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The Association of Serum Ferritin with Disease Severity in Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: It is widely acknowledged that non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the West. It is associated with insulin resistance and frequently coexists with metabolic syndrome symptoms. Ferritin is an acute phase reactant, though, thus its increase in a patient with fatty liver disease's serum could perhaps be a sign of inflammation in addition to disease activity.

Objective: The aim of our study was to evaluate the association of serum ferritin with non-alcoholic fatty liver disease in patients with normal and elevated lipid profile.

Patients and Methods: The study was cross sectional study, which conducted at Ain Shams University Hospital. This study was conducted on 80 patients. They were divided in to 2 groups as following: Group I included: 40 NAFLD patients with normal lipid profile. Group II included: 40 NAFLD patients with elevated lipid profile. Lipid profile and serum ferritin were done.

Results: Our research showed that patients with increased lipid profiles and non-alcoholic fatty liver disease had considerably higher serum ferritin levels than those with normal lipid profiles. However, there was no connection between serum ferritin and the fibrosis score for NAFLD, hepatic steatosis index, or fatty liver index.

Conclusion: Serum ferritin may be promising adjuvant inflammatory marker of predication and prognosis in NAFLD patients especially in those with elevated lipid profile. Also, serum ferritin level cannot alone reflect severity of NAFLD.

Keywords: Serum Ferritin; lipid profile, Disease Severity; Non-alcoholic Fatty Liver Disease.

INTRODUCTION

The risk of diabetes mellitus, cardiovascular disease, and chronic renal disease is increased by non-alcoholic fatty liver disease (NAFLD), which is regarded as a multisystem disease [(1)]. From basic steatosis through non-alcoholic steatohepatitis (NASH) to cirrhosis and its associated complications such hepatocellular cancer and mortality, there is a broad range of liver disease [(2)].

There is considerable evidence linking insulin resistance to the development of non-alcoholic fatty liver disease, even though the aetiology of the condition (non-alcoholic steatohepatitis/non-alcoholic fatty liver disease) is not yet fully understood [(3)].

One non-invasive marker, serum ferritin, has recently emerged as a potential predictor of the presence of non-alcoholic steatohepatitis as opposed to simple steatosios. Iron excess can be found in up to one-third of patients with non-alcoholic fatty liver disease. Steatosis, insulin resistance, and inflammation all contribute to an altered control of iron transport. Although ferritin is an acute phase reactant, its rise in the blood of a patient with fatty liver disease may not only indicate the presence of the disease but also the presence of other inflammatory conditions and some cancers (such as lymphoma) [(5)].

Numerous research have been interested in examining the role of altered iron metabolism in the onset and progression of non-alcoholic fatty liver disease. The generation of reactive oxygen species, impaired insulin signalling, changed lipid metabolism in hepatic tissue, and the harm they cause are only a few of the pathogenic pathways for iron that have been identified [(6)]. Since there is no consensus among research about the relationship between serum ferritin and the severity of NAFLD.,

AIM OF THE STUDY

Our study objective is to determine the association of serum ferritin with non-alcoholic fatty liver disease in predication of severity and progression in patients with normal and elevated lipid profile.

PATIENTS AND METHODS

The study was cross sectional study, which conducted at Ain Shams University Hospital. This study was conducted on 80 patients of both sexes, with age (18years old - 60 years), duration of study was 6 months. Patients were divided in to 2 groups as following: **Group I included:** 40 patients with normal lipid profile (Triglyceride < 150mg/dl, Cholesterol < 200mg/dl, HDL = 60mg/dl, LDL < 100mg/dl). **Group II included:** 40 patients with elevated lipid profile (Triglyceride >150mg/dl, Cholesterol > 200mg/dl, HDL = 60mg/dl, LDL >100mg/dl).

