The Korean Journal of Hepatology 2012;18:105-107
http://dx.doi.org/10.3350/kjhep.2012.18.1.105
pISSN: 1738-222X eISSN: 2093-8047

Body iron, serum ferritin, and nonalcoholic fatty liver disease

Jae-Jun Shim

Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea

Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease.

Kris V. Kowdley, Patricia Belt, Laura A Wilson, Matthew M. Yeh, Brent A. Neuschwander-Tetri, Naga Chalasani, Arun J. Sanyal, and James E. Nelson; for the NASH Clinical Research Network. *Hepatology 2012;55:77-85.*

Nonalcoholic fatty liver disease (NAFLD) is now recognized as a major cause of chronic liver diseases, including liver cirrhosis and hepatocellular carcinoma (HCC) in Western countries.[1,2] Like alcoholic liver disease, NAFLD covers a wide spectrum of disorders from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. Approximately 30% of the US population and 20% of the Korean population have NAFLD.[1,3]

Just as all heavy drinkers do not progress to cirrhosis and HCC, nor do all patients with nonalcoholic steatosis progress. In addition to its high prevalence, one of the challenges facing hepatologists is the diagnosis and risk stratification of NAFLD. There is no proven serologic marker to confirm the disease, which is diagnosed by excluding a history of alcohol consumption and other causes of liver disease using various serologic tests; sometimes a liver biopsy is needed. Moreover, after the diagnosis, it is not clear who will progress to cirrhosis or HCC. Central obesity is a well-known risk factor and hyperglycemia, diabetes, and age are associated with advanced fibrosis.[1,4] However, to evaluate the risk of disease progression, a liver biopsy is essential. Recently non-invasive methods to distinguish between simple steatosis and significant fibrosis have been introduced. Serological tests have been investigated, including α_2-macroglobulin, apolipoprotein A-I, hyaluronic acid, the platelet count, bilirubin, and gamma-glutamyl transpeptidase.[2] Direct and indirect inflammation mediators such as interleukin-6 (IL-6), CC-chemokine ligand 2, and N-glycans gave positive results, but further studies are needed to determine whether these have diagnostic roles.[2] An apoptosis product, cytokeratin-18 (CK-18) fragments, was also associated with NASH or fibrosis.[5]

Recently, hepatic iron overload and its correlation with chronic liver disease have been considered.[6,7] With recent progress in understanding iron metabolism in patients with hereditary hemochromatosis at the molecular level, accumulating evidence suggests a link between altered iron metabolism and NAFLD. In the last decade, many studies have found a relationship between hepatic iron and NASH or its progress.[8-11]

Iron (*ferrum* in Latin), atomic number 26, is the most common element on Earth. It is essential in most living organisms. Iron binds to cofactors in hemes, myoglobin,

Keywords: Fatty liver, Nonalcoholic; Ferritin; Iron overload

Abbreviations: CK-18, cytokeratin-18; HCC, hepatocellular carcinoma; IL-6, interleukin-6; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

Corresponding author: Jae-Jun Shim
Department of Internal Medicine, Kyung Hee University Hospital, 23 Kyungheedae-gil, Dongdaemun-gu, Seoul 130-872, Korea
Tel. +82-2-958-8155, Fax. +82-2-968-1848, E-mail; joyshim@khu.ac.kr

cytochrome P450, and catalases. When body iron accumulates, it promotes oxidative free-radical reactions, which have harmful effects. In hereditary hemochromatosis, accumulated iron in the liver, heart, and pancreas leads to cirrhosis, heart failure, and diabetes. Even mild iron overload might aggravate insulin resistance, diabetes, atherosclerosis, colonic neoplasia, and NAFLD.[6,12-15] Moreover, iron depletion therapy, such as with a phlebotomy, improves the metabolic complications and elevated liver enzymes in patients with NAFLD.[16] Iron is strictly regulated by a mechanism similar to that for glucose control.[17] Like glucose and insulin, the serum iron level is regulated by a hepatic peptide hormone, hepcidin. An elevated iron level stimulates hepcidin synthesis, which decreases the iron-exporter ferroportin in macrophages and intestinal cells and reduces serum iron, just as insulin controls excess glucose.[17,18] Currently, people in developed countries consume an overabundance of food. Since most food contains glucose and iron, excessive eating can increase the risks of hyperglycemia and iron overloading. Since accumulated iron is difficult to remove, males and the elderly are at higher risk for iron accumulation than females and younger people. Females lose body iron via regular menstruation. This "iron-theory" may explain the gender difference in cardiovascular diseases, although it has not been confirmed whether iron has the same effects on chronic liver diseases.[19]

