ELSEVIER

Journal of Hepatology 50 (2009) 249–251

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Iron in NASH, chronic liver diseases and HCC: How much iron is too much? ☆

Antonello Pietrangelo*

Center for Hemochromatosis, University Hospital of Modena, Via del Pozzo 71, 41100 Modena, Italy

See Article, pages 351–357

While iron is essential for many vital functions, there is no regulated means by which excess iron can be disposed of in humans. Therefore, whenever body iron exceeds its needs and storage capabilities are saturated, toxicity due to iron overload may arise. Many causes of iron overload in humans exist, both genetic and acquired. Traditionally, hereditary hemochromatosis and post-transfusion iron overload have been associated with large hepatic iron deposits. However, an increasing number of other conditions are being recognized in which an observed mild or moderate increase of iron stores may have significant clinical relevance [1]. These conditions include alcoholic and non-alcoholic fatty liver disease (ALD and NAFLD, respectively) and steatohepatitis (ASH and NASH, respectively), chronic hepatitis C, and end-stage liver disease (Table 1). In this issue of the Journal, Sorrentino et al. [2] have investigated the relationship between hepatic iron and the development of HCC in NASH patients. Raised hepatic iron seems to increase the risk for NASH or its progression [3,4]. Hyperinsulinemia is a risk factor for the development of NASH and the coexistence of iron may contribute to the development of insulin resistance [5,6], while iron removal by phlebotomy can improve the insulin resistance and liver function in patients with NAFLD [7]. While there is little doubt that different chronic liver diseases, including NASH, can be accompanied with some degree of hepatic iron "overload" (Table 1), the question is whether such a marginal increase of tissue iron is clinically meaningful.

Normal hepatic iron content, as assessed by chemical methods, is usually below 35 μmol/g of dry weight. Historically, HIC above 200–250 μmol/g of dry weight has been associated with liver fibrosis and cirrhosis in hemochromatosis and thalassemia [8,9]. However, the actual hepatic iron burden in NASH (and other chronic liver disease patients), is far below that threshold. Nevertheless, even the presence of mild iron excess in the liver represents a risk for toxicity: iron can act as a comorbid factor (along with fat, hepatitis viruses and alcohol), and fuel oxidative stress-driven cell toxicity, or signalling pathways involved in fibrogenesis and carcinogenesis [10].

In chronic liver diseases, iron deposits are found either in hepatocytes, Kupffer/sinusoidal cells, or in both. Iron excess in hepatocytes leads to oxidative stress, cell toxicity and genotoxicity (Fig. 1A). Hepatocytic iron usually reflects increased iron influx as a consequence of circulatory iron excess. A recognized cause for increased iron influx is hepcidin deficiency due to either genetic (e.g. C282Y HFE mutation) or acquired (e.g. alcohol, HCV etc.) factors [11] (Table 1). On the other hand, iron accumulation in Kupffer cells (historically attributed to phagocytosis of necrotic hepatocytes) may have another significance, but similar effects (Fig. 1B). Kupffer cells, naturally devoted to erythrophagocitosis, are likely better equipped than hepatocytes to handle excess iron and more comfortable with intracellular movements of free radicals (which are normally used by macrophages to kill pathogens). Nevertheless, whatever the cause, iron engulfed sinusoidal-Kupffer

Associate Editor: M. Colombo

☆ The author declares that he does not have anything to disclose regarding funding from industries or conflict of interest with respect to this manuscript.

* Corresponding author.
E-mail address: antonello.pietrangelo@unimore.it

doi:10.1016/j.jhep.2008.11.011

Table 1
Chronic liver diseases usually associated with detectable hepatic iron deposits.

Disease	Known or postulated causes for iron excess	Known or postulated effects of iron excess
NASH/NAFLD	• Necroinflammation	• Insulin resistance • Disease progression • HCC
Chronic viral hepatitis	• Necroinflammation • Hepcidin down-regulation	• Disease progression • Impaired response to antiviral drugs
Alcoholic liver disease	• Necroinflammation • Hepcidin down-regulation	• Disease progression • HCC

cells may have still to do with progression of the underlying liver disease and development of its complications. Excess iron deposits in Kupffer/sinusoidal cells may affect their immunomodulatory and inflammatory activity, cytokine biology, defense against pathogen and viral infection, immunosurveillance of tumor growth, or response to immunomodulatory drugs (Fig. 1B) [12]. Obviously, this consideration takes us to another question: does it only matter "how much" iron accumulates in the liver, or is it "where" iron deposits are located that makes the difference for disease progression? A simple way for quantifying hepatic iron excess and also gain information on iron distribution is staining biopsy specimen for iron by Perls' stain. The Scheuer-based iron grading systems have used the Perls' stain to score the percentage of iron loaded hepatocytes [13,14]. A more sophisticated method proposed by Deugnier [15] takes into account iron deposits in parenchymal, sinusoidal cells and in portal tracts, and offers a good opportunity to assess iron deposits and its cell distribution. In the article by Sorrentino et al. [2] hepatic iron deposits have been assessed retrospectively using the Deugnier Score (range 0–60) in 153 patients with NASH-related cirrhosis: 51 with and 102 without HCC, matched for age, sex and stage of liver disease. As expected, many patients with NASH had iron deposits in the biopsy, but the majority scored below, and none above 33. Interestingly, the iron score was significantly higher in HCC-NASH patients than in HCC-free NASH controls, and, more importantly, in the former group, liver "iron overload" was mainly sinusoidal. Although the study suffers from obvious flaws due to its retrospective design and the lack of mechanistic clues, it clearly underscores the strict association between iron deposits and HCC development in NASH, and stresses the pathogenic role of "sinusoidal" iron deposits. Interestingly, a recent prospective study in 301 consecutive cirrhotics found that in patients with alcoholic cirrhosis liver iron "overload" (mean score 2.0 ± 3.0 according to a modified version of Deugnier's method) was independently associated with a higher risk of HCC [16]. Unfortunately, no information was given on the effect of sinusoidal vs. hepatocytic iron deposits on HCC development.

