Original Article

Relationship between serum ferritin level and transient elastography findings among patients with nonalcoholic fatty liver disease

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD) is raising prevalence among children, and adolescence population in developed and developing countries as a major public health concern. The present study aims to determine the relationship between serum ferritin level and transient elastography findings in patients suffering from NAFLD. **Materials and Methods:** The demographic and biochemical profile of included individuals such as body mass index, age, level of serum transaminases, fasting blood sugar, lipid profile, and serum ferritin level were determined and a transient elastography was performed for all of them. **Results:** The mean serum ferritin level among men with mild and advanced liver stiffness was 154 ± 97 and 244 ± 214, respectively ($P < 0.001$), which showed a meaningful relationship. These figures among female patients with mild and advanced liver stiffness included 79 ± 91 and 161 ± 103, respectively ($P = 0.003$) and again revealed a significant relationship. The cutoff values of ferritin with 90% accuracy for differentiation of mild from advanced liver stiffness among male and female patients were determined as 255 ng/ml and 135 ng/ml, respectively. These cutoff values for ruling out of advanced liver stiffness with 90% accuracy among both sexes were 72.5 ng/ml and 65.5 ng/ml, respectively. **Conclusion:** The finding of this study revealed a significant relationship between serum ferritin level and liver stiffness among NAFLD patients, and if these results repeated in further investigations, it could be advisable to measure serum ferritin level for predicting possibility of advanced liver fibrosis.

Keywords: Ferritin, nonalcoholic fatty liver disease, transient elastography

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide,[1,2] and it is estimated to be as prevalent as 14%–20% of general population in the USA and Western Europe.[3] Savadkouhi *et al*, reported that NAFLD prevalence was about 32% among attendance patients to sonography clinics in Zahedan, Iran.[4] Increasing prevalence of NAFLD in children and adolescence is one of the major concerns of public health among developing and developed countries.[5] While the exact incidence and prevalence of this condition have not been determined yet, it has a strong correlation with metabolic syndrome and obesity[6-8] and potentially could progress toward liver cirrhosis and hepatocellular carcinoma.[9,10]

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Nonalcoholic steatohepatitis (NASH) is now the third cause of liver transplantation in the United States of America, and an increasing prevalence has been estimated in the current decade.[11]

Liver biopsy is the gold standard for determining the degree of liver fibrosis,[12] but as an invasive method, its role in proving NAFLD diagnosis is controversial.[6,11] Many physicians presume NAFLD as a diagnosis by exclusion of other chronic liver diseases.[6] On the other hand, it is clear that based on high prevalence of NAFLD, performing liver biopsy in a population of about 80 million is impractical and no therapeutic option has been approved by FDA;[11] therefore, the accepted strategy for performing liver biopsy in patients suspicious to NAFLD is based on two major criteria: first, patient willing and second, high possibility of NASH or advanced fibrosis based on clinical and/or laboratory findings.[11]

Recently, significant progressions have been made in introducing simple and noninvasive methods for estimating the degree of liver fibrosis among NAFLD.[6] One of this noninvasive methods is transient elastography (Fibroscan) which uses ultrasound for determining lever stiffness and estimating the degree of liver fibrosis.[6,13] Elevated serum iron level and ferritin have been found in some of the patients suffering from NAFLD while none of them had genetic hemochromatosis or accumulation of iron in the liver. Most of the researchers believe that elevated serum iron indexes are byproducts of liver inflammation.[6] Serum ferritin in NAFLD frequently raises due to systemic inflammation, elevated reserves of iron, and/or both reasons,[12] and serum ferritin has been assumed as an independent predictor of histologic involvement severity and progression of fibrosis among individuals with NAFLD.[14] The current study investigates serum ferritin level as a noninvasive biochemical test for substitution of liver biopsy for determining liver fibrosis and tries to verify if there is any relationship between serum ferritin level and degree of liver stiffness based on transient elastography among NAFLD patients?

Methods

In this cross-sectional descriptive study, all of the NAFLD patients who attended in hepatology clinic during a 4-month period were included. The exclusion criteria were age <18 years, alcohol consumption more than 20 g/d, alanine transaminase (ALT) >150, any history of advanced chronic liver disease, history of gastrointestinal (GI) tract surgery, total parenteral nutrition during last 6 months, autoimmune hepatitis, positive viral hepatitis profile, Wilson's disease, hemochromatosis, consumption of hepatotoxic drugs during the last 6 months, severe heart failure, hepatic vascular disorder such as Budd–Chiari Syndrome, overt diabetes mellitus, and/or any hepatic mass lesion. The participants were evaluated for components of metabolic syndrome such as obesity, hypertension, uncontrolled blood sugar, and hyperlipidemia. Thereafter, for all of the patients, the level of serum ferritin was measured and a liver elastography was performed to determine the degree of liver stiffness based on KPa. Our cutoff for advanced stiffness was >8.7 KPa as F3, >10.3 KPA as F4, and 11.5 KPa as liver cirrhosis. For performing liver elastography, we used EchoSens FibroScan (model 502, France).

