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Review article

Beyond hereditary hemochromatosis: New insights into the relationship between iron overload and chronic liver diseases

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ABSTRACT

Following the model of hereditary hemochromatosis, the possible role of iron overload as a cofactor for disease progression in acquired liver diseases has been investigated with controversial results. In recent years, progress has been made in understanding the regulation of iron metabolism, thereby allowing the evaluation of the mechanisms linking liver diseases to excessive iron accumulation. Indeed, deregulation of the transcription of hepcidin, emerging as the master regulator of systemic iron metabolism, has been implicated in the pathogenesis of hepatic iron overload in chronic liver diseases. Whatever the cause, hepatocellular iron deposition promotes liver fibrogenesis, while an emerging possible aggravating factor is represented by the strong link between iron stores and insulin resistance, a recently recognized risk factor for the progression of liver diseases. Overall, these pathogenic mechanisms, together with the known proliferative and mutagenic effect of excess iron, converge in determining an increased susceptibility to hepatocellular carcinoma. Finally, an association between serum ferritin levels and mortality in patients with end-stage liver disease has recently been reported.

Prospective, randomized studies are required to evaluate whether iron depletion may reduce fibrosis progression, hepatocellular carcinoma development, and eventually mortality in patients with chronic liver diseases.

1. Introduction

Following the model of hereditary hemochromatosis (HH), a common recessive genetic disease characterized by progressive hepatic iron accumulation with possible evolution to cirrhosis and hepatocellular carcinoma (HCC), considerable research efforts have been devoted to the evaluation of a possible role of hepatic iron overload as a cofactor for disease progression and HCC development in other acquired liver diseases, but with controversial results. Indeed, HH still represents an important cause of liver disease in Western countries, although, due to the increased awareness leading to earlier recognition and treatment, the prevalence of cirrhosis at the time of diagnosis is decreasing (about 13% in the last 10 years) [1]. However, once cirrhosis is established, HCC will develop in roughly 5% of patients per year, even if patients have been iron depleted [1,2].

In recent years, progress has been made in understanding the regulation of iron metabolism and HH pathogenesis [3,4], thereby allowing the evaluation of the mechanisms linking chronic liver diseases to excessive hepatic iron accumulation at the molecular level. Moreover, new evidence is accumulating suggesting a link between altered iron metabolism and the metabolic syndrome, a rapidly exploding health problem and already the leading cause of altered iron parameters and increased body iron stores in the general population [5–7]. Finally, evidence is accumulating that independently of the underlying liver disease, iron accumulation is a powerful risk factor for HCC development.

HH is most commonly related (70–95% of cases) to homozygosity for the C282Y mutation of the *HFE* gene, which impairs the expression of the HFE protein on the cell membrane, thereby impairing iron sensing by hepatocytes and the transcription and release of hepcidin, the hepatic hormone which controls iron absorption and recycling [3]. Missense mutations in other genes involved in the regulation of hepcidin release, transcription and biological activity, including *tranferrin receptor-2* (involved in iron sensing in hepatocytes), *hemojuvelin* (the major inducer of hepcidin transcription), *hepcidin* itself, *ferroportin* (the hepcidin receptor mediating cellular iron efflux and iron absorption), and *ceruloplasmin* (required for ferroportin activity in certain tissues) are responsible or rarer forms of adult onset HH, juvenile hemochromatosis, and other forms of hereditary iron overload [4]. However, a mild increase in body iron stores in the general population is more frequently related to secondary causes including alcohol abuse, the metabolic syndrome, chronic hepatitis C, hemolytic and dysery-

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thropoietic anemias and chronic transfusional therapy, and chronic inflammation and end-stage renal disease, the latter being also a frequent indication for chronic iron supplementation to support erythropoiesis.

2. Progression of chronic liver diseases

There is growing evidence that mildly increased amounts of liver iron can increase hepatic injury in combination with other insults, such as chronic hepatitis C virus (HCV) infection, excessive alcohol intake, or nonalcoholic fatty liver disease (NAFLD). The rationale that makes iron a potential hepatotoxic factor is based on the capability of this metal to induce oxidative stress by catalyzing hydroxyl radicals formation through the Fenton reaction. Iron-catalyzed oxidative stress causes lipid peroxidation and protein modification, DNA damage with consequent promotion of mutagenesis, and leads to the exhaustion of antioxidant defenses. These properties are typical of transition metals, of whom iron is the more represented in biological systems, the one for whom there is more direct evidence of a relationship with tissue damage, and whose concentration is more often increased in pathophysiological conditions characterized by genetic or secondary dysregulation of iron homeostasis, so that the term "ferrotoxic diseases" has been coined [8].

