



# Iron Status and Metabolic Syndrome in Patients with Non-Alcoholic Fatty Liver Disease

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## ABSTRACT

### BACKGROUND

A hypothesis has been presented about the role of serum iron, ferritin and transferrin saturation among patients with non-alcoholic fatty liver disease (NAFLD) and resistance to insulin (metabolic syndrome [MetS]), but there is much controversy. This study aimed at investigating the level of serum iron and demographic characteristics in patients with NAFLD with or without MetS.

### METHODS

A case-control study was conducted on patients with elevated liver enzymes referring to Baqiyatallah clinic, Tehran, Iran during 2010-2011. After ruling out other causes of increased aminotransferases and approving the diagnosis of NAFLD, the patients were divided into two groups of with or without MetS. Then, the individuals' demographic, sonographic, and laboratory characteristics were recorded.

### RESULTS

This research included 299 patients suffering from NAFLD who were divided into MetS (n=143; 47.8%) and non-MetS (n=156; 52.2%) groups. The age, systolic and diastolic blood pressure, body mass index, waist/hip ratio, glucose tolerance test, serum insulin, C. peptide, triglyceride, and HB A1c were different between MetS and non-MetS groups ( $p<0.05$ ). There was no significant difference in serum iron and ferritin levels between the two groups, however, a significant correlation was found between serum ferritin and alanine transaminase ( $p=0.005$ ) and also aspartate aminotransferase ( $p=0.032$ ).

### CONCLUSION

Our findings did not show a significant relationship between iron, in free or storage form, and the presence of MetS among patients with NAFLD, but serum ferritin can correlate with hepatocytes injuries indicated by raised aminotransferases. Nevertheless, to clarify this relationship further molecular, genomic, and histopathological studies are required.

### KEYWORDS

Non-alcoholic fatty liver disease; Metabolic syndrome; Iron; Ferritin

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## INTRODUCTION

Metabolic Syndrome (MetS) or syndrome of resistance to insulin involves metabolic abnormalities indicated by central obesity, hypertriglyceridemia, decreased high density lipoprotein (HDL), hypergly-

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chemia, obstructive sleep apnea, and hypertension.<sup>1-3</sup> According to the Adult Treatment Panel III (ATP III) report, the prevalence of MetS is about 22%, which is increased by age.<sup>4</sup> Many metabolic abnormalities such as non-alcoholic fatty liver disease (NAFLD) and steatohepatitis are observed along with MetS.<sup>5,6</sup> “NAFLD is a hepatic manifestation of metabolic syndrome; it is closely related to other clinical features of metabolic syndrome”.<sup>7</sup> NAFLD is an inflammatory liver disease in which fat accumulates in hepatocytes and results in increased number of inflammatory cells in liver tissue.<sup>8</sup> NAFLD is the most common liver disease in developed countries with the incidence rate of 20-40%, however, its prevalence is rising in developing countries such as Asian nations.<sup>9</sup> Most frequently, NAFLD is asymptomatic and is detected when a physician performs precise laboratory or ultrasound studies for check-up or increase in aminotransferases occurs.<sup>7,10</sup>

This disease was first observed among middle aged obese men with diabetes mellitus (DM) but recently it is believed that non-obese and non-diabetic men with iron overload could be predisposed to this disease.<sup>11</sup> Therefore, currently the role of serum iron, ferritin, and transferrin in this disease is more studied.<sup>12,13</sup> Also, a newly diagnosed condition of liver called “insulin resistance-hepatic iron overload IR-HIO” is observed in patients with hyper ferritinemia and normal transferrin without mutation in gene of hemochromatosis. Although patients with IR-HIO suffer from a wide variety of metabolic disorders, the relationship between IR-HIO and NAFLD is not yet definite.<sup>14</sup>

On the other hand, there are several hypotheses about the pathophysiology of the relationship between NAFLD and MetS. One of the most acceptable hypotheses is insulin resistance indicated by postprandial ineffective hyperinsulinemia and subsequently postprandial hyperglycemia and increase in free fatty acid.<sup>15</sup> Furthermore, oxidant and antioxidant imbalance is another trigger suggested for justifying this relationship whereas ferritin is an acute phase reactant.<sup>16</sup> Both mechanisms could support the hypothesis on the role of iron or iron carriers in this correlation between MetS and NAFLD.

