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Association of Serum Ferritin with NAFLD

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) refers to fat accumulation in the liver exceeding 5% to 10% by weight in the absence of excessive alcohol consumption .Nonalcoholic fatty liver disease comprises a wide spectrum of liver damage ranging from simple,uncomplicated steatosis to steatohepatitis to advanced fibrosis and cirrhosis. Serum ferritin (SFL) is a protein expressed in acute phase, so its level is elevated in the case of liver necrosis, inflammation. This cross-sectional observational study consisted of140 cases of Non-alcoholic fatty liver disease and 60 age matched healthy controls, between 35- 80 years of age.Serum ferritin estimation was done by CLIA method. Serum ferritin in NAFLD cases was 94±33.8ng/ml while in the control it was 43.5 26.4ng/ml with a p value <0.0001. Serum ferritin may be a simple,non-invasive useful marker for patients with NAFLD.

Keywords*: NAFLD, steatosis, steatohepatitis, metabolic syndrome, serum ferritin.*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to fat accumulation in the liver exceeding 5% to 10% by weight in the absence of excessive alcohol consumption Nonalcoholic fatty liver disease comprises a wide spectrum of liver damage ranging from simple,uncomplicated steatosis to steatohepatitis to advanced fibrosis and cirrhosis[1]. The mechanism of non-alcoholic fatty liver disease is unknown but involves the development of insulin resistance, steatosis, inflammatory cytokines, and oxidative stress. Nonalcoholic fatty liver disease is associated with physical inactivity, obesity, and metabolic syndrome[2]. NAFLD characterized by steatosis, inflammation is considered as one of the major causes of hepatocellular carcinoma (HCC) . NAFLD is frequently associated with insulin resistance and metabolic syndrome and it is typically manifested as type 2 Diabetes Mellitus ,dyslipidemia, obesity, as well as hypertension[3]. Therefore, the diagnosis of NAFLD at very early stage is necessary.Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide.The prevalence of NAFLD is increasing and has been estimated to range from 10% to 24% worldwide, including Asian populations[4].

Iron binds to cofactors in heme, myoglobin,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[5-9]. Moreover, iron depletion therapy, such as with a phlebotomy, improves the metabolic complications and elevated liver enzymes in patients with NAFLD[10].

Serum ferritin is a protein ,expressed in an acute phase, so its level is elevated in the case of liver necrosis, inflammation[11]. Some recent investigations have stated that the level of SFL can be an irrespective indicator to assess the progression of hepatic fibrosis in the patients with NAFLD because of its association with hepatic iron storage and hepatic inflammation. Researchers came to a conclusion that SFL is higher in patients with NAFLD that might be linked with insulin resistance and hepatocyte damage[12,13].

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The relationship of serum ferritin with severity of liver disease in NAFLD has been examined in several studies. The largest series found a significant association of ferritin levels with presence and severity of nonalcoholic steatohepatitis (NASH) and liver fibrosis[14-20]

MATERIAL AND METHOD

This study is a cross-sectional observational study.140 cases of Non-alcoholic fatty liver disease were selected for study.60 age and sex matched healthy controls were taken between 35- 80 years.Inclusion criteria is USG proven NAFLD cases.Patients with history of alcohol consumption, iron deficiency anaemia, iron supplementation in any form oral or parenteral,were excluded from the study.

Institutional ethical clearance was obtained.Written consent was taken from all the participating subjects.

2ml of venous blood was withdrawn for the assessment of serum ferritin and other biochemical parameters. Ferritin estimation was done by Chemiluminescence immunoassay on Beckman Coulter Access2.Biochemical parameters like lipid profile, fasting blood sugar,liver enzymes(AST,ALT,) were done by Auto-analyzer AU400.BMI was noted as weight in kg divided by square of height in meters.

Statistical analysis was done by MS Excel and SPSS. All the data were expressed in terms of mean and 1SD.

RESULTS

In this study,out of 60 control, 22 were females and 38 subjects were males.Among the case group, 54 were females and 86 were males. The mean age in control and case group were 40.7± 7.8 years and 42.6± 6.1 years respectively.BMI in the NAFLD cases was 28.3 ± 5.6 as opposed to 22.4 ± 4.9 in the control group. Mean Diastolic blood pressure in the cases was 90 ±8 mm Hg while in the control group it was84 ±10 mm Hg.There was significant difference in the serum ferritin level between male and female subjects of healthy control group as well as the case group.Serum ferritin in NAFLD cases was 94±33.8ng/ml while in the control it was 43.5 26.4ng/ml with a p value <0.0001 which is statistically significant.All other biochemical parameters like triglyceride,total cholesterol, LDL,fasting blood glucose,AST and ALT were raised significantly in the NAFLD cases.Serum HDL was found to be significantly low in NAFLD cases.It was 50.6 ± 12.6 mg/dl and 40.6 ± 8.4mg/dl in control and case group respectively.

