Razavi Int J Med. 2021; 9(3):e845 doi:10.30483/rijm.2021.249754.0

Published online 2021 September **Original Article**

The evaluation of metabolic syndrome in patients diagnosed with non-alcoholic fatty liver disease (NAFLD): a cross-sectional study of Iranian population

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Received 2020 April 29; **Accepted** 2021 June 29.

Abstract

Background and Objectives: This study aimed to assess the epidemiological aspects of nonalcoholic fatty liver disease (NAFLD) in an Iranian population and evaluate the relationship between NAFLD and metabolic syndrome.

Materials and Methods: This cross-sectional study was conducted on 145 subjects who were diagnosed with NAFLD and referred to the Gastroenterology Clinic of Ghaem Hospital, Mashhad, Iran in 2013. Ultrasonography was used to diagnose NAFLD as a fatty liver manifestation in the absence of other liver complications. Moreover, the National Cholesterol Education Program Adult Treatment Panel III criteria (ATP III) was used as a guideline to establish metabolic syndrome diagnosis.

Results: Metabolic syndrome had an overall prevalence of 49.7% among the subjects. The results showed no difference between the groups of patients with and without metabolic syndrome in terms of the mean levels of aspartate transaminase (AST) and alanine transaminase (ALT) . The results did not reveal any association between our targeted liver enzymes (AST and ALT) and different features of metabolic syndrome. In multivariate linear regression models, the presence of metabolic syndrome was unable to predict AST (P=0.631, r2=0.002) or ALT (P=0.122, r2=0.017) abnormalities.

Conclusion: The results indicated a high prevalence of metabolic syndrome in Iranian patients who were diagnosed with NAFLD. Contrary to previous reports, it was found that despite the high prevalence of metabolic syndrome conditions in NAFLD patients, the presence of metabolic syndrome did not increase the risk of NAFLD in the participants of this study.

Keywords: ALT, AST, Fatty Liver Disease, Non-Alcoholic fatty liver disease (NAFLD), Metabolic Syndrome

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most frequent chronic liver complication that is characterized as a lipid disposition in the liver parenchyma and persistent abnormality in liver enzymes levels in patients without a history of alcohol consumption (1). It should be mentioned that this disease is common in 20-30% of the general population (2). The NAFLDs include a broad range of liver disorders varying from benign hepatocellular steatosis to severe cryptogenic cirrhosis (3, 4). The NAFLD can occur in both children and adults and has the same incidence rate in both genders. The highest impact of the disease has been reported in the age range of 40-49 years old (5). The initial stages of the disease are asymptomatic and also the diagnostic tests are inaccurate; therefore, its early detection is difficult (6).

The gold standard method for diagnosis of NAFLD is a liver biopsy (7). Due to its invasive nature, a combination of different risk factor assessments, laboratory findings, and imaging techniques (ultrasonography is the most common technique due to its availability, low cost, and non-invasive nature) are commonly used for timely and accurate diagnosis of NAFLD (3, 8). The most significant risk factors of NAFLD are different features of metabolic syndrome which consist of obesity (body mass index [BMI]≥30kg/m2), glucose intolerance (9), or diabetes (fasting blood sugar [FBS]≥100mg/dL), hypertension (blood pressure>130/85mmHg), dyslipidemia, particularly elevated triglycerides (≥150mg/dL), and low levels of high-density lipoprotein cholesterol (HDL-C≤40 mg/dL in men and ≤50 mg/dL in women) (10, 11). The most notable risk factors for NAFLD and its progression to non-alcoholic steatohepatitis are insulin resistance, obesity, and old age (3, 9, 11).

Regarding the high prevalence of the risk factors of metabolic syndrome among the Iranian population, a high incidence of NAFLD accompanied with metabolic syndrome is expected among them. According to a report from northern Iran, the prevalence rate of NAFLD and

metabolic syndrome were 43.8% and 29.6%, respectively (12). In another study conducted in southern Iran, NAFLD was diagnosed in 21.5% of the subjects, where all features of metabolic syndrome were more prevalent in NAFLD patients, compared to the non-NAFLD subjects (13). These reports indicated a broad prevalence of NAFLD in Iran, emphasizing the necessity of further assessment of the disease and its leading risk factors among the Iranian population. The present study aimed to assess the epidemiological aspects of NAFLD in a group of patients from Northeast of Iran and evaluate the relationship of NAFLD with metabolic syndrome and its primary features.

