



## Iron, HCV and the liver

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### IRON

Iron is an essential element necessary for the survival of cells. Excess or deficiency of iron leads to diseases. The liver is a major target organ of injury in diseases causing iron overload, which is consistent with its central role in iron storage and metabolism<sup>[1]</sup>. Most of the iron is absorbed in the non-heme form, largely in the upper part of the small intestine. There is no physiological mechanism for the excretion of excessive iron. Therefore, normal iron balance is maintained by the regulation of iron absorption, although the underlying mechanism still remains unclear<sup>[2]</sup>. In blood, iron is bound to transferrin, a glycoprotein synthesized in the liver. Transferrin is responsible for the "total iron-binding capacity" of serum. Physiologically, this is saturated to one-thirds with iron. The hepatic uptake of iron from the blood is receptor mediated<sup>[3]</sup>. The receptor-iron complex is internalized and iron is released. However, alternative pathways of iron uptake across the plasma membrane of the liver cell seem to play important roles in iron-overload states<sup>[3,4]</sup>. In the liver, iron depots in the form of ferritin or hemosiderin are available for metabolism and hemoglobin formation, should the demand arise. In diseases of iron overload, the binding capacity of the iron-storage proteins (ferritin and hemosiderin) are saturated, leading to the accumulation of ionized ("free") iron in the cytosol.

Why is free iron ("prooxidant iron") toxic to the liver?

Despite convincing clinical evidence for the occurrence of liver

injury as a result of excessive iron accumulation, the specific pathophysiological mechanisms involved in this process are poorly understood. Some aspects, however, have aroused interests: (1) Iron-induced oxidative injury to phospholipid of subcellular membranes of liver cells seems to play a central role in initiating liver damage. Experimentally, iron overload leads to peroxidation, especially in mitochondria and microsomal membranes<sup>[5,6]</sup>, thereby resulting in decreased energy production by interference with the electron transport chain<sup>[7]</sup>. Therefore, one of the key characteristics of the pathogenesis of iron-induced liver damage is increased oxidative stress, which ultimately leads to cell death and secondary fibrogenesis; (2) There appears to be a direct iron-induced oxidative damage of nucleic acid. DNA strand breaks in rat hepatic nuclei subjected to iron-induced lipid peroxidation have been demonstrated *in vitro*<sup>[8]</sup>. Hepatocellular carcinoma (HCC) is a common complication of long-standing cirrhosis in genetic hemochromatosis, and iron-induced damage to DNA may play an important role in its development; and (3) A fibrous tissue reaction is observed wherever the iron is deposited. This is particularly true for patients with genetic hemochromatosis<sup>[9]</sup>. Therefore, it has been suggested that the triggering factor of fibrogenesis appears to be the accumulation of iron in the form of aggregates of activated non-parenchymal cells<sup>[10]</sup>.

It should be noted that in genetic hemochromatosis, hepatic fibrosis appears only subsequent to iron overload of Kupffer cells after the occurrence of sideronecrosis of periportal hepatocytes<sup>[11]</sup>. Thus, activation of Kupffer cells by a necrotic event might be required for initiation of the fibrogenetic process in iron overload states<sup>[10]</sup>.

Thus far, increased lipid peroxidation, and hence fibrosis, has been clearly demonstrated in several experimental *in vivo* models of iron overload<sup>[10,11]</sup>. Recent data in the gerbil model provide deeper insight into the molecular events underlying the profibrogenic action of iron and have shown that parenteral iron overload leads to hepatic cirrhosis<sup>[12]</sup>. In the animal model of iron overload, a dramatic increase of signals for collagen mRNA around iron foci in fat-storing liver cells has been documented<sup>[10]</sup>. The pattern of iron distribution in the liver of this animal model resembles that of secondary iron overload states, with the metal being mainly present in non-parenchymal cell foci<sup>[10]</sup>. The concept of the need for Kupffer cell activation by a necrogenic event for the initiation of the fibrogenic process is consistent with the findings obtained in genetic hemochromatosis, in which iron itself causes sideronecrosis of hepatocytes and activation of Kupffer cells. Interestingly, at least in the animal model, antioxidative treatment with dietary vitamin E supplementation arrested fibrogenesis and completely reversed hepatic cirrhosis, possibly by a blocking activity exerted on hepatic non-parenchymal cell proliferation triggered by iron<sup>[10]</sup>.

