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Review Article

Role of hepatic iron in non-alcoholic steatohepatitis

Yoshio Sumida,[1] Toshikazu Yoshikawa[2] and Takeshi Okanoue[3]

[1]*Center for Digestive and Liver Diseases, Nara City Hospital, Nara,* [2]*Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto,* [3]*Center of Gastroenterology and Hepatology, Saiseikai Suita Hospital, Suita, Japan*

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of clinical entities ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with possible evolution to cirrhosis and hepatocellular carcinoma. Iron is considered a putative element that interacts with oxygen radicals in inducing liver damage and fibrosis. The role of hepatic iron in the progression of NASH remains controversial, but in some patients, iron may have a role in the pathogenesis of NASH. Though genetic factors, insulin resistance, dysregulation of iron-regulatory molecules, erythrophagocytosis by Kupffer cells may be responsible for hepatic iron accumulation in NASH, exact mechanisms involved in iron overload remain to be clarified. Iron reduction therapy such as phlebotomy or dietary iron restriction may be promising in patients with NASH/NAFLD to reduce insulin resistance as well as serum transaminase activities.

Key words: insulin resistance, iron, nonalcoholic fatty liver disease, non-alcoholic steatohepatitis, oxidative stress, phlebotomy

INTRODUCTION

IRON IS A potent catalyst of oxidative stress and may act synergistically with other promoters of lipid peroxidation by catalyzing these reactions. Iron overload can also directly cause lipid peroxidation, and one of the subsequent products, malondialdehyde, has been shown to activate hepatic stellate cells in vitro, the major source of fibrogenesis in liver injury.[1]

Non-alcoholic liver disease (NAFLD) is defined as a constellation of clinical conditions characterized by predominantly macrovesicular steatosis of the liver. The histologic spectrum of this disease ranges broadly from simple steatosis and non-alcoholic steatohepatitis (NASH) through to cirrhosis. Although simple steatosis seems to be benign, NASH can have a progressive course. Diagnosis of NASH is defined by liver histology, which typically shows macrovesicular steatosis and lobular inflammation with or without fibrosis. Mallory bodies are occasionally seen in the absence of a history of excessive ethanol ingestion.[2] The exact mechanism of this progression is not known but probably involves two steps.[3] Excessive triglyceride accumulation is the most likely first step. The second step may relate to an increase in oxidative stress, which, in turn, triggers liver cell necrosis and activation of hepatic stellate cells, both leading to fibrosis and ultimately to the development of cirrhosis. One of the potential cofactors suspected to enhance this oxidative stress is excessive hepatic iron accumulation.

This article explores the role of hepatic iron in NASH/NAFLD, and the possible therapeutic implications of iron reduction therapy.

Iron indices and hepatic iron deposition in NASH/NAFLD

There is controversial evidence that hepatic iron may play a role in the pathogenesis of NASH/NAFLD. Bacon *et al.*[4] documented abnormal iron indices (serum ferritin and/or transferrin saturation), and elevated hepatic iron concentration in NASH. George *et al.*[5] first proposed the hypothesis of iron-related liver injury in NASH. In their study of 51 patients, increased hepatic iron was present in 41%, and 23% had hepatic iron concentration (HIC)

Correspondence: Dr Yoshio Sumida, Center for Digestive and Liver Diseases, Nara City Hospital, Higashi Kidera-cho 1-50-1, Nara 630-8305, Japan. Email: sumida@nara-jadecom.jp
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above the upper limit of normal. Their most significant conclusion was that increased hepatic iron had the greatest association with the severity of fibrosis; Perl's stain grade was assigned a relative risk of 5.5 (95% CI, 2.5–13.6). We also previously reported high frequencies of hyperferritinemia and increased hepatic iron stores in Japanese patients with NASH.[6,7] Serum thioredoxin (TRX) levels, an indicator of oxidative stress, were increased in proportion of the grade of hepatic iron accumulation.[6] Our data imply that the presence of excessive hepatic iron may be one of the possible cofactors for the induction of oxidative stress in NASH. Iron could potentially play a supporting role in the lipid peroxidation and fibrogenesis central to the development and progression of NASH.