2. Materials and Methods

Study subjects

This cross-sectional study was conducted on 145 subjects who were diagnosed with NAFLD and referred to the Internal Medicine Clinic of Ghaem Hospital, Mashhad, Iran in 2013. Patients with 1) chronic liver diseases, 2) positive HBsAg or HBCAb, 3) autoimmune hepatitis or Wilson disease, 4) alcohol consumption, and 5) cognitive disorders were excluded from the study.

Transabdominal ultrasonography

The NAFLD was diagnosed as a fatty liver manifestation in the absence of other liver complications. In this technique, hyperechogenicity of the liver parenchyma relative to the adjacent right kidney or spleen is interpreted as the diffuse fatty liver. Focal fat deposition is characterized as a hyperechoic area in the liver while focal fat sparing is diagnosed as a hyperechoic area in the diffused hyperechoic liver parenchyma.

Questionnaire and physical examination

Written informed consent was obtained from the patients, and a checklist was used to determine baseline characteristics and clinical data of all participants. Afterward, all participants underwent a physical examination to measure their anthropometric parameters.

Laboratory findings

For the purposes of the study, 10 mL of 12-h fasting venous blood sample was taken to measure biochemical parameters, including FBS, insulin level, lipid profile, and liver enzymes.

Metabolic syndrome assessment

The patients were divided into two groups based on the presence and absence of metabolic syndrome. In this study, metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria (ATP III) (14) concerning the presence of any three out of the five following risk factors:

1. Fasting blood sugar ≥ 100 mg/dL
2. Waist circumference > 102 cm in men and > 88 cm in women or BMI ≥ 30 kg/m2 in both gender
3. Serum triglyceride ≥ 150 mg/dL
4. HDL-C < 40 mg/dL in men / < 50 mg/dL in women
5. Blood pressure ≥ 130/85 mmHg

3. Results

The mean age of participants was 46.99±12.04 years old, and 53.1% of them were male. There was a significant difference in the mean age of male (42.58±11.87 years) and female (51.99±10.19 years) participants (P=0.000). The mean BMI of the subjects was 30.10±10.09 kg/m2, and 13.8% of them had normal BMI (<25kg/m2). Moreover, 46.2% of them were overweight (25-29.9kg/m2), and 40% of them were obese (>30kg/m2). There was no difference between the BMI values of male and female participants (P=0.089).

Abnormal ALT and AST levels were seen in 60.7% and 25.5% of participants, respectively. Both ALT (P=0.001) and AST (P=0.001) levels were significantly higher in males than females. Regarding the lipid profile, hypercholesterolemia, hypertriglyceridemia, high LDL-C levels, low HDL-C levels, and hypertension were found in 25.4%, 40%, 20.8%, 42.4%, and 29.6% of the participants, respectively. Moreover, the FBS values of 52.6%, 26.3%, and 21.2% of the participants were below 100 mg/dl, within the range of 101-125mg/dl, and ≥126mg/dl, respectively (Table 1).

Table 1. Demographic data and lab results of the patients diagnosed with fatty liver

	Male			Female				Total		
	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD
Age	77	42.58	11.87	68	51.99	10.19	0.000*	145	46.99	12.04
Height	77	173.90	9.92	68	158.24	6.21	0.000*	145	166.55	11.46
Weight	77	88.47	16.93	68	76.16	13.50	0.000*	145	82.70	16.55
AST	77	36.87	23.42	68	27.53	16.96	0.000*	145	32.49	21.10
ALT	77	56.22	38.18	68	32.32	24.17	0.000*	145	45.01	34.41
TC	75	213.97	52.20	67	218.91	41.34	0.464	142	216.30	47.29
LDL-C	77	124.16	35.38	67	126.57	34.19	0.711	144	125.28	34.74
BMI	77	29.95	12.93	68	30.27	5.40	0.089	145	30.10	10.09
FBS	73	106.26	36.72	64	116.64	32.86	0.014*	137	111.11	35.23
TG	77	238.52	207.92	68	199.63	102.61	0.576	145	220.28	167.61
HDL-C	77	44.65	10.33	67	47.40	14.31	0.347	144	45.93	12.37
SBP	72	130.76	17.85	63	133.65	19.72	0.523	135	132.11	18.73
DBP	72	92.29	9.82	63	93.33	11.14	0.636	135	92.78	10.43

***significant p-value < 0.05, AST:** aspartate transaminase, **ALT:** alanine transaminase, **TC:** total cholesterol, **LDL-C:** low-density lipoprotein cholesterol, **BMI:** body mass index, **FBS:** fasting blood sugar, **TG:** triglycerides, **HDL-C:** high-density lipoprotein cholesterol, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure

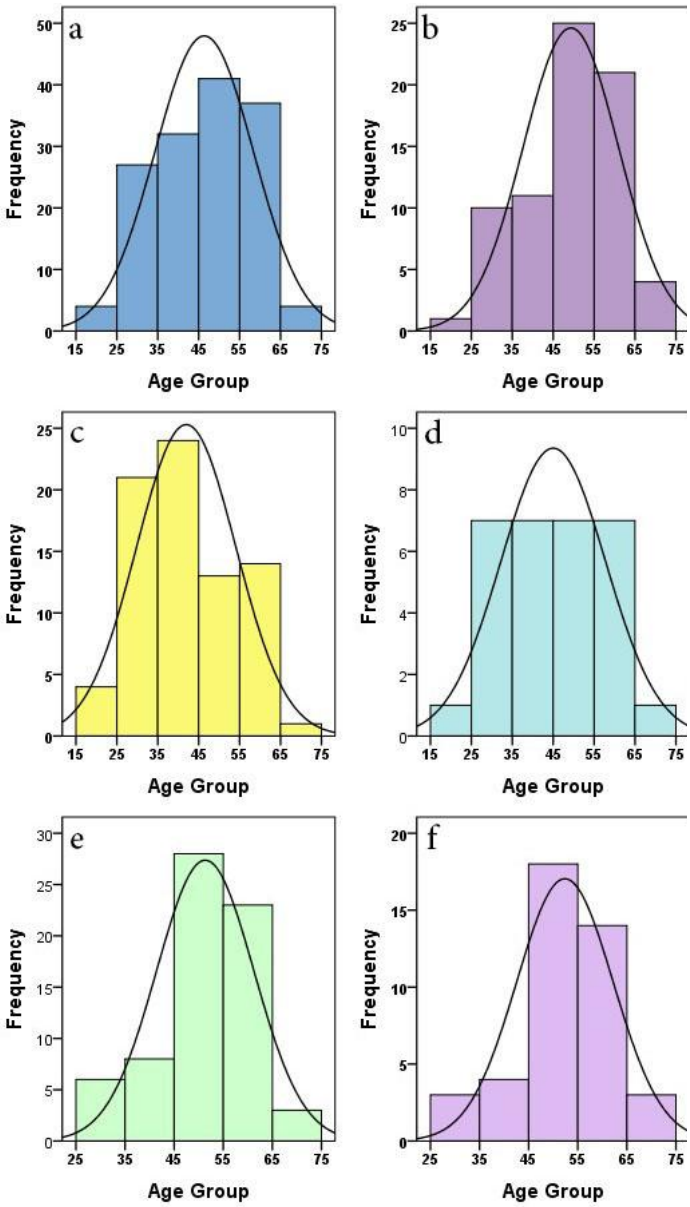

Figure 1. a: Age distribution of nonalcoholic fatty liver disease (NAFLD) in all subjects**. b:** Age distribution of metabolic syndrome in all subjects. **c:** Age distribution of NAFLD in Male subjects. **d:** Age distribution of metabolic syndrome in male subjects. **e:** Age distribution of NAFLD in female subjects**. f:** Age distribution of metabolic syndrome in female subjects

According to the ATP III criteria, the overall prevalence of metabolic syndrome was calculated at 49.7%. Moreover, the results indicated that patients with metabolic syndrome were older, compared to others (50.06±11.75 v.s. 43.97±11.62, P=0.003). Moreover, metabolic syndrome was more prevalent in females, compared to males (30 males v.s 42 females, P=0.001). In addition, it was found that patients with metabolic syndrome had higher mean BMI (P=0.000), lower HDL level (P=0.000), higher FBS (p=0.000), higher triglyceride (P=0.000), and higher systolic blood pressure (P=0.005) (Table 2).

Regarding gender, the findings indicated that both NAFLD and metabolic syndrome were more prevalent in the age group of 45-65 years in the general population (Figure 1: a and b). However, we found different results when we divided subjects by gender (Figures 1 c, d, e, and f). In male subjects, NAFLD was more prevalent in the age group of 25-45 years. However, the prevalence of metabolic syndrome in male subjects did not follow this pattern and was the same in the age group of 25-65 years. Moreover, in female subjects, both NAFLD and metabolic syndrome were more prevalent in the age group of 45-65 years.