The number of patients with confidence interval (CI) of 95% was calculated as 280 and the data were analyzed by SPSS software version 19 (SPSS, Chicago, IL, USA). The subject and aims of this study were explained for all of the participants and an informed consent was obtained from all of them.

Results

At first, patients were divided into two groups of mild liver stiffness (F0 – F2, liver stiffness measurement (LSM) <8.7) and advanced liver stiffness (F3, F4 and cirrhosis, LSM ≥8.7) based on the results of liver elastography. Overall, 226 patients were allocated as mild liver stiffness and 58 patients were diagnosed with advanced liver stiffness. The average level of serum ferritin in mild liver stiffness group was 132 ± 101/6 and 222/8 ± 194.4 in advanced liver stiffness group which revealed a meaningful relationship ($P < 0.001$).

In the next step, we evaluated difference of ferritin level based on sex. Overall, 202 patients were male (71%) who had an average ferritin level of 173 ± 136. This average in women was 98 ± 94 and there was a meaningful difference based on sex ($P < 0.001$). Therefore, the patients in mild and advanced liver stiffness groups were differentiated based on sex and again evaluated for serum ferritin level. Among male patients with mild and advanced liver stiffness, the average serum ferritin level was 154 ± 97 and 224 ± 214, respectively, which was meaningful ($P < 0.001$) [Table 1]. The difference between females with mild and advanced liver stiffness was again significant (serum ferritin 91 ± 79 and 161 ± 103, $P = 0.003$).

The sensitivity and specificity of serum ferritin level for differentiation of advanced liver stiffness from mild liver stiffness was determined by receiver operating characteristic (ROC) curve. Among men, serum ferritin more than 255 ng/ml can differentiate 90% of cases with advanced liver stiffness (sensitivity = 90%), and among females, this figure would be >135 ng/ml. Moreover, serum ferritin <72.5 ng/ml and 65.5 ng/ml among male and

Table 1: Comparison of serum ferritin level based on sex and liver stiffness

	Ferritin mean±SD	95% CI
Sex		
Male		
Advanced liver stiffness	224.2±214.3	178.3-310.2
Mild liver stiffness	154±97.9	138.6-169.3
Female		
Advanced liver stiffness	161.5±103.6	104.1-218.9
Mild liver stiffness	91.4±79.8	57.5-102.1

SD: Standard deviation; CI: Confidence interval

females can exclude advanced liver stiffness by sensitivity of 90% and 93%, respectively.

According to ROC-curve, we found area under the curve (AUC) equal to 0.59 among men (CI 95%, 0.489, 0.697) which was not significant, but in females, AUC was 0.79 (CI 95%, 0.663, 0.917) and statistically significant [Figure 1].

Thereafter, the relationship between serum ferritin level and liver stiffness measured by transient elastography was calculated [Table 2], and among 46 patients with raised serum ferritin level (>225 ng/ml in men and >135 ng/ml in women), 23 patients (50%) had mild liver stiffness, and among 238 patients with low levels of serum ferritin (<225 ng/ml in men and <135 ng/ml in women), 203 patients (85.3%) had mild liver stiffness and 35 patients (14.7%) suffered advanced liver stiffness, and overall, the relationship between serum ferritin level and liver stiffness was statistically meaningful ($P < 0.001$).

By dividing patients into two groups of high and low serum ferritin level (>225 ng/ml in male and >135 ng/ml in female), the data were extracted as shown in Table 3. Average fasting blood sugar was 99.7 ± 11.4 and 101.9 ± 14.3 in high and low ferritin groups, respectively, which was insignificant ($P > 0.05$). Average ALT and aspartate aminotransferase levels were 77.9 ± 41.3 and 58.2 ± 29.5 in group high and 59.8 ± 34.3 and 39.4 ± 29.1 in group low and showed a significant relationship ($P = 0.002$ and 0.0001, respectively). Average TG was 271 ± 150 and 242 ± 94 in groups high and low ($P = 0.374$) and also body mass index on average was 26.7 ± 4 and 27.9 ± 3.6 ($P = 0.241$). The mean systolic and diastolic blood pressure in group high were 117.5 ± 20.5 mmHg and 83.7 ± 6.9 mmHg while these measures were 120.2 ± 10.9 mmHg and 78.2 ± 8.4 mmHg in group low ($P = 0.551$ and 0.081, respectively).