In contrast, Younossi *et al.*,[8] Angulo *et al.*,[9] and Chitturi *et al.*[10] documented that significant iron accumulation is not seen in most patients with NASH. Younossi *et al.*[8] found no significant iron accumulation in NAFLD patients and no association between hepatic iron and aggressive histological or clinical outcome. Angulo *et al.*[9] studied 132 patients with NASH from Mayo Clinic database to find independent predictors of hepatic fibrosis. HIC and hepatic iron index were normal in all patients with abnormal iron indices (53% had elevated serum ferritin; 11% had elevated transferrin saturation). They found no association between increased iron indices and degree of fibrosis in multivariate analysis. Chitturi *et al.*[10] demonstrated that hyperferritinemia was present in 38 (40%) of 93 patients with NASH, but that only nine (10%) patients showed increased iron: 7 with grade 2 and 2 with grade 3. In India, Duseja *et al.*[11] showed that 71% of thirty-one NASH patients had negative iron staining. There was no association the degree of iron staining and fibrosis stage. These authors conclude that hyperferritinemia in NASH is a nonspecific effect of hepatic necroinflammation, reflecting its function as an acute phase protein. Serum ferritin is known to increase because of release from damaged hepatocytes. We also previously suggested that serum ferritin levels reflect oxidative stress as well as hepatic iron concentration and hepatocyte damage in chronic liver disease,[12] because the synthesis of ferritin seems to be influenced by oxidative stress or reduction/oxidation (redox) state.[13,14] It is possible that elevated serum ferritin in NASH may be derived from iron-unrelated oxidative stress,[12] such as free fatty acid, lipid peroxide, cytokines, and induction of cytochrome P450 enzymes (CYP2E1 and CYP4A).[15]

In this way, the role of hepatic iron in the pathogenesis of NASH or abnormal iron indices in NASH remains controversial and unsettled as of this time.[16]

The role of HFE mutation in hepatic iron deposition of NASH/NAFLD

The significance of hemochromatosis gene (HFE) mutations in the pathogenesis and progression of NASH/NAFLD also remains controversial.[5,10,17] George *et al.*[5] demonstrated a higher prevalence of the Cys282Tyr mutation of the HFE gene in patients with NASH, although there was no difference in the frequency of the His63Asp mutation. The presence of the Cys282Tyr mutation was associated with increased hepatic iron staining and hepatic iron concentration. Bonkovsky *et al.*[18] also reported a significantly higher prevalence of certain HFE mutation in patients with NASH. These authors found that Cys282Tyr heterozygotes had significantly more hepatic fibrosis than those without HFE mutations. However, the HIC was normal in all subjects and did not differ between those with and without HFE mutations. According to data from 126 NASH patients which were collected from 6 North American conters,[19] Cys282Tyr heterozygotes is associated with advanced hepatic fibrosis and stainable hepatic iron in Caucasians with NASH. They speculate that the mechanism is related to increased oxidative stress in the liver due to increased iron deposition. Chitturi *et al.*[10] found a trend toward higher serum ferritin levels among Cys282Tyr heterozygotes with NASH. Neither hepatic iron nor the presence of HFE mutations were identified as risk factors for fibrotic severity. Similarly, no evidence of an association of hepatic iron overload and HFE mutations with NASH was found in Brazilian or Asian Indian patients.[11,20,21] In Japan, there were no NASH/NAFLD patients with HFE mutations,[22] in agreement with a previous report indicating that the frequencies of HFE mutations in the Japanese population are extremely low (Cys282Tyr, 0%; and His63Asp, 0.99%).[23]

In this way, HEF gene mutation which is related to ethnicity[10] does not seem to have important roles in hepatic iron deposition in NASH/NAFLD.

Possible mechanisms involved in hepatic iron overload in NASH/NAFLD

As mentioned above, the precise mechanisms underlying hepatic iron deposition in NASH remain unknown. However, several possible mechanisms have been suggested in clinical or experimental studies (Fig. 1).