Kowdley et al[20] investigated the serum ferritin level and histological findings, including iron deposition, in 628 patients with NAFLD. This large cross-sectional study revealed that an elevated serum ferritin (>1.5×UNL) was associated with advanced hepatic fibrosis (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.05-2.62; P=0.028) and a higher NAFLD Activity Score (NAS) (OR, 1.99; 95% CI, 1.06-3.75; P=0.033). An elevated serum ferritin (seen in approximately 20% of the subjects) was associated with greater iron accumulation in the body (i.e., a high serum iron and transferrin-iron saturation) and greater hepatic iron deposition in both the reticuloendothelial system and hepatocytes. The patients with an increased serum ferritin also had higher serum transaminases and gamma-glutamyl transferase, and a lower platelet count. Interestingly, even in patients without a hepatic iron overload on histology, a higher serum ferritin was correlated with an advanced stage. This suggests the presence of systemic inflammation unrelated to iron overload. There are a few contradictory reports on the role of the iron burden in patients with NAFLD.[21,22] It is not clear whether the elevated serum ferritin is a consequence of systemic inflammation or a marker of iron overload in patients with NAFLD. The study by Kowdley et al[20] seems to keep to the middle path. I would like to know more about the proportion of patients who had an elevated serum ferritin, but no iron deposition, in their study. Further studies to confirm the role of iron in NAFLD are needed.

Should we use this simple, sensitive, and inexpensive test in all patients with NAFLD? Before approving its clinical use, one should consider the fact that most of the subjects in this study were severely obese (average BMI 34 kg/m^2) and had metabolic syndrome (69%). The study population might differ from the real general population. In less-obese populations, the serum ferritin might differ and the iron burden might not be complicated. The cut-off level for the serum ferritin (1.5×UNL) in this study was subjective and needs further supporting data.

In summary, not all patients with NAFLD progress to cirrhosis or HCC. It is not clear what factor(s) contribute to advanced liver disease. Dysregulated iron overload might be a contributing factor. Serum ferritin, a marker of iron accumulation, is related to advanced fibrosis in patients with NAFLD. However, it can also be elevated with systemic inflammation. Nevertheless, serum ferritin may be a simple, useful marker for obese patients with NAFLD. Further studies should confirm the role of iron overload and the meaning of hyperferritinemia in patients with chronic liver diseases, including NAFLD.

REFERENCES

1. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43(Suppl 1):S99-S112.
2. Lewis JR, Mohanty SR. Nonalcoholic fatty liver disease: a review and update. Dig Dis Sci 2010;55:560-578.
3. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, et al. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol 2006;21:138-143.
4. Fassio E, Alvarez E, Domínguez N, Landeira G, Longo C. Natural history of nonalcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. Hepatology 2004;40:820-826.
5. Tamimi TI, Elgouhari HM, Alkhouri N, Yerian LM, Berk MP, Lopez R, et al. An apoptosis panel for nonalcoholic steatohepatitis diagnosis. J Hepatol 2011;54:1224-1229.
6. Dongiovanni P, Fracanzani AL, Fargion S, Valenti L. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. J Hepatol 2011;55:920-932.

7. Fargion S, Valenti L, Fracanzani AL. Beyond hereditary hemochromatosis: new insights into the relationship between iron overload and chronic liver diseases. Dig Liver Dis 2011;43:89-95.
8. 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.
9. 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.
10. Manousou P, Kalambokis G, Grillo F, Watkins J, Xirouchakis E, Pleguezuelo M, et al. Serum ferritin is a discriminant marker for both fibrosis and inflammation in histologically proven non-alcoholic fatty liver disease patients. Liver Int 2011;31:730-739.
11. Pietrangelo A. Iron in NASH, chronic liver diseases and HCC: how much iron is too much? J Hepatol 2009;50:249-251.
12. Kim CH, Kim HK, Bae SJ, Park JY, Lee KU. Association of elevated serum ferritin concentration with insulin resistance and impaired glucose metabolism in Korean men and women. Metabolism 2011;60:414-420.
13. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA 2004;291:711-717.
14. Minqin R, Rajendran R, Pan N, Tan BK, Ong WY, Watt F, et al. The iron chelator desferrioxamine inhibits atherosclerotic lesion development and decreases lesion iron concentrations in the cholesterol-fed rabbit. Free Radic Biol Med 2005;38:1206-1211.
15. Nelson RL, Davis FG, Sutter E, Sobin LH, Kikendall JW, Bowen P. Body iron stores and risk of colonic neoplasia. J Natl Cancer Inst 1994;86:455-460.
16. Valenti L, Moscatiello S, Vanni E, Fracanzani AL, Bugianesi E, Fargion S, et al. Venesection for non-alcoholic fatty liver disease unresponsive to lifestyle counselling--a propensity score-adjusted observational study. QJM 2011;104:141-149.
17. Pietrangelo A. Hemochromatosis: an endocrine liver disease. Hepatology 2007;46:1291-1301.
18. Fleming RE, Ponka P. Iron overload in human disease. N Engl J Med 2012;366:348-359.
19. Sullivan JL. Iron and the sex difference in heart disease risk. Lancet 1981;1:1293-1294.
20. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, et al. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 2012;55:77-85.
21. 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.
22. Moon JH, Park SH, Oh KC, Jung JO, Shin WG, Kim JP, et al. Association of hepatic iron deposition and serum iron indices with hepatic inflammation and fibrosis stage in nonalcoholic fatty liver disease. Korean J Gastroenterol 2006;47:432-439.