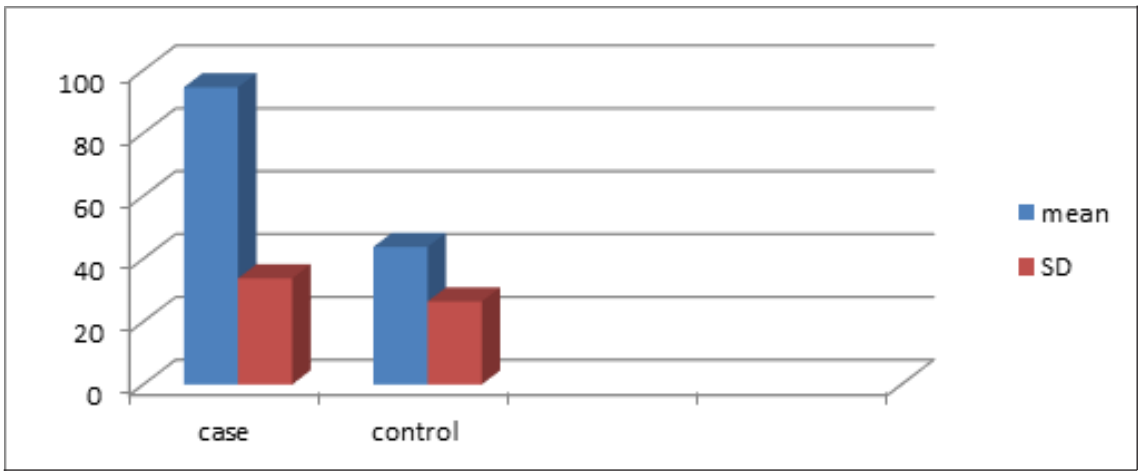

Fig 1: serum ferritin level in case and control group

Table 1: Biochemical parameters in control vs case group

Parameters	Control	Case	p value
FBG	90.8 ± 23.5mg/dl	102.7±16.8mg/dl	0.0001
TChol	180.4± 45.5mg/dl	213.0± 50.6mg/dl	0.0001
TG	122.8 ± 35.4mg/dl	212.0± 48.6mg/dl	0.0001
HDL	50.6± 12.6 mg/dl	40.6 ± 8.4 mg/dl	0.0001
LDL	100.4± 30.6 mg/dl	134.7± 25.4mg/dl	0.0001
AST	34.9± 9.6IU/l	45.8 ±10.7 IU/l	0.0001
ALT	35.8 ±8.9 IU/l	49.7 ±11.9 IU/l	0.0001

DISCUSSION

Serum ferritin level showed significant positive correlations with BMI, AST, ALT level in all the study subjects. Ferritin level was significantly increased in obese subjects and those with Metabolic syndrome even in the control group.Serum ferritin was found to be significantly low in females of both control and case group.Among the cases diagnosed with NAFLD ,it was seen that serum ferritin has positive correlation with the severity of NAFLD.

Kowdley et al investigated the serum ferritin level and histological findings, including iron deposition, in 628 patients with NAFLD. The cross-sectional study revealed that an elevated serum ferritin (>1.5×UNL) was associated with advanced hepatic fibrosis[20].

In a study by Jeong DW et al ,serum ferritin level showed a significant increase with severity of US-NAFLD, and increase in the quartile of serum ferritin level was significantly associated with the incidence of US-NAFLD in men[21]. WMA Al-Zibair etal, aimed to investigate the serum ferritin level among Nonalcoholic fatty liver disease (NAFLD) in Sudanese patients. The results revealed a significant increase in ferritin among case (87.60 ± 35.29) and control (57.24 ± 29.28) with P Value = 0.003 and this may be due to hepatic inflammation, steatosis, and/or fibrosis. Ferritin also showed significant increase among case male (133.54 ± 65.32) compared with case female (60.02 ±19.15) with P. Value = 0.000. Also in their study, results showed positive moderate correlation between age in years and serum ferritin level[22].

In one study by Williams et al. , serum ferritin was significantly associated with CRP, waist circumference, BMI, and TG in 443 women in New Zealand[23]. Manousou P, et al. reported that the elevated serum ferritin level may reflect the occurrence of hepatic failure and metabolic syndrome because of the activation of inflammatory cytokines in NAFLD patients[18]. Nelson JE, et al. reported that hepatic iron accumulation is correlated with hepatic fibrosis in NAFLD subjects, what is confirmed in a large number of studies focused on the pathophysiological point of view[24]. Valenti L, et al. reported that the accumulation of hepatic iron may contribute to the production of inflammatory cytokines, what might lead to the hepatic fibrosis[25].

Du et al in a meta-analysis explored that NAFLD patients showed a higher serum ferritin level, what can be related with the severity of NAFLD. These results are consistent with the hypothesis that the elevated SFL is related with hepatocyte damage and it also plays a fibrotic and pro-inflammatory role during the progression of the disease[26].

A large Italian series reported a 1.67-fold greater likelihood for advanced fibrosis in patients with NAFLD with increased serum ferritin levels[27].Based on this, it has been proposed that serum ferritin levels could potentially be used to predict the presence and severity of liver fibrosis in patients with NAFLD.

CONCLUSION

Patients with NAFLD have higher serum ferritin level than those without fatty liver changes. Serum ferritin levels rise as the grade of liver steatosis increases.

. So, serum ferritin may be a simple and non-invasive useful marker for patients with NAFLD.

Ethical Clearance: Institutional ethical committee, IGIMS, Patna.

Source of Funding: Self

Conflict of Interest: None

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