Exclusion criteria: Alcohol abuser, chronic or acute viral hepatitis patient (hepatitis A, B, C), patients with other chronic metabolic liver disease as Wilson disease, hereditary hemochromatosis, auto immune hepatitis, primary sclerosing cholangitis, pregnancy and lactation, alpha-1 antitrypsin deficiency, patients with malignancy, immunocomprimised patients, anemia and the patients who refuse to be entitled in the study.

All cases had underwent:

- Medical history taking according to pre-designed questionnaire.

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- **Clinical assessment: Generally included:** pallor, jaundice, body mass index and edema of foots and legs. **And locally included:** Any palpable mass in abdomen and organomegaly.

- **Investigations:**
  Laboratory assessment by:
  1. Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST).
  2. Iron profile included (serum ferritin, serum iron, TIBC).
  3. Blood sugar test (fasting blood sugar, postprandial blood sugar, Hemoglobin A1c).
  4. Serum albumin. Complete blood picture, international Normalized ratio (INR), Partial thromboplastin time (PTT).
  5. Kidney function tests: creatinine, blood urea nitrogen (BUN), Alpha fetoprotein.
  6. Lipid profile: Triglyceride, HDL, LDL, Cholesterol.
  7. Hepatitis C virus Ab, Hepatitis B virus surface antigens, ANA, AMA, ASMA.
  8. Fatty liver index, Hepatic steatosis index, NAFLD fibrosis score.

Pelviabdominal ultrasonography.

1- **Fatty liver index: FLI =** (e0.953×loge(triglycerides)+0.139×BMI+0.718×loge(GGT)+ 0.053×waistcircumference−15.745)/ (1 + e0.953×loge(triglycerides)+0.139×BMI+0.718 × loge(GGT)+0.053×waistcircumference−15.745) × 100.
   - Fatty liver index < 30 to rule out hepatic steatosis.
   - Fatty liver index > 60 to rule in hepatic steatosis.

2- **Hepatic steatosis index** = 8 x Alt/Ast+BMI+2(if patient is diabetic)+2(if patient is female).
   - Hepatic steatosis index value < 30 rules out steatosis.
   - Hepatic steatosis index value > 36 rules in steatosis.

3- **NAFLD fibrosis score =** -1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelet (×10^9/L) – 0.66 × Albumin (g/dL).

ELISA (enzyme-linked immunosorbent assay) technique is used to measure serum ferritin level in Ain Shams University laboratories.

Principle: This kit is an Enzyme-linked Immunosorbent Assay (ELISA).

Ethical consent:

The Academic and Ethical Committee at Ain Shams University approved the study. Each patient signed a written informed consent form to agree to participate in the study. The Declaration of Helsinki **(Ref)**, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Statistical analysis

SPSS software version 18 for Windows 7 was used to gather and analyze data. For quantitative variables, mean, standard deviation (SD), and range were utilized. The terms used for qualitative variables were number and percentage. To assess qualitative variables between groups, the Chi-square test was performed. The following power of significance evaluation was made: P-value (probability level) > 0.05 indicates insignificance, P-value 0.05 indicates significance, and P-value 0.01 indicates highly significant. In order to compare quantitative data between more than two groups, the analysis of variance (ANOVA) test was performed.

To compare variables positively or negatively to one another, the Pearson correlation co-efficient test was utilized. To compare quantitative data between two groups, the t-test was used. Sensitivity, specificity, positive predicted value (PPV), and negative predictive value were evaluated using the receiver operating characteristic curve (ROC curve) (NPV). The Tukey test was used to compare quantitative data with a non-parametric distribution between more than two groups.

RESULTS

Regarding age and gender of the examined patients, there was no statistically significant difference between non-alcoholic fatty liver with normal lipid profile group and with increased lipid profile group, with p-values = 0.259 and 0.361, respectively (Table **1**).