### IRON AND HEPATITIS C VIRUS

It has been reported that iron is also an important factor involved in

**Table 1 Laboratory and histological findings in transfusion-dependent patients with thalassemia major and chronic hepatitis C before interferon therapy<sup>[25]</sup>**

Lab and histologic findings	Responders (n = 24)	Non-responders (n = 30)	Control subjects (n = 14)
Age (yr)	153 ± 34	145 ± 29	115 ± 29
Units of blood received	369 ± 145	318 ± 117	243 ± 86
ALT (U/L)	270 ± 180	255 ± 46	244 ± 50
Serum ferritin (μg/L)	1812 ± 962	2463 ± 850	1621 ± 745
Hepatitis C virus-RNA	Positive	Positive	Positive
Hepatic histologic findings	CAH	CAH	CAH

the progression of chronic liver disease and that the effect of iron is concomitant with that of other hepatotoxins (viruses, alcohol) which are able to initiate a damaging event in the liver<sup>[10]</sup>.

Markers of viral infection are present in about one-fourth of all Italian patients with genetic hemochromatosis<sup>[13]</sup>. The prevalence of HBsAg in Italian patients with genetic hemochromatosis has been reported to be slightly more than double (5%) that in a healthy population<sup>[14]</sup>. The prevalence of anti-HCV in this group, however, reached 20.5%. Interestingly, although most of the patients with associated viral hepatitis had cirrhosis and their serum ferritin levels and amount of mobilizable iron were significantly lower than those in patients with fibrosis/cirrhosis ( $P < 0.01$ ) without concomitant viral infection; this suggests that hepatitis viruses may act synergistically with iron in accelerating the liver damage<sup>[14]</sup>. It has recently been shown that some viruses may promote hepatocyte damage by activating lipid peroxidation *via* an iron-mediated mechanism<sup>[15]</sup>. This evidence is consistent with the finding that Japanese encephalitis virus causes the accumulation of iron in the liver and spleen, apparently by stimulating the release of a macrophage-derived iron-regulating factor that could be related to IL-8<sup>[16]</sup>. Another consideration is that chronic viral hepatitis might alter hepatocyte function in such a manner that there is increased hepatocellular iron concentration, perhaps by upregulating transferrin receptor expression<sup>[17]</sup>.

Elevated iron and ferritin levels have been reported in the serum of some patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infections<sup>[18]</sup>. Moreover, parenchymal iron overload has been shown in the nontumorous liver of most patients presenting with HCC developed in a non-cirrhotic liver<sup>[19]</sup>. It must be stressed, however, that in a large series of 80 patients with chronic viral hepatitis, only very few had elevated hepatic iron concentrations, despite the fact that elevated iron and ferritin levels in the serum were present in about one-third of the patients<sup>[18]</sup>. Thus, it has been concluded that abnormal results of serum iron status tests are clinically insignificant. Other authors, however, found significantly elevated serum ferritin concentration and elevated tissue iron specifically in some patients with HCV infection<sup>[20,21]</sup>. In fact, 59% of patients with HCV infection had high ( $> 26.85 \mu\text{mol/L}$ ) serum iron levels, whereas only 14% of the HBV-infected patients and 21% of the patients with a non-viral etiology had abnormal serum iron levels<sup>[21]</sup>. Further, serum transferrin saturation was significantly higher in HCV patients than in others<sup>[21]</sup>. Interestingly, there was no significant correlation with the degree of inflammation or transaminases, thus confirming that increased storage of iron is not a function of the inflammatory process *per se*<sup>[20]</sup>. Surprisingly, HBV infection was not associated with increased markers of iron metabolism. Therefore, it has been speculated that in contrast to HBV infection, HCV infection triggers free radical production, which may lead to interference with mitochondrial function<sup>[19]</sup>.

## HCV, IRON AND INTERFERON (IFN) TREATMENT

There is some evidence that patients chronically infected with HCV have a decreased response to (IFN) therapy in the presence of iron overload<sup>[22,23]</sup>.

This feature seems to be specific for HCV infection. It has been discussed that both the increased serum iron concentration and transferrin saturation blunt the action of IFN, since they have opposite effects on the immune system<sup>[22]</sup>. Bacon *et al*<sup>[24]</sup> studied

8 non-responders to IFN therapy, who were subjected to repetitive phlebotomies. Seven of them had a significant decrease in serum alanine transaminase (ALT) activity. After a second course of IFN (3 million units three times per week for 4 mo), the serum ALT level restored to the normal range in 3 of 8 patients. This led the authors to conclude that iron depletion seems to improve the response of chronic HCV infection to IFN therapy. In patients with thalassemia major and chronic hepatitis C, non-responders and responders to IFN did not differ with regard to mean ALT activity (Table 1). However, serum ferritin concentration was markedly elevated in non-responders, and response to therapy was inversely related ( $P < 0.002$ ) to the liver iron burden<sup>[25]</sup>.