In this study we assessed clinical and para-clinical evidence for this relationship.

## MATERIALS AND METHODS

A case-control study was conducted between 2010 and 2011 among patients with elevated aminotransferases referred to Baqiyatallah clinic, Tehran, Iran. The diagnosis of NAFLD was confirmed after ruling out other causes of elevated aminotransferases such as viral hepatitis (by testing HBS Ag, HBS Ab, HBC Ab, and HCV Ab), alcohol consumption, infectious diseases, and other medical conditions, which could affect liver function test. Based on the following criteria (table 1), the patients were divided into two groups with MetS (MetS group) or without MetS (non-MetS group). Guideline of ATP version 3 was used for diagnosis of MetS.<sup>17</sup> Clinical and paraclinical assessments were done. The clinical assessment, included demographic and anthropometric characteristics, and physical examination were done by a clinical practitioner.

Paraclinical studies were also performed consisting of ultrasonography and lab tests aspartate aminotransferase (AST), Alanine transaminase (ALT), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), triglyceride (TG), cholesterol, fasting blood sugar (FBS), ferritin, and serum iron), which were done in the laboratory of Baqiyatallah Hospital after 12 hours fasting. Diagnosis and grading of NAFLD (Diffuse hepatic steatosis) based on ultrasonography was determined by a radiologist according to the following guideline;

1- increased echogenicity and beam attenuation, which is known as a diffuse hyperechoic texture (bright liver)

2- Increased echo texture compared with kidney (liver and renal cortex have normally a similar echogenicity)

3- vascular blurring (absence of the normal echogenic walls of the portal veins and hepatic veins).

Using the sample size formula shown below, the sample size was calculated as 280 cases, while  $d=0.05$ ,  $p=0.68$ , and  $\alpha=0.05$ .

for aminotransferases was 40 mg/dL. For serum

iron it was 190 µg/dL for men and 175 µg/dL for women. Cut point for serum ferritin was 300 µg/dL for men and 200 µg/dL for women. Chi2 (or Fisher

$$n = \frac{(Z_{1-\alpha/2})^2 \times P(1-P)}{d^2}$$

exact test), independent t test, one way ANOVA, and Pearson (or spearman) tests were used for univariate analysis in using SPSS software version 16. P value less than 0.05 were considered as statistically significant. Finally, variables with P value less than 0.2 was entered in a model of logistic regression.

## RESULTS

A total of 299 patients (198 men and 101 women) with NAFLD were included and were divided into MetS (n=143; 47.8%) and Non-MetS (n=156; 52.2%) groups. The mean age of the patients was 44.99±12.77 years. The baseline characteristics of each group are illustrated in table 2 and 3. There is a significant difference between mean age and sex ratio in the two groups ( $p=0.001$ ).

As expected, the age, systolic and diastolic blood pressure, body mass index (BMI), waist/hip ratio, glucose tolerance test (GTT), serum insulin, C-peptide, TG, and hemoglobin A1c (HbA1c) were different between MetS and non-MetS groups ( $p<0.05$ ). Moreover, the history of diabetes mellitus, hypertension, and coronary artery disease was significantly different between the groups ( $p<0.05$ ). There was no significant difference in grade of disease according to the ultrasound study, aminotransferases and bilirubin levels between MetS and non-MetS groups. After adjusting for confounder variables such as age, we found no differences in ALT ( $p=0.557$ ) and AST level ( $p=0.205$ ) among the two groups. However, a significant correlation was found between serum ferritin and ALT ( $p=0.005$ ) and also AST ( $p=0.032$ ).

