hepcidin expression on atherogenesis would be of interest.

## 10. Conclusions and future directions

The hypothesis that iron depletion protects against atherosclerosis may apply even in hemochromatosis homozygotes because of the mutational effect of selective iron depletion of the macrophage, a key cell type in atherogenesis. In homozygotes, a sea of tissue iron deposition surrounds islands of iron depleted cells of the reticuloendothelial system. Low hepcidin expression is a mutational feature of hemochromatosis and also of systemic iron deficiency that may protect against iron-mediated atherogenesis in both conditions. What is known at present about disease patterns in genetic iron overload is compatible with the hypothesis that iron depletion protects against atherosclerosis. Hereditary hemochromatosis may be a special case of selective cellular iron depletion that inhibits atherogenesis.

More detailed investigations are needed on hepcidin as a risk factor for atherosclerosis including more studies of atherosclerotic disease in patients with hemochromatosis mutations. Work is also needed on the effects of the inflammatory response on iron metabolism, especially the impact of inflammatory processes on hepcidin and macrophage iron in patients with hemochromatosis mutations.

It would be of interest to replicate the low hepcidin levels of those with hemochromatosis mutations in normal subjects and to assess the effects of low hepcidin levels on atherogenesis. A well established and safe method that would have the effect of reducing hepcidin production in normal subjects is induced iron depletion. Long-term modest reduction in storage iron can be achieved in patients with established vascular disease and is associated with decreased cancer mortality [69] and, among younger participants, decreased cardiovascular mortality [7].

In humans with intact hepcidin responses, atherosclerotic plaque has a substantially higher iron concentration than that in healthy arterial wall [15]. Increased lesional iron is also seen in cholesterol fed animals. In a series of studies with rabbits fed a 1% cholesterol diet, Watt and colleagues [70-74] used nuclear microscopy to show a 7-fold increase in iron concentration within newly formed atherosclerotic lesions compared to healthy arteries. Iron accumulation was seen at the onset of lesion formation.

A role for iron in foam cell formation and lesion progression has been implicated by numerous observations and experiments [4-6;75-83]. Recent work shows that iron can be mobilized out of atherosclerotic plaque by manipulation of body iron status, and that this process may be associated with reduction in lesion size. Animal experiments suggest that systemic lowering of stored iron levels reduces intralésional iron content and also the size of atherosclerotic plaques [70;84]. It is well known that iron-deficient erythropoiesis can mobilize and relocate almost all stored iron in the body to maturing erythroid precursors. In iron deficiency, mobilization is facilitated by extreme downregulation of hepcidin. Key questions in future human studies include the following: What duration and degree of iron reduction therapy is needed for restoring iron levels in atherosclerotic vessel segments to the much lower level seen in healthy vascular tissue? How much reduction in the level of hepcidin is required to facilitate the relocation of stored iron from intralésional macrophages to erythroid precursors? And, is it possible in normal subjects to inhibit the formation of atherosclerotic foam cells by rendering their macrophages as iron poor as in those with hemochromatosis mutations?

## 11. Conflict of interest disclosures

None.

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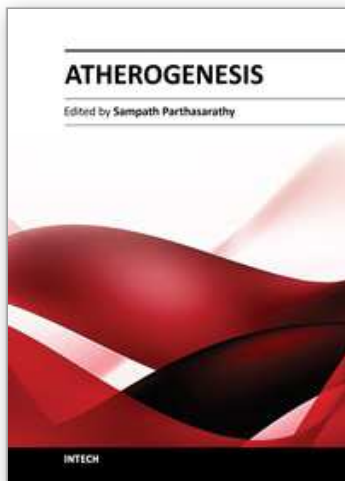
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