An association between insulin resistance (IR) and hepatic iron overload has been recently described.[24] First, it is quite plausible that the unhealthy diets contribute to IR not only through excess fat intake but also through excess iron supply (for example, in meat or in

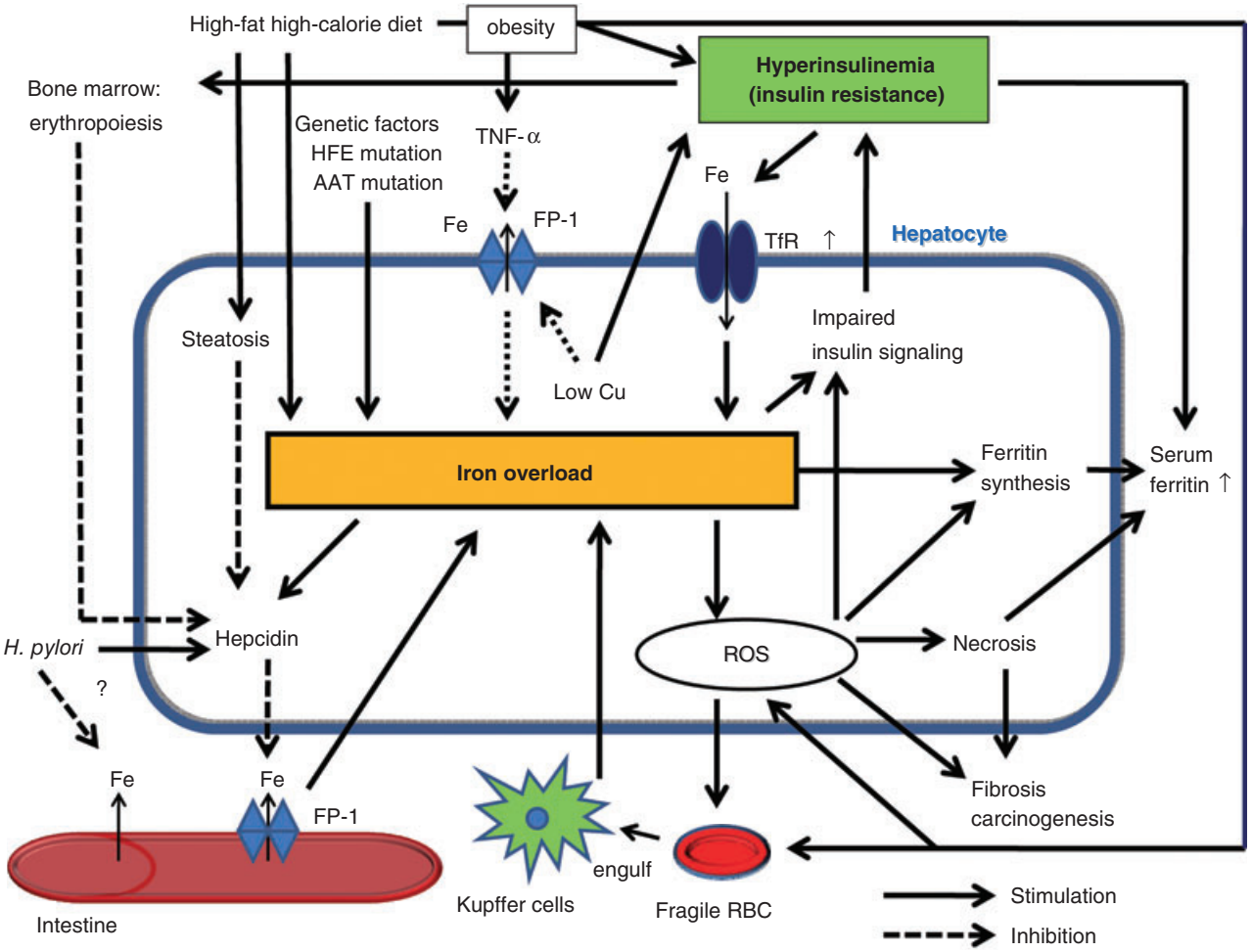

Figure 1 Possible mechanisms of hepatic iron deposition and pathogenetic roles of iron in nonalcoholic steatohepatitis/nonalcoholic fatty liver disease. AAT, alpha 1-antitrypsin; FP-1, ferroporitn-1; *H. pylori*, *Helicobacter pylori*; RBC, red blood cell; ROS, reactive oxygen species; TfR, transferrin receptor; TNF-α, tumor necrosis factor-α.