Table (1): Comparison between non-alcoholic fatty liver disease with normal lipid profile group patients and those with elevated lipid profile group patients regarding age and gender

		Non-alcoholic fatty liver disease with normal lipid profile	Non-alcoholic fatty liver disease patients with elevated lipid profile	Test value	P-value	Sig.
		No. = 40	No. = 40			
Age	Mean ± SD Range	51.88 ± 6.86 34 – 60	49.68 ± 10.14 27 – 60	1.137	0.259	NS
Gender	Male Female	14 (35.0%) 26 (65.0%)	18 (45.0%) 22 (55.0%)	0.833	0.361	NS

Regarding waist circumference and body mass index, there was no statistically significant difference between non-alcoholic fatty liver patients with normal lipid profiles and those with raised lipid profiles (BMI) (Table **2**).

Table (2): Comparison between non-alcoholic fatty liver disease with normal lipid profile and those with elevated lipid profile regarding waist circumference and body mass index (BMI)

		Non-alcoholic fatty liver disease with normal lipid profile	Non-alcoholic fatty liver disease patients with elevated lipid profile	Test value	P-value Sig.
		No. = 40	No. = 40		
Waist circum-ference (cm)	Mean ± SD Range	113.20 ± 4.10 106.2 – 119.4	113.32 ± 4.8 106 – 122	0.00603	0.9954 NS
BMI	Mean ± SD Range	32.86 ± 1.26 30.5 – 35.2	35.55 ± 1.9 30 – 36	-0.0656	0.9508 NS

Regarding fasting blood sugar, postprandial blood sugar, hemoglobin A1C, pelvic abdominal ultrasonography finding, and incidence of DM, there was no statistically significant difference between non-alcoholic fatty liver with normal lipid profile group and with increased lipid profile group (Table **3**).

Table (3): Comparison between non-alcoholic fatty liver disease with normal lipid profile and those with elevated lipid profile regarding fasting blood sugar, postprandial blood sugar, HemoglobinA1C, pelvi abdominal ultrasound finding and incidence of Diabetes mellitus ---- In last column show Sign.

		Non-alcoholic fatty liver disease with normal lipid profile	Non-alcoholic fatty liver disease patients with elevated lipid profile	Test value	P-value	
		No. = 40	No. = 40			
DM	No Yes	21 (52.5%) 19 (47.5%)	22 (55.0%) 18 (45.0%)	0.050	0.823	
Fasting Blood Sugar (FBS) (mg\dl)	Mean ± SD	150.05 ± 33.62	142.48 ± 31.21	0.495	0.622	
Post Prandial Blood Sugar (PPBS) (mg\dl)	Mean ± SD	135.5 ± 31.21	136.5 ± 32.12	-0.409	0.683	
HbA1c%	Mean ± SD	6.66 ± 1.20	6.66 ± 1.44	-0.008	0.993	
Pelvi-abdominal ultrasound	Enlarged fatty liver Shrunken cirrhotic liver	17 (42.5%) 23 (57.5%)	17 (42.5%) 23 (57.5%)	0.000	1.000	

With a p-value of 0.003, the elevated group's serum ferritin level increased significantly more than the normal group's (Table **4**).

Table (4): Comparison between non-alcoholic fatty liver disease with normal lipid profile group and those with elevated lipid profile group regarding serum ferritin level

		Non-alcoholic fatty liver disease with normal lipid profile	Non-alcoholic fatty liver disease patients with elevated lipid profile	Test value	P-value	Sig.
		No. = 40	No. = 40			
Serum Ferritin (mg\dl)	Mean ± SD	68 ± 15.34	181 ± 41.32	-3.007	0.003	HS

In the non-alcoholic fatty liver group, the fatty liver index increased statistically significantly (p-value > 0.01) as compared the elevated lipid group with normal lipid profiles. The following table demonstrates that there was no statistically significant difference in the hepatic steatosis index and NAFLD fibrosis score between non-alcoholic fatty livers with normal lipid profiles and those with increased lipid profiles (Table **5**).