As can be seen in Table 3, we also divided subjects with metabolic syndrome by gender and found that the age range of female patients was significantly higher than that of male patients (53.40±9.74 years old v.s. 45.37±12.85 years, P=0.004). Moreover, the range of AST was normal in both genders, while the mean value of ALT was significantly higher in males, compared to females (49.57±27.57 U/L v.s. 34.12±26.74 U/L, P=0.001). In addition, female subjects had higher levels of FBS than men and the mean FBS of women was in the diabetic range (128.05±33.27 mg/dL v.s. 118.86±47.13 mg/dL, P=0.040). Finally, women had a significantly higher HDL-C, compared to men (43.44±9.20 mg/dL v.s. 41.07±11.20 mg/dL, P=0.046)

but, notably, the mean HDL-C of men was in the normal range while that of women was lower than the normal range.

Results of the present study did not reveal a significant relationship between liver enzymes (AST and ALT) and different conditions of metabolic syndrome. In multivariate linear regression models, the presence of metabolic syndrome was unable to predict AST (p=0.631, r2=0.002) or ALT (p=0.122, r2=0.017) abnormalities while we set gender and age as the baseline confounders. However, old and female subjects were found to have higher ALT enzyme levels.

Table 2: Demographic data and lab results of patients diagnosed with fatty liver while divided based on metabolic syndrome

Metabolic Syndrome	Positive			Negative			
	N	Mean	SD	N	Mean	SD	p-value
Age	72	50.06	11.75	73	43.97	11.62	0.003*
Hight	72	164.11	11.93	73	168.96	1052	0.015*
Weight	72	85.40	18.27	73	80.03	14.29	0.044*
AST	72	31.64	20.53	73	33.33	21.75	0.719
ALT	72	40.56	27.97	73	49.41	39.47	0.276
TC	71	221.66	46.38	71	210.94	47.90	0.076
LDL-C	71	130.25	38.21	73	120.44	30.47	0.068
BMI	72	32.41	13.50	73	27.83	3.67	0.000*
FBS	69	124.19	39.62	68	97.84	23.88	0.000*
TG	72	227.32	92.04	73	213.34	218.49	0.000*
HDL-C	71	42.44	10.09	73	49.33	13.64	0.000*
SBP	66	136.89	18.82	69	127.54	17.58	0.005*
DBP	66	94.39	10.97	69	91.23	9.71	0.112

***significant p-value < 0.05, AST**: aspartate transaminase, **ALT:** alanine transaminase, **TC:** total cholesterol, **LDL-C:** low-density lipoprotein cholesterol, **BMI:** body mass index, **FBS:** fasting blood sugar, **TG:** triglycerides, **HDL-C:** high-density lipoprotein cholesterol, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure

Table 3. Demographic data and lab results of the patients diagnosed with fatty liver and metabolic syndrome

	Male			Female				Total		
	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD
Age	30	45.37	12.85	42	53.40	9.74	0.004*	72	50.06	11.75
Hight	30	172.10	13.63	42	158.40	6.76	0.000*	72	164.11	11.93
Weight	30	92.47	21.21	42	80.36	14.04	0.001*	72	85.40	18.27
AST	30	34.37	22.27	42	29.69	19.24	0.056	72	31.64	20.53
ALT	30	49.57	27.57	42	34.12	26.74	0.001*	72	40.56	27.97
TC	29	216.83	46.82	42	225.00	46.53	0.470	71	221.66	46.38
LDL-C	30	126.13	41.29	41	133.27	36.01	0.441	71	130.25	38.21
BMI	30	33.10	20.04	42	31.92	5.57	0.073	72	32.41	13.50
FBS	29	118.86	47.13	40	128.05	33.27	0.040*	69	124.19	39.62
TG	30	241.03	94.42	42	217.52	90.15	0.084	72	227.32	92.04
HDL-C	30	41.07	11.20	41	43.44	9.20	0.046	71	42.44	10.09
SBP	27	136.85	17.71	39	136.92	19.79	0.896	66	136.89	18.82
DBP	27	94.26	10.44	39	94.49	11.46	0.921	66	94.39	10.97

***significant p-value < 0.05, AST:** aspartate transaminase, **ALT:** alanine transaminase, **TC:** total cholesterol, **LDL-C:** low-density lipoprotein cholesterol, **BMI:** body mass index, **FBS:** fasting blood sugar, **TG:** triglycerides, **HDL-C:** high-density lipoprotein cholesterol, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure

4. Discussion

Despite previous reports, about half of the participants of this study who were diagnosed with NAFLD also suffered from metabolic syndrome. It was found that the incidence of metabolic syndrome was associated with gender and age as it was more common in old and female subjects. When we divided patients with both NAFLD and metabolic syndrome based on gender, we found that NAFLD was more prevalent in men and women within the age ranges of 25-45 and 45-65 years, respectively. Moreover, it was revealed that the prevalence of metabolic syndrome had the same pattern as NAFLD in female subjects (highest incidence rate in the age range of 45-65 years). However, this was not the case with the NAFLD distribution pattern in male subjects which had the same incidence rate in the age group of 25-65 years.