Despite adjusting the confounding role of sex on serum ferritin and iron, we could not find any significant difference in serum iron and ferritin level between the two groups (table 4). In a regression model, only sex ( $p<0.001$ , Exp B: 3.912, CI 95%: 1.892-8.088), systolic blood pressure ( $p=0.013$ , Exp

**Table1: Guideline of ATPIII 2005 (National Cholesterol Education Program; NCEP)**

NCEP'ATP3
3 items and more;
abdominal circumference $\geq 102$ cm for men and $\geq 88$ cm for women
Triglyceride $\geq 150$ mg/dl or under treatment with lipid lowering agents
Blood pressure $\geq 130$ systolic or $\geq 85$ diastolic or under treatment for hypertension
FBS $\geq 100$ mg/dl or under treatment for diabetes mellitus
HDL $\geq 40$ mg/dl in men or $\geq 50$ mg/dl in women or under treatment for decreased HDL

B: [1.040] CI 95%: 1.008-1.072), BMI ( $p=0.001$ , Exp B: 1.158, CI 95%: 1.061-1.264), DM ( $p=0.007$ , Exp B: 4.305, CI 95%: 1.481-12.509), total iron binding capacity (TIBC) ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), hemoglobin ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), TG ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), HDL ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), alkaline phosphatase (ALP) ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), AST ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), ALT ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017), and serum insulin ( $p=0.017$ , EXP B: 1.007, CI 95%: 1.001-1.017) could predict MetS in patients with NAFLD.

## DISCUSSION

Given the results of this study, no significant relationship was observed between serum iron and presence of MetS in patients with NAFLD. Also, the same results were obtained for serum ferritin. In other words, there is no prominent difference in the role of iron (both serum iron and ferritin as a form of iron for storage) in presence of NAFLD in both groups.

A hypothesis has been presented on the role of iron especially iron deposit in liver in patients with NAFLD on resistance to insulin, however, there is much controversy in determination of definite mechanism.<sup>18</sup>

In late 1990s, two studies posed the hypothesis about irrespective resistance to insulin among patients with hepatic iron overload, which was indicated by hyperferritinemia and normal transferrin.<sup>19</sup> Mendler and colleagues demonstrated that

**Table 2: baseline characteristics (quantitative variable) in terms of groups**

Variables	NON-METS	METS	p-value (r)
Age	42.65±13.08	47.45±11.87	0.001(-3.245)
SBP	119.01±11.77	125.09±17.10	0.001(-3.553)
DBP	79.01±6.19	82.05±6.47	0.001(-3.504)
Weight	83.92±16.64	85.37±14.77	0.776
Height	168.95±13.49	166.12±10.39	0.556
Abdominal Girth	101.47±9.98	107.42±11.34	0.374
Pelvic Girth	102.344±9.69	105.83±10.43	0.955
BMI	28.56±3.46	30.95±4.69	0.000(-4.66)
Waist/hip ratio	1.25±0.48	1.49±0.60	0.001(-3.514)
Pack/year	3.20±6.69(15)	8.71±18.23(7)	0.464
GTT	116.24±49.06	145.52±66.52	0.000(-3.95)
Serum Insulin	10.88±5.69	14.54±7.46	0.000(-0.450)
C. peptide	2.49±1.07	3.02±0.99	0.000(-3.93)
HBA1C	5.76±0.91	7.00±6.40	0.033(0.215)
Cholesterol	199.49±45.54	196.86±43.62	0.905
TB	175.78±114.05	240.37±124.54	0.000(-4.63)
HDL	117.49±36.33	43.23±9.88	0.000(4.61)
LDL	117.49±38.33	110.91±34.13	0.124
Total Bilirubin	1.08±0.615	1.04±0.54	0.644
Direct Bilirubin	5.95±1.33	6.10±1.68	0.455
ALP	188.32±57.38	197.90±67.75	0.205
AST	30.94±15.78	32.87±22.67	0.404
ALT	48.03±32.70	46.31±38.23	0.678
ALB	4.69±0.85	4.56±0.43	0.169
PT	12.54±0.90	12.53±1.49	0.964
TSH	2.31±2.01	2.33±3.11	0.946
T3	1.97±6.71	1.29±0.37	0.266
T4	92.42±21.79	89.61±18.76	0.272
Serum Ferritin	163.78±246.33	151.54±205.82	0.682
Serum Iron	108.92±39.37	151.86±490.62	0.305
TIBC	317.84±59.20	334.45±59.99	0.032(-2.15)
Ceruloplomin	33.24±51.82	24.32±10.68	0.501
HB	15.27±1.47	14.52±1.44	0.0001(4.28)
MCV	85.03±7.70	86.06±5.32	0.199
PIT	238.67±56.790	276.33±30.391	0.160

