Serum Ferritin and Transaminases in Non-Alcoholic Steatohepatitis

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are emerging as important non-communicable causes of progressive liver dysfunction. Lack of clear-cut treatment target in the pathogenesis is hampering its management. Study aimed to assess the relationship between serum ferritin levels with demographic parameters, to assess the relationship of serum ferritin to parameters of inflammatory liver disease, namely serum ALT and AST, and to assess whether high serum ferritin is associated with altered hemoglobin level.

Material and Methods: The present case-control study was undertaken at Jubilee Mission Medical College and Research Institute, Thrissur to ascertain whether serum ferritin has a role in non-alcoholic fatty liver disease as an inflammatory marker. Thirty patients diagnosed to have NASH from USG findings by the Department of General Medicine with Thirty controls were selected for the study. Blood test were carried out to access various parameters.

Results: Elevated serum ferritin levels and marked increases in inflammatory liver enzymes- alanine transaminase and aspartate transaminase were associated with non-alcoholic fatty liver disease patients.

Conclusion: The correlation between serum ferritin and enzyme markers of inflammatory liver diseases in the present study possibly indicate target for treatment.

Keywords: Non-alcoholic fatty liver disease, Liver enzymes

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one among a spectrum of manifestations with the histological unifying feature of macrovesicular hepatic steatosis in the absence of significant alcohol intake.[1] NAFLD can be either simple steatosis or steatohepatitis (non-alcoholic steatohepatitis-NASH). Lobular inflammation, zone-3 pericellular fibrosis, macrovesicular steatosis and balloon degeneration of hepatocytes can be demonstrated in an ideal case of NASH. Estimates of prevalence of NAFLD showed 20 to 30% by ultrasound and lower using abnormal transaminase levels.[2] Among obese individuals, 50–75% may have NAFLD. The corresponding rates for non-alcoholic steatohepatitis (NASH) are 3–4% among general population while it is 15–20%, in obese.[3]

In India, non-alcoholic fatty liver disease (NAFLD) is a significant cause of liver disease. Prevalence of NAFLD is found in one-third of the general population in India as evidenced in epidemiological studies. Higher prevalence is seen in those with obesity, diabetes mellitus and metabolic syndrome.[4] The basis of increased hepatic transaminases, hepatocellular carcinoma and cryptogenic cirrhosis is NAFLD.

Increasing age has been associated with increasing prevalence of NAFLD; older patients have a higher likelihood of disease progression to severe hepatic fibrosis and hepatocellular carcinoma. This association between age and prevalence, stages of fibrosis and cirrhosis in NAFLD, may be related to the duration of disease rather than to age itself. Male gender is associated with elevated aminotransferase levels, histological NASH and overall mortality.[5,6]

The prevalence of NAFLD has been assessed with diagnostic tools such as ultrasonogram (USG), liver enzymes, biopsy, etc. Though liver biopsy is benchmark for NASH, it cannot be used as it is an invasive procedure. Several studies have established that due to inconsistent sampling and conflicting inter- observer results, liver biopsy is a less appealing option. The exact histological definition of NASH is not fully recognized and diagnosis is established preferably by pattern identification than individual constituents like fibrosis, ballooning and steatosis.[7]

Ferritin, the primary tissue iron-storage protein in the liver, is induced in iron overload disorders (primary or secondary), and in systemic inflammation leading to increased hepatic and circulating ferritin levels. Heightened modulation of ferritin by inflammatory stimuli (proinflammatory cytokines, oxidative stress and tumor necrosis factor-alpha) is seen at transcription and translation levels.[8] Serum levels of ferritin can thus reflect increased disease severity in NAFLD either because of increased hepatic or systemic inflammation or increased body iron stores or both. Discrepancies regarding correlation of histologic severity and serum ferritin level in NAFLD with some scientists claiming higher levels related to NASH and increased histologic severity, and others claiming that no associations have been found in previous studies.[9] Patients with NASH have significantly higher median serum ferritin levels, compared to those with NAFLD. Several studies have substantiated that high serum ferritin correlates well with high serum levels of alanine transaminase (ALT) and aspartate transaminase (AST). Kowdley *et al* established that increased serum ferritin level is a distinct prognostic test in NAFLD patients with liver damage, and is useful to identify NAFLD patients at risk of non-alcoholic steatohepatitis (NASH) and advanced fibrosis. The study suggested incorporation of serum ferritin level to improve the performance of non-invasive scoring of liver damage in patients with NAFLD.[10] As already established, ALT and AST levels in serum are elevated in inflammatory conditions of the liver. Concomitant increases in these enzymes and serum ferritin may suggest more towards an inflammatory reaction as a cause for elevated serum ferritin in NASH.

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The present study was conducted to assess the relationship between serum ferritin levels with demographic parameters, to assess the relationship of serum ferritin to parameters of inflammatory liver disease, namely serum ALT and AST, and to assess whether high serum ferritin is associated with altered hemoglobin level.

MATERIAL AND METHODS

The study was carried out at Jubilee Mission Medical College and Research Institute, Thrissur. Thirty patients diagnosed to have NASH from USG findings by the Department of General Medicine were selected for the study. Informed consent was obtained from all the patients. Ethical clearance was obtained from the Institutional ethics committee. The design of the study used was case-control method. Patients diagnosed to have NASH without any other hepatic complications in the age group 40 – 60 years of both sexes were included in the study. Those patients with previous history of infective hepatitis and history of alcohol intake were excluded from the study. Thirty age and sex matched controls were selected as controls. After obtaining the demographic parameters, blood samples were analyzed for hemoglobin, ALT and AST using standard methods. Serum ferritin was measured by latex turbidimetric method.