Discussion

NAFLD is one of the most common liver diseases around the world[1,5] which is more prevalent among obese people and diabetics and has been identified as one of the components of the metabolic syndrome.[2,3] Our study investigated the relationship between liver fibrosis and hyperferritinemia among NAFLD patients without any history of diabetes mellitus and/or significant chronic liver disease. The findings of this study indicated that the mean serum ferritin levels in women and men with mild liver stiffness were 79 ± 91 ng/ml and 154 ± 97

Table 2: Relationship between serum ferritin and liver stiffness based on transient elastography

Liver stiffness	Mild (LSM <8.7 KPa), *n* (%)	Advanced (LSM >8.7 KPa), *n* (%)	Total, *n* (%)
Serum ferritin			
High	23 (50)	23 (50)	46 (16.2)
Low	203 (85.3)	35 (14.7)	238 (83.8)
Total	226 (79.6)	58 (20.4)	284 (100)

LSM: Liver stiffness measurement; KPa: Kilopascal

Table 3: Demographic characters of patients based on serum ferritin levels

Ferritin levels character	Mean±SD	
	High	Low
FBS	99.7±11.4	101.9±14.3
ALT	77.9±41.3	59.8±34.3
AST	58.2±29.5	39.4±19.1
TG	271±150	242±94
BMI	26.7±4.0	27.9±3.6
DBP	83.7±6.9	78.2±8.4
SBP	117.5±20.5	120.2±10.9

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; TG: Triglyceride; AST: Aspartate aminotransferase; ALT: Alanine transaminase; FBS: Fasting blood sugar; SD: Standard deviation

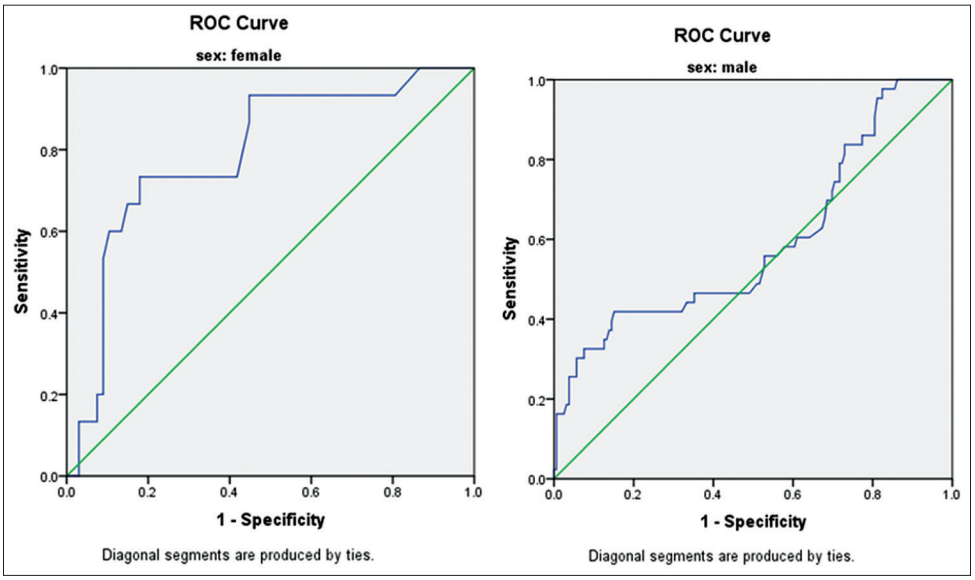

Figure 1: Relationship of serum ferritin level with liver stiffness in male and female based on receiver operating characteristic curve

and the average serum ferritin in patients with advanced liver stiffness (LSM >8.7 kPa; F3) among women and men were 161 ± 103 and 244 ± 214, respectively, which is statistically significant ($P = 0.001$).

In a study by Kowdley *et al.* in 2011, an increase of the serum ferritin level more than 1.5 times (i.e., 300 ng/ml in women and 450 ng/ml in men) was an independent factor predicting the advanced fibrosis of liver and NASH.[14] Valenti *et al.* found patients with NAFLD had increased serum ferritin levels without an increase in hepatic iron store.[15] In a study by Bugianesi *et al.*, hyperferritinemia even without the increase in hepatic iron concentration showed an increase in serum ferritin and liver fibrosis progression.[16] In the cohort studies by Manousou *et al.* in Japan and Sanyal in Britain, the relationship between increasing serum ferritin and liver fibrosis progression was shown.[17,18]

Furthermore, Walker *et al.* and Weismüller *et al.* showed that serum ferritin level is a predictor of mortality in patients with end stage liver disease before and after liver transplantation.[19,20] According to the results of this study and other mentioned studies, hyperferritinemia is associated with serum liver fibrosis progression in patients with NAFLD and this relationship is statistically significant.