Olynyk *et al*<sup>[26]</sup> found that hepatic iron concentration (HIC) was a good predictor of response to IFN therapy in 58 patients with chronic hepatitis C. Overall, 41% of their patients responded to therapy. However, in a subgroup of patients with an HIC of  $> 1100 \mu\text{g/g}$  liver, 88% failed to respond favorably to IFN therapy. The reason for the higher HIC in patients not responding to IFN therapy remained unclear. The authors thought that iron could impair host lymphocyte-dependent clearance of HCV. They proposed to determine HIC before starting IFN treatment in cases of chronic HCV infection. In another study<sup>[27]</sup>, the mean liver iron concentration of non-responders was also significantly higher than that of the responders ( $1252 \mu\text{g/g}$  dry weight vs  $828 \mu\text{g/g}$  dry weight). It should be mentioned, however, that both of these mean values were within the normal range of HIC. The authors thought that an "iron threshold" of  $600 \mu\text{g/g}$  dry weight would characterize patients not responding to IFN therapy. Similar results were obtained in a study of 44 patients with chronic HCV infection<sup>[28]</sup>. Again, liver iron concentration was in the normal range, but nearly twice as high in non-responders as compared to responders. Thus far, there is no agreement regarding which of the iron indices most accurately predicts response to therapy. In a recent study<sup>[29]</sup>, total hepatic iron scores, mean serum ferritin level as well as mean quantitative HIC were higher in patients with incomplete IFN response, however without reaching statistical significance. Interestingly, the morphologic distribution of iron in liver biopsies and not total liver iron differed significantly in IFN responders and non responders. Scores for stainable iron in sinusoidal cells and portal tracts were significantly lower in responders ( $P = 0.02$  and  $P = 0.05$ , respectively) to IFN therapy as compared to non-responders.

At present, it is unclear whether iron removal in patients with chronic HCV infection enhances the effect of IFN. In a pilot study conducted on 26 patients, repeated phlebotomies were performed to remove excessive iron (with the endpoint set at serum ferritin concentration below  $10 \mu\text{g/L}$ ) before initiation of IFN treatment. Again, iron removal alone effectively reduced the serum ALT levels [from  $125 \text{ U/L}$  to  $49 \text{ U/L}$  (mean)], but did not enhance the effect of treating viremia<sup>[30]</sup>. Whatever the practical consequences of this studies are, it should be mentioned that significant reductions in serum ALT levels were achieved by phlebotomy alone<sup>[24]</sup> and that compared to IFN therapy alone, phlebotomy plus IFN therapy resulted in greater reduction of serum ALT levels and improvement in histological picture<sup>[31]</sup>.

## CONCLUSIONS

Recent studies have suggested that there is a close link between iron metabolism and viral hepatitis, especially hepatitis C. Some studies seem to indicate that the total quantity of iron present in the liver as well as the lobular and cellular distribution of iron are important determinants of the long-term outcome. Interestingly, Kupffer cell function may play a critical role, since the degree of stainable iron in these cells or cells in the portal tracts is significantly lower in complete responders as compared to those in non-responders or incomplete responders<sup>[29]</sup>.

These findings lead to the conclusion that patients with lesser amounts of hepatic iron respond better to antiviral therapy than those with larger amounts of hepatic iron. It is assumed that differences in the pretreatment levels of total hepatic iron and serum ferritin are less striking than those in the cellular and zonal

distribution of iron. However, whether iron removal prior to IFN therapy enhances the percentage of IFN responders in chronic HCV infection is open to discussion. An ongoing randomized controlled study (phlebotomy ribavirin interferon; PRINT) in IFN non-responders with chronic hepatitis C is expected to further clarify whether iron removal will prove useful in the long-term management of this disease.

