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. Excess or deficiency of iron leads to diseases. The liver is a major organ of injury in diseases causing iron overload, which is consistent with its central role in iron storage and metabolism. Excess or deficiency of iron leads to diseases. The liver is a major organ of injury in diseases causing iron overload, which is consistent with its central role in iron storage and metabolism.

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IRON AND HEPATITIS C VIRUS

It has been reported that iron is also an important factor involved in...
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[20].

Markers of viral infection are present in about one-fourth of all Italian patients with genetic hemochromatosis[19]. 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[11]. 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[10]. It has recently been shown that some viruses may promote hepatocyte damage by activating lipid peroxidation via an iron-mediated mechanism[11]. 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[11]. 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[11].

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[11]. Moreover, parenchymal iron overload has been shown in the nontumorous liver of most patients presenting with HCC developed in a non-cirrhotic liver[11]. 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[11]. 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[11]. In fact, 59% of patients with HCV infection had high (> 26.85 μg/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[11]. Further, serum transferrin saturation was significantly higher in HCV patients than in others[11]. 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[11]. Surprisingly, HBV infection was not associated with increased markers of iron metabolism. Therefore, it has been speculated that in contrast to HCV infection, HCV infection triggers free radical production, which may lead to interference with mitochondrial function[11].

### Table 1: Laboratory and histological findings in transfusion-dependent patients with thalassemia major and chronic hepatitis C before interferon therapy[11]

| Laboratory and histological findings | Responders (n = 24) | Non-responders (n = 30) | Control subjects (n = 14) |
|-------------------------------------|---------------------|------------------------|--------------------------|
| ALT (U/L)                           | 369 ± 145           | 318 ± 117              | 242 ± 86                 |
| Serum ferritin (μg/L)               | 270 ± 180           | 255 ± 66               | 244 ± 50                 |
| Hepatitis C virus-RNA               | Positive            | Positive               | Positive                 |
| Hepatic histologic findings        | CAH                 | CAH                    | CAH                      |

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[28].

Böök et al[28] 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 μg/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[29], the mean liver iron concentration of non-responders was also significantly higher than that of the responders (1252 μg/g dry weight vs 828 μg/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 μg/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[29]. Again, liver iron concentration was in the normal range, but merely twice as high in non-responders as compared to responders. Thus, there is no agreement regarding which of the iron indices most accurately predicts response to therapy. In a recent study[29], 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 μg/L) before initiation of IFN treatment. Again, iron removal alone effectively reduced the serum ALT levels [from 125 U/L to 49 U/L (mean)], but did not enhance the effect of treating viremia[29]. Whatever the practical consequences of this studies are, it should be mentioned that significant reductions in serum ALT levels were achieved by phlebotomy alone[29] and that compared to IFN therapy alone, phlebotomy plus IFN therapy resulted in greater reduction of serum ALT levels and improvement in histological picture[29].

### 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[29].

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 an open question. An upcoming 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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