iron-supplemented food). Second, iron overload can interfere with insulin signaling through the induction of reactive oxygen species (ROS) (Fig. 1), the latter impairing insulin uptake through a direct effect on insulin receptor function,[25] by inhibiting the translocation of glucose transporter 4 (GLUT4) to the plasma membrane and iron induces IR of glucose transport in adipocytes through a mechanism independent of fatty acids.[26] Moreover, iron has been found to reduce hepatic extraction/metabolism of insulin and to interfere with insulin action on the liver, leading to peripheral hyperinsulinemia.[27,28] Another mechanism is the enhancement of GLUT 1 and 4 activities in skeletal muscle after iron depletion.[29] By contrast, hyperinsulinemia may cause rapid stimulation of iron uptake into the liver, because insulin is known to redistribute transferrin receptors from an intracellular membrane compartment to the cell surface (Fig. 1).[30,31] The association of unexplained hepatic iron overload with metabolic disorders has recently been coined as the insulin resistance-associated hepatic iron overload syndrome (IR-HIO) proposed by Mendler *et al.*[32] Although patients with IR-HIO have a high prevalence of IR-related metabolic disorders, the relationship of IR-HIO to NASH is unclear. It is plausible that IR, which is often associated with NASH,[33] may be directly responsible for the accumulation of iron in the liver.[34] In general population, the association of elevated serum ferritin concentrations and IR was already demonstrated.[35–37] Several studies have demonstrated that serum ferritin is a good indica-

Table 1 Similarities between chronic hepatitis C and non-alcoholic steatohepatitis

1. Histological findings
Steatosis
Iron deposition (hyperferritinemia)
2. Pathogenesis
Oxidative stress
Insulin resistance
3. Progression
Cirrhosis or hepatic failure
Hepatocellular carcinoma
4. Treatments
Diet therapy
Medication (ursodeoxycholic acid, vitamin E)
Iron reduction therapy (phlebotomy, dietary iron restriction)

tor of IR also in hepatitis C patients.[38,39] In Japan, we also previously reported that serum ferritin levels were positively correlated with homeostasis assessment model for IR (HOMA-IR) in non-diabetic patients with chronic hepatitis C.[40] One problem of these previous studies is that the iron concentration of liver tissue was not measured, because serum ferritin cannot always reflect total body iron stores as mentioned above. We recently studied 56 non-obese non-diabetic patients with chronic hepatitis C to investigate whether hepatic iron deposition is really correlated with IR. HOMA-IR was significantly correlated not only with serum ferritin but also with the grade of hepatic iron deposition.[41] Our results suggest that chronic hepatitis C may be one of the IR-HIO. Marcheisini *et al.*[42] have reported that serum indices of iron overload are present in 10 or 43% patients with NAFLD, but that those do not correlate with measures of insulin sensitivities. We demonstrated that serum ferritin levels and HOMA-IR in patients with NASH were significantly higher than in those with simple steatosis.[43] Our study did not show the correlation of HOMA-IR with serum ferritin levels or hepatic iron concentrations in patients with NASH/NAFLD,[43] in contrast with previous studies showing the positive correlation of IR with hepatic iron deposition in hepatitis C.[40,41] In this way, further studies are required to clarify the association of IR with iron deposition in NASH/NAFLD. On the other hand, high frequencies of hepatic steatosis in hepatitis C as previously shown[44] have suggested that chronic hepatitis C may be named a virus-associated steatohepatitis (VASH).[45] Between chronic hepatitis C and NASH, there are several similarities such as steatosis, insulin resistance, hepatic iron accumulation, and oxidative stress (Table 1).