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## REFERENCES

- 1 **Deugnier YM**, Loréal O, Turlin B, Guyader D, Jouanolle H, Moirand R, Jacquelinet C, Brissot P. Liver pathology in genetic hemochromatosis: a review of 135 homozygous cases and their biochemical correlations. *Gastroenterology* 1992; **102**: 2050-2059 [PMID: 1587423]
- 2 **Halliday JW**. The regulation of iron absorption: one more piece in the puzzle? *Gastroenterology* 1992; **102**: 1071-1073 [PMID: 1537499]
- 3 **Bonkovsky HL**. Iron and the liver. *Am J Med Sci* 1991; **301**: 32-43 [PMID: 1847276 DOI: 10.1097/0000441-199101000-00006]
- 4 **Adams PC**, Powell LW, Halliday JW. Isolation of a human hepatic ferritin receptor. *Hepatology* 1988; **8**: 719-721 [PMID: 2839401 DOI: 10.1002/hep.1840080402]
- 5 **Britton RS**, Ferrali M, Magiera CJ, Recknagel RO, Bacon BR. Increased prooxidant action of hepatic cytosolic low-molecular-weight iron in experimental iron overload. *Hepatology* 1990; **11**: 1038-1043 [PMID: 2365281 DOI: 10.1002/hep.1840110620]
- 6 **Hanstein WG**, Sacks PV, Muller-Eberhard U. Properties of liver mitochondria from iron-loaded rats. *Biochem Biophys Res Commun* 1975; **67**: 1175-1184 [PMID: 1201066 DOI: 10.1016/0006-291X(75)90797-4]
- 7 **Bacon BR**, Healey JF, Brittenham GM, Park CH, Nunnari J, Tavill AS, Bonkovsky HL. Hepatic microsomal function in rats with chronic dietary iron overload. *Gastroenterology* 1986; **90**: 1844-1853 [PMID: 3009259]
- 8 **Shires TK**. Iron-induced DNA damage and synthesis in isolated rat liver nuclei. *Biochem J* 1982; **205**: 321-329 [PMID: 7138506 DOI: 10.1042/bj2050321]
- 9 **Gordeuk VR**, Bacon BR, Brittenham GM. Iron overload: causes and consequences. *Annu Rev Nutr* 1987; **7**: 485-508 [PMID: 3300744 DOI: 10.1146/annurev.nu.07.070187.002413]
- 10 **Pietrangelo A**, Gualdi R, Casalgrandi G, Montosi G, Ventura E. Molecular and cellular aspects of iron-induced hepatic cirrhosis in rodents. *J Clin Invest* 1995; **95**: 1824-1831 [PMID: 7706489]
- 11 **Bacon BR**, Britton RS. The pathology of hepatic iron overload: a free radical-mediated process? *Hepatology* 1990; **11**: 127-137 [PMID: 2153094 DOI: 10.1002/hep.1840110122]
- 12 **Iancu TC**, Rabinowitz H, Brissot P, Guillouzo A, Deugnier Y, Bourel M. Iron overload of the liver in the baboon. An ultrastructural study. *J Hepatol* 1985; **1**: 261-275 [PMID: 4067258 DOI: 10.1016/S0168-8278(85)80054-4]
- 13 **Lustbader ED**, Hann HW, Blumberg BS. Serum ferritin as a predictor of host response to hepatitis B virus infection. *Science* 1983; **220**: 423-425 [PMID: 6301008 DOI: 10.1126/science.6301008]
- 14 **Piperno A**, Fargion S, D'Alba R, Roffi L, Fracanzani AL, Vecchi L, Failla M, Fiorelli G. Liver damage in Italian patients with hereditary hemochromatosis is highly influenced by hepatitis B and C virus infection. *J Hepatol* 1992; **16**: 364-368 [PMID: 1487615 DOI: 10.1016/S0168-8278(05)80671-3]
- 15 **Schwarz KB**, Larroya S, Vogler C, Sippel CJ, Homan S, Cockrell R, Schulze I. Role of influenza B virus in hepatic steatosis and mitochondrial abnormalities in a mouse model of Reye syndrome. *Hepatology* 1991; **13**: 96-103 [PMID: 1846348 DOI: 10.1002/hep.1840130114]
- 16 **Bharadwaj M**, Khanna N, Mathur A, Chaturvedi UC. Effect of macrophage-derived factor on hypoferraemia induced by Japanese encephalitis virus in mice. *Clin Exp Immunol* 1991; **83**: 215-218 [PMID: 1847096 DOI: 10.1111/j.1365-2249.1991.tb05617.x]
- 17 **Bacon BR**, Fried MW, DiBisceglie AM. A 39-year-old man with chronic hepatitis, elevated serum ferritin values, and a family history of hemochromatosis. *Semin Liver Dis* 1993; **13**: 101-105 [PMID: 8446904 DOI: 10.1055/s-2007-1007342]