The typical model of iron-induced liver damage is HH due to homozygosity for the C282Y *HFE* mutation, in which progressive iron overload is responsible for liver damage through enhanced oxidative stress, whose markers decrease with phlebotomy [9]. A relatively recent acquisition is that duration and amount of exposure to iron is crucial in the development of hepatic damage [1,10].

Interestingly, experimental data have recently suggested that ferritin, behaving as a cytokine [11], may also directly induce the fibrogenic process by activating hepatic stellate cells [12]. The effect of ferritin on hepatic stellate cells activation has been reported to be mediated by the phosphoinositide 3-kinase phosphorylation, and activation of the kinases protein kinase C zeta and p42/44 mitogen activated protein kinases, resulting in NFκB activation and expression of proinflammatory mediators including interleukin-1β, independently of the interaction with a proposed H-ferritin receptor, namely T cell immunoglobulin domain and mucin domain (Tim-2) [12].

Several lines of evidence strongly suggest that iron is a cofactor in hepatitis B virus (HBV) and hepatitis C virus (HCV) chronic hepatitis, porphyria cutanea tarda (PCT), alcoholic liver disease (ALD), nonalcoholic steatohepatitis (NASH), and HCC. An overview of selected recent studies, arbitrarily identified on the basis of the quality of the experimental design and data collection, analyzing the relationship between iron overload and/or the presence of *HFE* mutations and progressive liver disease is shown in Table 1.

3. Chronic hepatitis C

Mild to moderate iron overload is present in 30–40% of chronic hepatitis C (CHC) patients [13,14], and data from the third National Health and Nutrition Examination Survey (14,500 cases) indicate that CHC is associated with higher serum levels of iron and serum

Table 1
An overview of selected recent studies, arbitrarily identified based on the quality of the experimental design and data collection, analyzing the relationship between iron overload and/or the presence of *HFE* mutations and progressive liver disease.

Disease	Study	Patients no.	Association with progressive disease for	
			Iron overload	HFE mutations
CHC	Ferrara 2009 [34]	206	Associated with fibrosis	NA
	Sartori 2006 [29]	100	NA	No association with fibrosis *Beta-globin* mutations associated with fibrosis
	Valenti 2007 [12]	143	NA	Association with iron overload
	Guyader 2007 [30]	580	Associated with fibrosis, but lost at multivariate analysis including serum iron parameters and various confounders	NA
	Erhardt 2003 [27]	401	NA	Associated with iron overload and fibrosis
	Tung 2003 [23]	316	NA	Associated with iron overload ad advanced fibrosis
	Thorburn 2002 [25]	164	Associated with inflammation	No association
	Smith 1998 [24]	137	NA	C282Y associated with fibrosis
NAFLD	Valenti, 2010 [52] (includes patients of Valenti, 2008 [50] Bugianesi 2004 [49])	587 Italian	Hepatocellular but not non-parenchymal iron associated with fibrosis	No association with fibrosis
	Nelson, 2007 [99]	126 NASH	NA	C282Y associated with fibrosis in Caucasians
	Chitturi 2002 [48]	93	No association	No association
ALD	Gleeson 2006 [63]	254	NA	Not associated with decompensated ALD
	Grove 1998 [62]	257	NA	Not associated with ALD
HCC	Jin 2010 [89]	1102 meta-analysis	NA	Associated with HCC in ALD
	Sorrentino 2009 [92]	153 cirrhosis NASH	Sinusoidal iron associated with HCC (case-control)	NA
	Nahon 2008 [76]	301 cirrhosis	Associated with HCC in ALD but not in HCV (prospective)	C282Y associated with HCC in ALD but not in HCV (prospective)
	Fracanzani 2005 [73]	303 case only	NA	Association with HBV and HCV infection
	Hellerbrand 2003 [77]	247	NA	C282Y associated with iron and HCC
	Boige s2003 [78]	233	NA	No association with iron nor with HCC
	Lauret 2002 [87]	277	NA	C282Y associated with HCC in ALD but not in HCV (case-control)

CHC: chronic hepatitis C, NAFLD: nonalcoholic fatty liver disease; ALD: alcoholic liver disease, HCC: hepatocellular carcinoma; NA: not assessed.