Hepcidin is a disulfide-bonded peptide that was first identified as an antimicrobial peptide and was subsequently shown to be central player in systemic iron homeostasis.[46,47] Hepcidin is believed to be a negative regulator of dietary iron absorption and of iron release by macrophages via inducing internalization and degradation of the iron exporter ferroportin in absorptive enterocytes and reticuloendothelial cells.[48] The synthesis of hepcidin, which is specifically produced by the liver,[49] is greatly stimulated by inflammation or by iron overload.[50] The expression is down-regulated by hypoxia, anemia, iron deficiency, erythropoietin, and erythropoietic stimulation.[51] Though the role of hepcidin in the iron loading of patients with hepatitis C is unknown, one hypothesis is that low expression of hepcidin in the liver may be responsible for hepatic iron overload in hepatitis C.[52–54] Nagashima *et al.* reported that serum prohepcidin levels were decreased and negatively correlated with serum ferritin levels or hepatic iron concentration in hepatitis C patients.[52] They have suggested that failure of homeostatic regulation of serum prohepcidin concentrations may be induced by HCV infection. Fujita *et al.* demonstrated that hepatic hepcidin mRNA was relatively low in chronic hepatitis C patients, as compared to chronic hepatitis B.[53] This relative impairment of hepcidin production was fully reversible after successful eradication of HCV.[54] In contrast, Aoki *et al.* concluded that liver hepcidin, whose mRNA was correlated with iron concentration, cannot play a role in the hepatic iron accumulation in hepatitis C.[55] According to a recent experimental study using transgenic mice expressing HCV polyprotein by Nishina *et al.*, HCV-induced ROS may down-regulate hepcidin transcription, which in turn leads to increased duodenal iron transport and macrophage iron release, causing hepatic iron accumulation.[56] In alcoholic liver disease, hepatic iron loading seems to be contributed to the down-regulated hepcidin leading to the increase of iron absorption from the intestine.[57,58] The expression of hepcidin in NASH/NAFLD patients remains unknown. In animal model of IR, IR can lead to a downregulation of hepcidin expression via stimulation of erythropoiesis, which in turn increases the needs for iron (Fig. 1).[59] It has been recently shown that hepcidin is expressed, at both the mRNA and protein levels, in adipose tissue and that this expression is enhanced in severely obese patients.[60] Human studies focused on iron absorption rates and hepcidin expression in NASH/NAFLD or metabolic syndrome should be performed to unravel the mechanisms behind the iron metabolism disturbance.[61] According to a recent study from Australia,[62] analysis of

iron-regulatory molecules in liver tissue revealed a striking down-regulation of the liver iron exporter ferroporitn-1 (FP-1) and the iron sensing molecule hemojuvelin (HJV). They suggest that TNF-α, highly expressed in NAFLD patients, play a role in exerting these regulatory changes, because they found inverse correlations of TNF-α concentrations and expression of FP-1 or HVJ in vivo and decreased formation of FP-1 and HVJ in HepG2 cells on stimulation with TNF-α in vitro. Thus, they concluded that iron accumulation in NAFLD may result from decreased iron mobilization from hepatocytes due to low expression of FP-1 and HVJ (Fig. 1). The same group found that NAFLD patients with iron overload had low levels of serum and hepatic copper along with low serum ceruloplasmin levels.[63] They suggested that copper deficiency may be responsible for hepatic iron overload, because the copper-dependent ferroxidase ceruloplasmin is required for the mobilization of iron from storage sites such as the liver. Moreover, FP-1 mRNA expression and protein were found to be lowest in NAFLD patients with low hepatic copper concentrations. They detected significantly lower FP-1 protein levels in rats kept on a copper-deficient diet as compared with rats with a normal copper diet. Lower copper bioavailability causes increased hepatic iron stores via decreased FP-1 expression and ceruloplasmin ferroxidase activity thus blocking liver iron export in copper-deficient NAFLD patients (Fig. 1). These studies observed hepatic expression of hepcidin, which reflects the physiologic response to liver iron accumulation.

On the other hand, several lines of evidences have suggested an association between *Helicobacter pylori* (Hp) infection and iron deficiency.[64] If Hp infection is associated with iron deficiency anemia, then eradicating the organism should increase iron stores and resolve the anemia. Reversal of iron deficiency anemia after successful eradication of Hp has been observed not only in children[65,66] but also in adults.[67–69] These findings have supported an association between Hp infection and iron deficiency. Several possible mechanisms may correlate Hp infection with decreased iron accumulation.[70] Recent findings support the hypothesis that in patients with Hp positive gastritis, concomitant changes in intragastric pH and ascorbic acid are present that might play a role in impairing alimentary iron absorption with consequent iron deficiency.[64,71] It has also been speculated that Hp infected antrum could act as a sequestering focus for iron. Hp infection enhances gastric lactoferrin,[72,73] which captures iron from transferrin. The iron bound to lactoferrin is in turn picked up by the bacterium, by means of its outer membrane receptors,[74] for its own growth.[64] Though the exact mechanisms of iron deficiency in Hp-infected individuals are unknown, one hypothesis[75] is that up-regulated expression of hepcidin by Hp infection via releasing cytokines such as IL-6 could impair intestinal iron absorption with consequent lower iron deposit in the liver (Fig. 1). Dr Beutler hypothesizes that Hp may produce hepcidin mimicks preventing the absorption of iron in a manner analogous with the suppression of iron absorption by hepcidin associated with inflammation.[76] We previously reported that Hp infection may decrease hepatic iron deposition in hepatitis C patients.[77] Our preliminary study also demonstrated that the grades of hepatic iron deposition in NAFLD patients with Hp infection were lower than those without.[43]