“patients with unexplained hepatic iron overload are characterized by a mild to moderate iron burden and the nearly constant association of an insulin resistance syndrome irrespective of liver damage.”<sup>20</sup> Moirand and co-workers also presented this condition as a new non-HLA-linked iron overload syndrome, which suggests a relationship between iron excess and an abnormal metabolic condition in-

cluding obesity, hyperlipidemia, abnormal glucose metabolism, or hypertension known as MetS.<sup>21</sup> An epidemiological finding that “the dysmetabolic iron overload syndrome is detected in about one third of patients with NAFLD and the MetS” and also a therapeutic-based approach that showed decreased metabolic alterations and liver enzymes in NAFLD patients undergone iron depletion by phlebotomy

**Table 3: baseline characteristics (qualitative variable) in terms of groups**

Item	Sub group	NON-METS	METS	p-value	OR (CI)
Gender	M	76.6%	47.5%	<0.001	1.614 (1.32-1.96)
	F	23.4%	52.5%		
Education	Illiterate	0%	0.7%	<0.001	-
	Under D	20.3%	45.3%		
	Diploma	73.9%	50.4%		
	Scholar	5.9%	3.6%		
Symptoms	+	24%	39.6%	0.004	0.607 (0.429-0.860)
	-	76%	60.4%		
Sonography	NL	2.6%	0.7%	0.119	-
	Grade 1	51.3%	40.3%		
	Grade 2	32.2%	42.4%		
	Grade 3	13.8%	16.5%		
DM	+	5.2%	18%	0.001	0.289 (0.135-0.619)
	-	49.8%	82%		
CAD	+	96.8%	3.2%	0.030	0.347 (0.127-0.947)
	-	90.6%	9.4%		
HTN	+	7.8%	30.4%	<0.001	0.256 (0.141-0.466)
	-	92.2%	69.6%		
Hypothyroid	+	5.2%	7.9%	0.345	-
	-	94.8%	92.1%		
Smoking	+	9.7%	5.8%	0.205	-
	-	90.3%	94.2%		
FX of DM	+	36.4%	44.2%	0.148	-
	-	63.6%	55.8%		
INR	>2.5	45%	81.3%	<0.001	0.554 (0.452-0.677)
	<2.5	18.7%	55%		

**Table 4: Report of serum iron and ferritin in term of gender**

Item	Gender	MetS	Mean	SD	p-value
Serum iron	female	yes	101.29	44.45	0.850
		no	102.65	28.88	
	male	yes	109.58	70.09	0.639
		no	111.77	43.17	
Serum ferritin	female	yes	106.52	44.46	0.004
		no	162.21	90.04	
	male	yes	132.73	113.87	0.952
		no	139.41	95.78	

uphold this hypothesis.<sup>22,23</sup>

Mechanisms of the relationship between iron accretion and insulin resistance, as the main pathogenesis of MetS, in patients with NAFLD have been poorly studied. Genetic factors, oxidative stress, cell toxicity, and genotoxicity can predis-

pose iron deposits due to circulatory iron excess. These factors can induce iron storage in hepatocytes and Kupffer/sinusoidal cells.<sup>19,24</sup> In molecular and histopathological point of view, Kupffer cells can accumulate iron via phagocytosis of necrotic hepatocytes, or probably erythrophagocytosis.<sup>24</sup>