Table (5): Comparison between non-alcoholic fatty liver disease with normal lipid profile and those with elevated lipid profile regarding hepatic steatosis index, fatty liver index,NAFLD fibrosis score

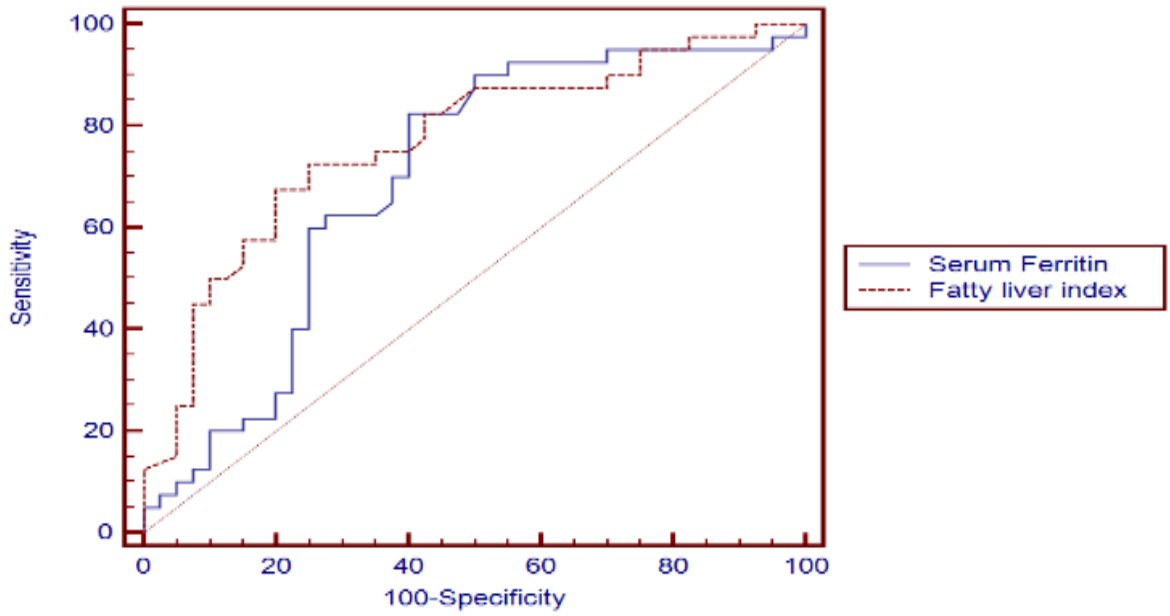
		Non-alcoholic fatty liver disease with normal lipid profile	Non-alcoholic fatty liver disease patients with elevated lipid profile	Test value	P-value	Sig.
		No. = 40	No. = 40			
Hepatic steatosis index	Mean ± SD	41.99 ± 2.72	42.19 ± 3.42	-0.293	0.770	NS
Fatty liver index	Mean ± SD	81.23 ± 8.51	88.50 ± 7.13	-4.138	0.000	HS
NAFLD fibrosis score	Mean ± SD	0.85 ± 0.18	1.015 ± 0.21	-0.284	0.776	NS

Serum ferritin levels did not significantly correlate with hepatic steatosis index, fatty liver index, or NAFLD fibrosis score. Additionally, there was no statistically significant relationship between the lipid profile and serum ferritin level. While the serum triglyceride level and the fatty liver index showed a positive association. Additionally, there was no discernible connection between serum ferritin and Fasting blood sugar, postprandial blood sugar, or hemoglobin AIC (Table **6**).

Table (6): Correlation between serum ferritin and lipid profile and hepatic steatosis index, fatty liver index and NAFLD fibrosis score, fasting blood sugar, postprandial blood sugar, Hemoglobin AIC.