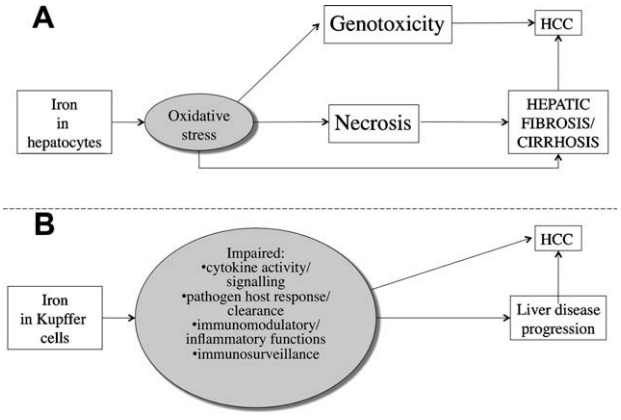

Fig. 1. Known or postulated effects of hepatocytic or Kupffer cell iron on chronic liver disease progression and HCC development.

What are the take-home messages? First, positive iron stain in a liver biopsy is important. Although the term "iron overload" as used in hemochromatosis and thalassemia may not be appropriate, the detectable presence of hepatic iron deposits in the biopsy of patients with chronic liver diseases does indicate a condition that is not normal and potentially deleterious. Second, there may be a pathogenic role of sinusoidal iron accumulation in the progression of chronic liver diseases and/or HCC development. Overall, does this mean that "no detectable iron" in a liver biopsy is good, and "any" iron stain is bad? Maybe... but to conclusively answer this and other related key questions we need large prospective studies in selected groups of patients with chronic liver diseases where the independent pathogenic role of hepatic iron deposits is evaluated, also taking into account epidemiologic factors that are known to be associated with both iron imbalance and disease progression/HCC, such as age and male gender. Hopefully, this will pave the way for controlled clinical trials using iron removal strategies/iron chelators to prove that lowering hepatic iron deposits prevents liver disease progression and its complications, including HCC.

References

[1] Pietrangelo A. Iron chelation beyond transfusion iron overload. Am J Hematol 2007;82:1142–1146.

[2] Sorrentino P, D'Angelo S, Ferbo U, Micheli P, Bracigliano A, Vecchione R. Liver iron excess in patients with hepatocellular carcinoma developed on non-alcoholic steato-hepatitis. J Hepatol 2009;50:351–357.
[3] George DK, Goldwurm S, MacDonald GA, Cowley LL, Walker NI, Ward PJ, et al. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. Gastroenterology 1998;114:311–318.
[4] Fargion S, Mattioli M, Fracanzani AL, Sampietro M, Tavazzi D, Fociani P, et al. Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis. Am J Gastroenterol 2001;96:2448–2455.
[5] Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. Hepatology 2004;39:179–187.
[6] Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, et al. Insulin resistance-associated hepatic iron overload [see comments]. Gastroenterology 1999;117:1155–1163.
[7] Valenti L, Fracanzani AL, Dongiovanni P, Bugianesi E, Marchesini G, Manzini P, et al. Iron depletion by phlebotomy improves insulin resistance in patients with nonalcoholic fatty liver disease and hyperferritinemia: evidence from a case-control study. Am J Gastroenterol 2007;102:1251–1258.
[8] Guyader D, Jacquelinet C, Moirand R, Turlin B, Mendler MH, Chaperon J, et al. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. Gastroenterology 1998;115:929–936.
[9] Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000;343:327–331.
[10] Pietrangelo A. Metals, oxidative stress, and hepatic fibrogenesis. Semin Liver Dis 1996;16:13–30.
[11] Pietrangelo A. Hemochromatosis: an endocrine liver disease. Hepatology 2007;46:1291–1301.
[12] Pietrangelo A. Hemochromatosis gene modifies course of hepatitis C viral infection. Gastroenterology 2003;124:1509–1523.
[13] Scheuer P, Williams R, Muir AR. Hepatic pathology in relatives of patients with hemochromatosis. J Pathol Bacteriol 1962;84:53–64.
[14] Ludwig J, Batts KP, Moyer TP, Baldus WP, Fairbanks VF. Liver biopsy diagnosis of homozygous hemochromatosis: a diagnostic algorithm. Mayo Clin Proc 1993;68:263–267.
[15] Deugnier YM, Loreal O, Turlin B, Guyader D, Jouanolle H, Moirand R, et al. Liver pathology in genetic hemochromatosis: a review of 135 homozygous cases and their bioclinical correlations. Gastroenterology 1992;102:2050–2059.
[16] Nahon P, Sutton A, Rufat P, Ziol M, Thabut G, Schischmanoff PO, et al. Liver iron, HFE gene mutations, and hepatocellular carcinoma occurrence in patients with cirrhosis. Gastroenterology 2008;134:102–110.