STATISTICAL ANALYSIS

The data analysis was done using SPSS version 22. The continuous variables as mean, standard deviation and/or 95% confidence intervals, and categorical variables as frequencies and percentages are given in tabular form. The statistical analysis was done using student *t*- test of significance. The relationship between parameters was assessed by Pearson's R.

RESULT

The age of both the patients and controls were between 40-60 years. The cases consisted of 30% of females and 70% males. The controls included 47% females and 53% males (Table-1). The mean serum ferritin in cases and controls showed a significant difference ($P < 0.001$) with higher values in cases (Table-2). A significant difference ($P < 0.001$) was present in the serum ferritin among female cases and controls. The corresponding values among male cases and controls also had significant difference ($P < 0.001$). Both values are shown in table-3. There was a significant difference in the mean of serum ALT in cases and controls ($P < 0.001$). Likewise, the mean of serum AST in cases and controls showed similar result ($P < 0.001$). The Pearson's R value indicating correlation of serum ferritin to ALT in cases was 0.242 (P value of 0.197) and the corresponding value in controls was 0.144 (P value of 0.449). The Pearson's R value for serum ferritin compared to AST in cases was 0.13 (P value of 0.49) and the corresponding value in controls was -0.12 (P value of 0.53). Among the cases, serum ferritin when compared to hemoglobin had a correlation coefficient (R) of 0.31 (p value of 0.094), whereas among controls, correlation coefficient (R) was found to be 0.48 (p value of 0.008).

DISCUSSION

Bugianesi et al, validated that high ferritin levels is indicative of metabolic status of patient and severity of liver fibrosis rather than of peripheral or hepatic iron overload.[11] Moreover, patients with NAFLD having hepatic fibrosis had no significant link with iron burden and High iron Fe (HFE) gene mutations[11], while decreased hepatic iron burden is seen in patients with increased steatosis and/or type II diabetes mellitus.[12] The most appropriate prognostic test to observe severe fibrosis

Group	Sex	Frequency	Percent
Cases	F	9	30.0
	M	21	70.0
	Total	30	100.0
Controls	F	14	46.7
	M	16	53.3
	Total	30	100.0
(F-female, M- male)			

Table-1: Distribution of patients and control subjects based on gender

Group	Statistics	Age(years)	Hb(g/dl)	Ferritin(µg/L)	AST(U/L)	ALT(U/L)
Cases	N	30	30	30	30	30
	Mean	49.13	13.32	381.22	178.47	327.27
	SD	6.46	1.70	145.44	78.63	141.09
Control	N	30	30	30	30	30
	Mean	49.10	12.99	195.06	24.23	33.03
	SD	6.27	1.57	78.19	7.69	10.18
P- values between cases and controls		0.98	0.43	<0.001	<0.001	<0.001
(N – number, SD- standard deviation, AST-aspartate transaminase, ALT – alanine transaminase)						

Table-2: The demographic and metabolic profiles of NASH cases and controls

Gender	Group	N	Mean ferritin	SD	P
F	Cases	9.00	286.51	84.60	<0.001
	Control	14.00	163.93	69.47	
M	Cases	21.00	421.81	148.46	<0.001
	Control	16.00	222.30	77.07	
(F-female, M- male, N – number, SD- standard deviation)					

Table-3: Serum ferritin levels in cases and controls based on gender

Ferritin vs. AST	Pearson's R	P
Cases	0.13	0.49
Control	- 0.12	0.53
Ferritin vs. ALT	Pearson's R	P
Cases	0.242	0.197
Control	0.144	0.449
(AST-aspartate transaminase, ALT – alanine transaminase, Pearson's R- correlation coefficient)		

Table-4: Relationship between serum ferritin vs. AST and serum ferritin vs. ALT in cases and controls

in NAFLD is rise in serum ferritin levels.[11] Previous review reports have ascertained the relation of high ferritin levels and risk of NASH.[10] In the present study, there was a significant difference in mean serum ferritin in cases and controls (381.223 and 195.060 respectively). Both female cases and controls had a lower mean value when compared to corresponding values in males. The finding is similar to a study conducted in India.[13] A female preponderance seen in the earlier studies[14] seems to have shifted and more males are presenting with NASH. This may be due to dietary and lifestyle changes. Association between liver enzyme abnormalities and increased C-reactive protein (CRP) concentration found was postulated to be due to the inflammatory processes that accompany NAFLD in turn contributing to the systemic inflammation.[15] The serum enzymes ALT and AST were elevated to almost ten-fold in cases when compared to controls in our study. The higher values may indicate severity of the inflammatory process. Serum ferritin showed a positive but insignificant correlation with the ALT and AST in serum. The correlation indicates that serum ferritin elevation has an inflammatory origin, a larger sample size may show significant relationship, if any. In the case of correlation between serum ferritin and hemoglobin (Hb) levels, there was no significant relationship in the cases, whereas in the controls, the positive correlation was significant. A parallel increase was found in Hb level with increasing serum ferritin values in controls, possibly pointing to absence of inflammatory stimulus for serum ferritin level alterations. The limitations of our study are the small sample size and liver biopsy could not be used for comparison.

CONCLUSION

In the present study, almost two-fold increase in mean levels of serum ferritin in cases, with higher values in males point to the need for inclusion of serum ferritin in investigating NAFLD patients. The elevation in liver enzymes ALT and AST supporting inflammatory origin for high serum ferritin indicates an anti-inflammatory therapeutic option for NAFLD.

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