Otogawa K *et al.*[78] newly proposed that hepatic iron in NASH may be derived from erythrophagocytosis by liver macrophages (Kupffer cells), using rabbits fed a cholesterol-rich high-fat diet (HFD) with IR who exhibit pathological changes very similar to those of human NASH (Fig. 1). In addition, immunohistochemistry in liver tissue from NASH patients revealed that the aggregation of erythrocytes in inflammatory hepatic sinusoids was increased, leading to hepatic iron deposition and oxidative stress. How erythrocytes in patients with NASH become easy to be engulfed by Kupffer cells is not fully understood, though ROS may be involved in the mechanism (Fig. 1).

Recently, another element has been examined that could affect iron metabolisim. Alpha 1-antitrypsin (AAT) protein, an acute-phase protein, has been demonstrated to interact with transferrin receptor inducing ferritin synthesis. Valenti *et al.*[79] demonstrated that NAFLD patients with AAT mutations had higher ferritin levels than those without. In liver histology, AAT mutations were associated with higher prevalence of sinusoidal siderosis, but not with more severe liver damage in NAFLD. AAT mutations did not affect parenchymal or portal siderosis.

Iron reduction therapy in NAFLD/NASH

Although the causes of NASH are not well defined and several therapies including diet,[80] antioxidants,[81] and approaches that improve IR[82] have been tried, the optimal therapy for NASH has not been established.

In Japan, we previously confirmed a significant improvement in serum transaminase activities after 3-month iron reduction therapy by phlebotomy for chronic hepatitis C in a multicenter, prospective, randomized, controlled trial.[83] We have also demonstrated that the efficacy of phlebotomy is superior to that of

Table 2 Phlebotomy in nonalcoholic steatohepatitis/non-alcoholic fatty liver disease

Study	Location	Study design	Patients, *n* (F/M)	Disease	ALT (IU/mL)	Ferritin (ng/mL)	HFE mutation	Insulin resistance (IRI, HOMA-IR)	Histological evaluation
Facchini *et al.* (2002)[85]	San Francisco, US	Open	17 (5/12)	NAFLD IGT (+)	From 61 ± 5 to 32 ± 2 ($P < 0.001$)	From 299 ± 41 to 15 ± 1 ($P < 0.001$)	Excluded	Improved	NA
Valenti *et al.* (2003)[86]	Milano, Italy	Open	12 (0/12)	NAFLD IGT (–)	From 62 ± 45 to 33 ± 22 ($P = 0.0074$)	From 583 ± 274 to 36 ± 22	C282Y (+/–): 3/12	Improved (independently of serum ferritin levels)	Only at entry
Riquelme *et al.* (2004)[88]	Santiago, Chile	Case report	1 (1/0)	NASH (PCT, β thalassemia minor)	From 68 to normal (<20)	From 762 to normal (<417)	H63D (+/–)	NA	Complete resolution of steatosis and inflammation
Fargion *et al.* (2005)[28]	Milano, Italy	Open	42 (9/33)	NAFLD	From 44 ± 30 to 32 ± 19 ($P = 0.03$)	From 361 ± 222 to 123 ± 100 ($P = 0.0001$)	NA	Improved (independently of serum ferritin levels)	NA
Sumida *et al.* (2006)[87]	Nara, Japan	Open	11 (5/6)	NASH	From 126 ± 47 to 56 ± 17 ($P = 0.002$)	From 563 ± 322 to 18 ± 9 ($P = 0.001$)	NA	NA	Only at entry
Valenti *et al.* (2007)[89]	Milano, Italy	Case-control	64 (11/53)	NAFLD	From 57.9 ± 47.4 to 34.3 ± 27 (NS *versus* controls)	From 438 {21–628} to 52 {27–96}	C282Y (+/–): 11/54 H63D (+/–): 19/54	Improved (especially in patients with hyperferrtinemia and carrying HFE mutation)	Only at entry

{}: interquartile range. IGT, impaired glucose tolerance; IRI, immuno-reactive insulin; HOMA-IR, homeostasis model assessment for insulin resistance; NA, not assessed; NAFLD, nonalcoholic fatty liver disease; NS, not significant; PCT, porphyria cutanea tarda.