	Serum Ferritin		Hepatic Steatosis Index		Fatty Liver Index		NAFLD Fibrosis Score	
	r	p-value	r	p-value	r	p-value	r	p-value
Serum Ferritin	-	-	0.090	0.582	0.199	0.219	-0.025	0.876
Hepatic Steatosis Index	0.090	0.582	-	-	**0.694**	**0.000**	0.091	0.576
Fatty Liver Index	0.199	0.219	**0.694**	**0.000**	-	-	0.259	0.106
NAFLD Fibrosis Score	-0.025	0.876	0.091	0.576	0.259	0.106	-	-
Cholesterol	-0.209	0.195	0.217	0.178	0.246	0.127	0.058	0.720
Triglyceride	0.089	0.584	0.234	0.147	**0.564**	**0.000**	0.075	0.646
HDL	0.012	0.942	0.042	0.795	0.006	0.972	-0.085	0.600
LDL	-0.123	0.450	0.099	0.544	0.006	0.970	0.109	0.504
Fasting Blood sugar	0.217	0.179	**0.335**	**0.034**	**0.354**	**0.025**	**0.459**	**0.003**
Post Prand. Blood Sugar	0.168	0.300	**0.377**	**0.016**	**0.351**	**0.026**	**0.376**	**0.017**
HbA1C%	0.177	0.274	0.284	0.076	0.282	0.078	**0.344**	**0.030**

The following figure (**1**) show diagnostic character of ferritin and fatty liver index in NAFLD patients with ferritin Sensitivity 82.5% and Specificity 60% and fatty liver index sensitivity 67.5% and specificity 80%.



Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
Serum Ferritin	**0.695**	**>80**	**82.5%**	**60.0%**	**67.3**	**77.4**
Fatty liver index	**0.768**	**>89**	**67.5%**	**80.0%**	**77.1**	**71.1**

Figure (1): Receiver operating characteristic (ROC) curve for serum ferritin and fatty liver index as diagnostic markers for elevated lipid profile.

DISCUSSION

Approximately 25% of people globally have NAFLD, which is the most prevalent liver condition. Additionally, it is particularly prevalent in developed countries as the United States in 2017, it afflicted between 75 and 100 million people. It affects up to 20% of adults with normal weight, 90% of obese people, and 60% of diabetics [(1)].

Since serum ferritin is a protein expressed in the acute phase, liver necrosis and inflammation cause an increase in its level. Because of its link to hepatic iron accumulation and inflammation, some new studies claim that the level of serum ferritin level can be a reliable indication of the advancement of hepatic fibrosis in individuals with NAFLD [(7)]. Researchers came to the conclusion that SFL, which may be related to insulin resistance and hepatocyte injury, is higher in patients with NAFLD. The stage of NAFLD cannot be determined by serum ferritin level, according to certain empirical data. These links continue to be debated [(8)].

Our study objective is to determine the association of serum ferritin with non-alcoholic fatty liver disease and the correlation between ferritin level and the severity of disease. In this work, we not only assess the value ferritin in NAFLD patients, we also compare between NAFLD with normal lipid profile and NAFLD with high lipid profile regarding the laboratory finding beside serum ferritin and the relation of it in each group with degree or severity of liver disease in NAFLD patients. While no or little previous studies showed this comparison, most of these researches highlights comparison between NAFLD and control persons.

Our study shows higher incidence of NAFLD in females in both normal and elevated lipid profile groups with no statistical significant difference between 2 groups. This disagree with the study done by **Paulina *et al.*** [(9)] as this study revealed that the incidence of non-alcoholic fatty liver disease increased among men and even postmenopausal women probably due to increase tendency towards visceral fat accumulation. This difference may be due to number of patients selected in this study was greater.

High BMI and waist circumference were positively correlated with high blood lipid profiles in the study by **Abdelraheem *et al.*** [(10)] of NAFLD patients. This is in contrast to our study, which found no discernible difference between NAFLD patients with normal lipid profiles and those with high lipid profiles in terms of BMI or waist circumference.

The study, which was conducted in collaboration with **Tutunchi *et al.*** [(11)] on a group of Iranian people referred to the gastrointestinal clinic at the Imam Reza hospital in Tabriz, Iran. The patients' average age was 49.27 years old, with 53.68 percent men and 46.33 percent women. Overall, this study's findings show that in Iranian individuals, the degree of ultrasosographic liver stetosis was substantially correlated with aberrant metabolic parameters (such as BMI). This variation might result from varied geographic distribution.