Conversely in this study, a significant correlation was obtained between serum ferritin and ALT and also AST indicating for hepatocytes injuries by depositing fat. Also, we found higher levels of hemoglobin and TIBC in MetS group compared with non-MetS group. This finding is in accordance with the mentioned hypothesis. Regularly, these indexes correlate with red blood cell (RBC) count and also erythrophagocytosis. There are some pivotal factors that induce hepatic iron uptake such as deficiency of micronutrients, inflammation, dysregulation of iron trafficking molecules, and hyperinsulinemia. "Insulin stimulates cellular iron uptake through increased externalization of the transferrin receptor in adipocytes".<sup>19,25</sup>

On the other hand, in the adipocyte, the stored iron can affect insulin sensitivity of the cell. Both aforementioned mechanisms can cause unsuppressed lipolysis, and therefore liver is predisposed to fat storage.<sup>26</sup> Stimulation of intestinal iron absorption, by hyperinsulinism and insulin resistance, is the other mechanism for the increase of body iron stores while in the present study we did not find any difference between the amount of storage form of iron, ferritin, between the two groups,<sup>14,27,28</sup> although there was a difference in serum insulin levels between the two groups.

Given the findings of the present study in keeping with previous findings, TIBC (indicator for the transferrin activity) is the sole iron trafficking index that was different between the two groups.<sup>29</sup> As expected, age, blood pressure, BMI, hip/waist ratio, prevalence of DM and coronary artery diseases (CAD), serum TG, and HDL were higher in MetS group compared with non-MetS group. It was previously clarified that patients with MetS with or without other medical conditions, such as NAFLD, are more frequently involved in DM, CAD, hypertension, obesity, and hyperlipidemia which is in line with our findings. Abdominal obesity indicated by high waist/hip ratio albeit is an important risk factor for metabolic disturbances, including fatty liver.<sup>30</sup> After adjusting the confounders, we could not find a significant relationship between abdomi-

nal fat levels and presence of MetS.

But international normalized ratio (INR) as a coagulation status index was different between the two groups. Usually coagulation defect occur when NAFLD leads to cirrhosis while none of the patients suffered from cirrhosis. The sonographic grade of NAFLD was not significantly different between MetS and non-MetS group. The role of iron in coagulation was previously declared,<sup>31</sup> however, we could not precisely associate these two with the difference in INR and iron level in the two groups.

One of the limitations of this study was the lack of pathological and genomic studies to compare MetS and non-MetS groups. To verify this comparison, liver biopsies would be helpful but this is ethically unfeasible since it is unnecessary in patients with uncomplicated NAFLD. The other limitation was lack of further immunological assessments such as inflammatory markers. Ferrannini demonstrated an association between hyperinsulinemia and the excess hepatic iron storage in inflammatory conditions.<sup>32</sup> Over transcriptions of ferritin mRNA in macrophages due to inflammatory cytokine can be responsible for ferritin transfer to hepatocytes.

Consistent with our findings, previous studies that showed a prominent relationship between the presence of MetS and serum iron or ferritin in patients with NAFLD recommended searching for hepatic iron accumulation in biopsy samples of patients with NAFLD, even in cases with normal serum iron, ferritin, and transferrin.<sup>33</sup> Conversely, Choi and colleagues, evaluated serum ferritin and aminotransferases among 994 post menopause women. They found that women with MetS had a higher level of serum ferritin compared with women without MetS.<sup>34</sup> Many other studies indicated a probable relationship between NAFLD as one of the manifestations of MetS and serum level of ferritin.<sup>35-38</sup> But, consistent with our findings, Freixenet and co-workers also demonstrated that iron level had no correlation with existing DM and MetS.<sup>39</sup> Moreover, this difference between the findings of various reports can be due to sociodemographic varieties. Therefore, if an adapted cut point is deter-

mined for every population, a significant relationship may be obtained. Although we could not find a similar relationship, but we found that serum level of ferritin in patients with NAFLD and MetS was above 125-130.

Our findings did not show a significant relationship between iron, in free or storage form, and the presence of MetS among patients with NAFLD, but serum ferritin can correlate with hepatocytes injuries indicated by raised aminotransferases. Nevertheless, to clarify this relationship further molecular, genomic, and histopathological studies are required.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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