dietary iron reduction in Japanese patients with chronic hepatitis C.[84] The efficacy of phlebotomy for NASH/NAFLD patients has never been established (Table 2). Facchini *et al.* have shown improvement in liver enzymes levels in 17 NAFLD patients with impaired glucose tolerance undergoing serial phlebotomy for iron reduction.[85] The estimated body iron stores (based on phlebotomy need) in these patients were with the normal range. At the end of phlebotomy schedule, however, there was a 40% to 55% improvement of both fasting and glucose-stimulated plasma insulin concentrations. This efficacy of phlebotomy was confirmed even in NAFLD patients with normal glucose tolerance.[86] According to Fargion *et al.*,[28] in 42 NAFLD patients, HOMA-IR was significantly decreased after 4-month hypocaloric diet, and a further reduction was observed after phlebotomies. We also reported that phlebotomy declined serum transaminase activities in Japanese patients with biopsy-proven NASH.[87] One of them obtained improvement of serum TRX after phlebotomies. These studies have not proved histological improvement. Therefore, the effect of phlebotomy on liver histology in NASH/NAFLD must be evaluated further. Riquelme *et al.*[88] reported a 52-year non-obese woman with biopsy-proven NASH obtaining not only improvement of transaminase activities but also complete resolution of fatty infiltration and inflammatory changes after iron depletion therapy. According to a case-control study by Valenti *et al.*,[89] iron depletion produced a significantly larger decrease in IR compared with nutritional counseling alone, independent of changes in BMI, baseline HOMA-IR, and the presence of the metabolic syndrome. Likewise, phlebotomy has been suggested in patients with high-ferritin diabetes, in whom bloodletting led to significant decreases in IR.[90] Similarly, declines in post-glucose load plasma glucose and insulin levels were also observed in healthy volunteers with normal glucose and ferritin levels.[91] Also in patients with IR-HIO, phlebotomy improved the presenting symptoms (chronic fatigue and /or polyarthralgias), serum transaminase activities, and metabolic indices.[92,93] The result of the study by Facchini *et al.*[85,91] raise the question of whether patients with NAFLD and even normal body iron stores should undergo phlebotomies. Fargion *et al.*[28] showed that the effect of phlebotomy was observed also in patients with normal iron parameters at enrolment. In contrast, Valenti L *et al.*[89] indicated that iron depletion was more effective in reducing HOMA-IR and ALT in patients with hyperferritinemia, and in carriers of the HFE mutations. Thus, investigators are needed to examine whether NAFLD patients without hepatic iron overload should be phlebotomized to ameliorate insulin resistance or hepatic inflammation.

Now phase II clinical trials provided by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are currently recruiting patients. The goal of this pilot study is to determine the effect of iron depletion on insulin sensitivity in patients with type 2 diabetes mellitus and NAFLD. Secondary outcome measures will include the effect of iron depletion on hepatic necroinflammation, markers of oxidative stress and intrahepatic fat content. Because an increase in hepatic iron has been found to correlate with severity of fibrosis,[5] phlebotomy to remove excess iron may potentially have a beneficial effect in preventing the progression of fibrosis. In the HFD-fed rabbits with IR,[78] phlebotomy significantly reduced hepatic fibrosis as well as lipid peroxide. In the future, prospective human studies using a large number of patients are essential to clarify whether phlebotomy can really prevent the progression of fibrosis or carcinogenesis in NASH patients.

According to Yamamoto *et al.*,[94] twelve NAFLD patients (NASH, $n = 9$; simple steatosis, $n = 3$) were given a dietary prescription including restriction of energy, fat and iron (< 6 mg/day). The average energy intake, fat energy fraction and iron intake decreased significantly 6 months after the beginning of the diet in all patients. In addition, the levels of serum transaminase and ferritin were significantly decreased. They suggest that dietary iron reduction should be recommended not only in hepatitis C patients[95] but also in NAFLD patients.

CONCLUSIONS

IRON-ASSOCIATED OXIDATIVE stress may at least partly play a role in the pathogenesis in NASH/NAFLD, but the mechanisms of hepatic iron deposition remains unknown. Iron reduction by phlebotomy, which is well tolerated, may be of clinical use to reduce transaminase activities and insulin resistance. Larger controlled trials of longer duration are warranted to assess the long-term clinical benefit of phlebotomy.

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