Our study also concluded statistically significant increase in serum ferritin in elevated group than normal group with p-value 0.003. This is consistent with **Buzzetti *et al.* [12],** who conducted a study on 468 individuals with biopsy-proven NAFLD from two European centers. At the time of the liver biopsy, iron, hepatic, and metabolic parameters were collected, and it was discovered that serum ferritin is elevated in non-alcoholic fatty liver patients, and it is even higher in fibrosis. Moreover, our research supports **Manousou *et al.* [13]**. This study was performed on 2029 Chinese adults aged 35-70 years and it revealed elevated serum ferritin level in non-alcoholic fatty liver patients than control.

Abdelraheem *et al.*[10] highlighted that there was high ferritin level in NAFLD male smoking patients and these more linked with more aggressive disease. Also with partial agreement with our study, **Galarregui *et al.*[14]** confirmed good association between serum ferritin level in combination with ALT, glucose level and liver disease in NAFLD patients. Serum ferritin level is potential non-invasive predictive biomarker in NAFLD. **Hassan *et al.* [15]** again highlights that there was high ferritin level in NAFLD group and there was positive correlation with ultrasound grades of liver steatosis and fibrosis.

Furthermore, our findings match those of **El Nakeeb *et al.* [16]**, in this study, 113 participants were separated into three groups, as follows: In groups 1, healthy people served as the control group. Group 2 NAFLD patients without fibrosis. Group 3 patients had hepatic fibrosis as well as NAFLD. Hepatic fibrosis and NAFLD patients had greater serum ferritin levels, according to this study.

In contrast to our findings, **Kim *et al.* [17]** discovered a positive link between serum ferritin level and total cholesterol, LDL, and triglyceride levels in boys but not in girls, and no significant relationship between serum ferritin level and HDL level in boys.

In our study, both the normal and elevated groups of diabetic individuals had high frequencies of NAFLD, and there was no significant association between serum ferritin levels and diabetes mellitus, hemoglobin A1C, fasting blood sugar, or postprandial blood sugar in the NAFLD groups. Unlike the work by **Yan *et al.* [18],** which discovered higher serum ferritin levels in NAFLD patients with type 2 diabetes.

Our study found a high hepatic steatosis index in non-alcoholic fatty liver patients with normal lipid profiles and those with elevated lipid profiles, with no difference statistically between both groups. **Lee *et al.*[19]** concurred with this conclusion after conducting a cross-sectional study in which 5362 cases of non-alcoholic fatty liver disease were compared to 10724 healthy controls of similar ages and sexes. This study found that the Hepatic Steatosis Index is a simple screening tool for non-alcoholic fatty liver disease that may be used to select people for hepatic ultrasonography and determine whether a lifestyle change is required.

Fennoun *et al.* [20] this study revealed that hepatic steatosis index raised among diabetics with dyslipidemia, obesity and hypertriglyceridemia. That go against our result which showed no correlation between hepatic steatosis index and DM or lipid profile. This difference is due to larger numbers of patients participated in this study. Also Our study shows highly significant increase in NAFLD fibrosis score in diabetics in non-alcoholic fatty liver with elevated lipid profile group with p-value =0.001 which agree with **Singh *et al.* [21].** This study found that non-invasive approaches such as the non-alcoholic fatty liver disease fibrosis score (NAFLD FIBROSIS SCORE) are strongly connected to non-alcoholic fatty liver disease progression.

Our results showed elevated fatty liver index in NAFLD patients with elevated lipid profile with no significant correlation between serum ferritin and fatty liver index. Also there was positive correlation between fatty liver index and serum triglycerides level. This was agree with **Bedogni *et al.* [22]** that found significant relation between fatty liver index and triglycerides level.

CONCLUSION

Serum ferritin may be promising adjuvant inflammatory marker of predication and prognosis in NAFLD patients especially in those with elevated lipid profile. Also, serum ferritin level cannot alone reflect severity of NAFLD.

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