- 18 **Di Bisceglie AM**, Axiotis CA, Hoofnagle JH, Bacon BR. Measurements of iron status in patients with chronic hepatitis. *Gastroenterology* 1992; **102**: 2108-2113 [PMID: 1587431]
- 19 **Turlin B**, Juguet F, Moirand R, Le Quilleuc D, Loréal O, Campion JP, Launois B, Ramée MP, Brissot P, Deugnier Y. Increased liver iron stores in patients with hepatocellular carcinoma developed on a noncirrhotic liver. *Hepatology* 1995; **22**: 446-450 [PMID: 7635411 DOI: 10.1016/0270-9139(95)90564-2]
- 20 **Farinati F**, Cardin R, De Maria N, Della Libera G, Marafin C, Lecis E, Burra P, Floreani A, Cecchetto A, Naccarato R. Iron storage, lipid peroxidation and glutathione turnover in chronic anti-HCV positive hepatitis. *J Hepatol* 1995; **22**: 449-456 [PMID: 7545199 DOI: 10.1016/0168-8278(95)80108-1]
- 21 **Arber N**, Konikoff FM, Moshkowitz M, Baratz M, Hallak A, Santo M, Halpern Z, Weiss H, Gilat T. Increased serum iron and iron saturation without liver iron accumulation distinguish chronic hepatitis C from other chronic liver diseases. *Dig Dis Sci* 1994; **39**: 2656-2659 [PMID: 7995192 DOI: 10.1007/BF02087705]
- 22 **Arber N**, Moshkowitz M, Konikoff F, Halpern Z, Hallak A, Santo M, Tiomny E, Baratz M, Gilat T. Elevated serum iron predicts poor response to interferon treatment in patients with chronic HCV infection. *Dig Dis Sci* 1995; **40**: 2431-2433 [PMID: 7587826 DOI: 10.1007/BF02063249]
- 23 **Piperano A**, D'Alba R, Roffi L, Fargion S, Mancina G, Fiorelli G. Relation between alpha interferon response and liver iron stores in chronic hepatitis C. *Hepatology* 1993; **18**: 250A [DOI: 10.1016/0270-9139(93)92524-4]
- 24 **Bacon BR**, Rebholz AE, Fried M, Di Bisceglie AM. Beneficial effect of iron reduction therapy in patients with chronic hepatitis C who failed to respond to interferon. *Hepatology* 1990; **12**: 105A
- 25 **Clemente MG**, Congia M, Lai ME, Lilliu F, Lampis R, Frau F, Frau MR, Faa G, Diana G, Dessi C. Effect of iron overload on the response to recombinant interferon-alfa treatment in transfusion-dependent patients with thalassemia major and chronic hepatitis C. *J Pediatr* 1994; **125**: 123-128 [PMID: 8021761 DOI: 10.1016/S0022-3476(94)70138-5]
- 26 **Olynyk JK**, Reddy KR, Di Bisceglie AM, Jeffers LJ, Parker TI, Radick JL, Schiff ER, Bacon BR. Hepatic iron concentration as a predictor of response to interferon alfa therapy in chronic hepatitis C. *Gastroenterology* 1995; **108**: 1104-1109 [PMID: 7698578 DOI: 10.1016/0016-5085(95)90209-0]
- 27 **Van Thiel DH**, Friedlander L, Fagioli S, Wright HI, Irish W, Gavalier JS. Response to interferon alpha therapy is influenced by the iron content of the liver. *J Hepatol* 1994; **20**: 410-415 [PMID: 8014455 DOI: 10.1016/S0168-8278(94)80017-0]
- 28 **Olynyk J**, Reddy R, Di Bisceglie AM. Hepatic iron concentration as a predictor of response to alpha interferon therapy in chronic hepatitis C. *Hepatology* 1993; **18**: A90
- 29 **Barton AL**, Banner BF, Cable EE, Bonkovsky HL. Distribution of iron in the liver predicts the response of chronic hepatitis C infection to interferon therapy. *Am J Clin Pathol* 1995; **103**: 419-424 [PMID: 7537017]
- 30 **Hayashi H**, Takikawa T, Nishimura N, Yano M. Iron removal as premedication for treatment of chronic active hepatitis C (abstract). *Hepatology* 1994; **20**: 72J [DOI: 10.1016/0270-9139(94)90455-3]
- 31 **Van Thiel DH**, Friedlander L, Molloy PJ, Kania RJ, Fagioli S, Wright HI, Gasbarrini A, Caraceni P. Retreatment of hepatitis C interferon non-responders with larger doses of interferon with and without phlebotomy. *Hepatogastroenterology* 1996; **43**: 1557-1561 [PMID: 8975965]

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