In the previous research performed by Kotronen et al. (15), Chen et al. (16), Hamaguchi et al. (17), Uchil et al. (18), and Fattahi et al. (19), it was found that 33%, 21%, 21-33%, 47%, and 65% of the studied subjects with NAFLD had metabolic syndrome. These results are reported from different regions of the world, and we assume that the incidence rate of metabolic syndrome in NAFLD patients is race-dependent. Nevertheless, the incidence rate reported by Fattahi et al. (19) in the Iranian population was still about 15% higher than that of the present study which was also conducted in Iran.

Based on the results of this study, in subjects below 45 years old, NAFLD was more prevalent in men than women mostly due to the protective effects of estrogen in women. Fan et al. (20), Hu et al. (21), and Eguchi et al. (22) also reported similar results, but they did not expand their data to check the prevalence of metabolic syndrome in their subjects as well. In this study, it was also found that the age distribution of metabolic syndrome was similar to that of NAFLD in female patients. However, this was not the case with the NAFLD distribution pattern in male subjects which had the same incidence rate in the age group of 25-65 years.

It can be assumed that like NAFLD, metabolic syndrome development in women is dependent on their sex hormones status as they develop this syndrome more often when they enter the menopausal phase of their lives. Nevertheless, in the case of men, the development of NAFLD is more prevalent during the early stages of their lives (25-45 years old) that also count as their sexually active years during which testosterone (that counters estrogen) is at its highest levels. However, the prevalence of the metabolic syndrome is not dependent on their hormonal status and maybe is more related to their lifestyle.

As clearly shown in this study, obesity, assessed by BMI higher than 30 kg/m2, effectively increased the risk of metabolic syndrome in NAFLD patients. Marchesini et al. reported in two independent studies that the incidence of metabolic syndrome increased from 18% (in people with normal BMI) to more than 67% in the patients who had a BMI of more than 30kg/m2. According to the above-mentioned reports, progression to NAFLD was also associated with different features of metabolic syndrome (23, 24).

In the present study, 40.0%, 21.2%, and 29.6% of patients were obese, diabetic, and hypertensive, respectively. Moreover, hypercholesterolemia and hypertriglyceridemia were found in 25.4% and 40.0% of the study participants, respectively. In a study carried out by Cortez-Pinto et al., type two diabetes mellitus was reported in 33% of patients with NAFLD (25). Results of another study performed on the Japanese population by Donati et al. revealed that the prevalence rates of NAFLD were 43% and 62% in individuals with impaired fasting glucose and type two diabetes mellitus, respectively. They also reported that hypertriglyceridemia and low HDL-cholesterol level were seen in 64% and 30-42% of patients with NAFLD, respectively, which is higher than the results of the present study in the case of hypertriglyceridemia and the same as our data in the case of HDL-C (26). They also reported that the prevalence rate of fatty liver in non-obese and non-diabetic patients with primary hypertension was more than two-fold higher than the control group (26).

Despite the higher prevalence of the metabolic syndrome features in NAFLD patients, compared to the healthy population, the results of this study did not indicate an association between metabolic syndrome and the incidence of NAFLD. In fact, by investigating gender and age, the presence of metabolic syndrome could not predict the incidence of NAFLD assessed by the increased level of liver enzymes.

The obtained results could have been due to the lack of a definition of metabolic syndrome based on the characteristics of the study population. In other words, it might be necessary to modify the definitive conditions of metabolic syndrome in compliance with the characteristics of individuals. However, some previous studies introduced metabolic syndrome as a potential risk factor for NAFLD. In a prospective observational study performed on 4401 healthy individuals, Hamaguchi et al. found that the metabolic syndrome is counted as a substantial risk factor for NAFLD where participants with the metabolic syndrome had a 4-11-folds higher risk of having NAFLD (17).

Furthermore, Hsiao et al. demonstrated a significant correlation between the presence of the severe fatty liver condition and the prevalence and degree of hypertension, abnormal glucose, and triglyceride metabolism (27). Therefore, considering the significantly higher prevalence of metabolic syndrome conditions in NAFLD patients, the higher likelihood of metabolic syndrome in these patients can be predictable.

5. Conclusion

Results of this study showed the high prevalence rate of metabolic syndrome in Iranian NAFLD patients which was within the global range. However, contrary to previous reports, despite the high prevalence of metabolic syndrome features, the presence of metabolic syndrome could not predict the risk for NAFLD in this study, which needs further investigations.

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