Our study shows that the serum ferritin levels more than 255 ng mg/ml in men and 135 ng/ml in women can differentiate patients with advanced liver stiffness from mild liver stiffness (F3, and more in elastography equals LSM ≥ 8.7 kPa) with specificity of 90%; moreover, serum ferritin <72.5 ng/ml in men and 65.5 ng/ml in females can refuse the possibility of advanced liver stiffness with a sensitivity of higher than 90%. In a study by Kowdley *et al.*, the serum ferritin levels higher than 450 ng/ml in men and higher than 300 ng/ml in women were associated with advanced liver fibrosis. The difference of our findings about serum ferritin with the study of Kowdley *et al.* could be due to the genetic, environmental factors, and diet habituates differences in the study population. Given that, the European and American diet is richer in red meat while the diet in Iran has less amount of red meat and consequently a lower amount of ferritin is predictable.

Conclusion

In this study, a significant relationship was seen between the serum ferritin level and liver stiffness in patients with NAFLD, and it is recommended to use serum ferritin level as a noninvasive economic option in comparison with liver biopsy and elastography for predicting the severity of liver fibrosis among NAFLD patients. This study has been derived from the final thesis of Dr. Seyed Saeed Seyedian for his course of GI fellowship.

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Conflicts of interest

There are no conflicts of interest.

References

1. Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1682-98.
2. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, *et al.* Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454-62.
3. Wiener C, Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, *et al.* Harrisons Principles of Internal Medicine Self-Assessment and Board Review. 18th ed. New York: McGraw Hill Professional; 2012
4. Savadkouhi F, HosseiniTabatabaei SMT, Shahabi Nezhad S. The frequency of fatty liver in sonographu of patients without liver disease background and its correlation with blood cholesterol and triglyceride. Zahedan J Res Med Sci 2003;5:177-83.
5. Adibi A, Kelishadi R, Beihaghi A, Salehi H, Talaei M. Sonographic fatty liver in overweight and obese children, a cross sectional study in Isfahan. Endokrynol Pol 2009;60:14-9.
6. Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management, expert consult premium edition-enhanced online features. Melbourne, VIC, Australia, Elsevier Health Sciences; 2010.
7. Wong VW, Wong GL, Chim AM, Tse AM, Tsang SW, Hui AY, *et al.* Validation of the NAFLD fibrosis score in a Chinese population with low prevalence of advanced fibrosis. Am J Gastroenterol 2008;103:1682-8.
8. Guha IN, Parkes J, Roderick PR, Harris S, Rosenberg WM. Non-invasive markers associated with liver fibrosis in non-alcoholic fatty liver disease. Gut 2006;55:1650-60.
9. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214-20.
10. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, *et al.* Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. Gastroenterology 2008;134:960-74.
11. Loomba R. Should we routinely do liver biopsy in NAFLD patient? AGA Prespectives 2012;8:20-1.
12. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. Short Guide to Hepatitis C. Frankfurt, Germany: Flying Publisher & Kamps; 2013. p. 178.
13. Hajiani E, Hashemi SJ, Masjedizadeh AR, Shayesteh AA, Nejad PA, Kadkhodae A, *et al.* Comparison of liver biopsy with transient elastography as a non-invasive method for assessment of liver fibrosis. J Gastroenterol Hepatol Res 2014;3:1013-6.
14. 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.
15. Valenti L, Fracanzani AL, Bugianesi E, Dongiovanni P,

Galmozzi E, Vanni E, *et al.* HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology 2010;138:905-12.

16. 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;39:179-87.
17. 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;31:730-9.
18. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, *et al.* Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675-85.
19. Walker NM, Stuart KA, Ryan RJ, Desai S, Saab S, Nicol JA, *et al.* Serum ferritin concentration predicts mortality in patients awaiting liver transplantation. Hepatology 2010;51:1683-91.
20. Weismüller TJ, Kirchner GI, Scherer MN, Negm AA, Schnitzbauer AA, Lehner F, *et al.* Serum ferritin concentration and transferrin saturation before liver transplantation predict decreased long-term recipient survival. Hepatology 2011;54:2114-24.