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Non-alcoholic Fatty Liver Disease and its Predictive Factors Among High-Risk Employees of Health Insurance Organization in Tabriz, Iran

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Abstract

Objective: Non-alcoholic fatty liver disease (NAFLD) has been known as the most frequent type of liver disease, with the occurrence of 20% to 30% in developed countries and 33.9% in Iran. In this study, we aimed to evaluate the prevalence of fatty liver among high-risk individuals and its predictive factors.

Materials and Methods: This analytic cross-sectional study was performed on 70 men and women, aged 32–62 and BMI ≥25, who were divided into 2 groups: 1) the patient group (n = 45) with positive results of fatty liver disease, and 2) the healthy group (n=25). An anthropometry assessment (weight and BMI), blood tests (AST, ALT, FBS, TC, and TG), and determination of fatty liver grade were done.

Results: In our study, the rate of NAFLD was 64 among 100 susceptible individuals (BMI ≥25).

We found significant differences in sex ($P=0.020$), weight ($P<0.001$), BMI ($P=0.001$), AST ($P<0.001$), ALT ($P<0.001$), and AST/ALT ($P<0.025$) between the groups. A direct association was observed between the increase in BMI and NAFLD ($P=0.001$). In the study of relationship between fatty liver grade, BMI, and biochemical factors, there were significant differences in mean BMI, weight, AST, ALT, and AST/ALT between patients with NAFLD grades 1 and 3. However, no significant changes were observed for FBS, TC, and TG between patients with NAFLD grades 1, 2 and 3. Sex, BMI and AST were estimated as independent predictors of NAFLD. The risk of NAFLD increased in male sex ($P=0.053$), by the increment of BMI ($P=0.002$) and AST ($P=0.002$) in the study.

Conclusion: This study verified the relationship between NAFLD and obesity, and liver aminotransferase was repeatedly reported in NAFLD.

Keywords: Prevalence, Predictive factors, NAFLD

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a phrase used to define a wide range of conditions to describe macrovesicular hepatic steatosis in non-alcoholic people (1). In the classic form of NAFLD, liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are increased; and negative viral, inherited, and autoimmune test results are observed (2).

Fatty liver is characterized as the hepatic indication of the metabolic syndrome (3-6). The source of fats accumulating in the liver is still unclear. Thus, diagnosing this cause will be remarkable in preventing this feature.

NAFLD is one of the main causes of liver disease, and its prevalence in developed countries is 20% to 30%. Its incidence has significantly increased during the past years due to the growth of obesity in western societies (7). It is evaluated that 33.9% of the Iranian people have NAFLD (8).

Obesity, type II diabetes mellitus, and hyperlipidemia are intertwined with NAFLD (9). A straight relationship is observed between the intensity of obesity and frequency and intensity of NAFLD. NAFLD is 4.6 times higher in obese people (10).

NAFLD affects every age range and is characterized in most ethnics. Some studies believe NAFLD is more common among adult woman; but others claim it is more common in males in comparison to females (11-13).

In NAFLD patients, the seldom laboratory abnormality is mild to moderate increase in serum aminotransferases (ALT, AST). The AST/ALT ratio is a useful measurement for distinguishing NAFLD from alcoholic liver disease (14). In most cases of NAFLD, the AST/ALT ratio is less than 1. Prognosis of liver disease to cirrhosis increases the AST/ALT ratio, which could not be further used as a

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diagnostic measure in cirrhosis (15).

In the present study, authors investigated the rate of NAFLD and its association with some of the biochemical factors (AST, ALT, fasting blood sugar [FBS], total cholesterol [TC], and triglyceride [TG]), weight and body mass index (BMI) in high risk participants who had BMI ≥25. The inefficiency of medication in treating NAFLD/NASH (nonalcoholic steatohepatitis) and its high prevalence provoked us to accomplish research in this field, specifically among susceptible population. Therefore, the aim of this study was to evaluate NAFLD and its predictive factors among high-risk employees of Health Insurance Organization in Tabriz, Iran.

Materials and Methods

The present analytic cross-sectional study was accomplished in the summer, 2016. Participants were recruited from the employees of Health Insurance Organization in Tabriz, Iran. All Tabriz Health Insurance employees were 248. The research population included 88 eligible staff. Sampling was performed according to purposive sampling method and the research sample (n = 70) was selected from among the eligible participants who completed the informed consent form of the study. The inclusion criteria were as follows: men and women aged 32–62 who had BMI ≥25. The exclusion criteria were as follows: pregnant and lactating women; individuals with cardiovascular, thyroid, diabetes, kidney, hepatitis, inflammatory, or autoimmune disease; use of vitamin supplements including vitamins A, E, and C; and alcohol consumption. Seventy subjects were divided into 2 groups: in general, 45 patients with a positive ultrasound result for fatty liver disease were considered as patient group. The healthy group (n = 25) enrolled patients with a negative ultrasound result. The study was registered according to the letter No. 95/357757 dated 8/10/95, from the Director of the Office of Statistics and Budget Planning of the Health Insurance Organization.

Measurements

All of the measurements including anthropometry assessment, blood tests, and determination of fatty liver grade were done.

Anthropometry Assessment

Each patient's height and weight were measured by standard anthropometric equipment (16). Body weight was measured with minimum clothing (nearest 0.5 kg) using a Seca scale (Seca, Hamburg, Germany). Height was recorded to the nearest 0.1 cm (without shoes) using Seca stadiometer. The BMI was calculated using the following formula: [BMI = weight (kg)/height^2 (m^2)].

Biochemical Parameters

Blood samples were obtained by venipuncture. Sera were obtained, after that samples were completely clotted by centrifugation at 2000 × g for 10 minutes. After liquidating sera, the tubes were stored at -70°C, until some of the biochemical factors of serum were measured.

TC, TG, FBS, AST, and ALT were measured by PARS AZMUN (Tehran, Iran) kits using auto analyzer machine (Alcyon 300, abbott, USA).

Ultrasonography

The liver ultrasound was accomplished by a specialist at the Ultrasonic Center of Tabriz University of Medical Sciences. The size, echogenicity and structure of the liver were assessed and the penetration of the ultrasound beam was measured (Medison Sonoace x6). A normal liver echo texture indicated a normal liver, without steatosis (grade 0). It is noteworthy to mention that NAFLD is classified into 3 subscale grades (grade I, II, and III) based on echogenicity, beam penetration, and portal vessel wall distinction (17).

Statistical Analysis

The Kolmogorov–Smirnov test was used for assessing data normality. Data were expressed as mean ± SD for continuous variables. Comparison between groups was evaluated by independent samples *t* test for quantitative and chi-square test or Fisher exact test for qualitative variables. Kruskal-Wallis test was used for comparison of classified BMI between groups. To evaluate correlations between fatty liver grade and biochemical markers, analysis of variance (ANOVA) test was used. To predict the association between NAFLD and some of the general, anthropometric, and serum measurements which had $P < 0.02$ in bivariate statistical tests, backward logistic regression was used. Classification for 3 classes of BMI was derived through Kruskal-Wallis Test.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (version 22.0; SPSS Inc, Chicago, IL, USA). In this study, $P < 0.05$ was considered significant.

Results

Anthropometric and Demographic Results

In our study, rate of non-alcoholic fatty liver was 64 among 100 high-risk individuals with BMI ≥25 kg/m^2. In total, 70 participants (65.7% male, 97.1% married) were divided into patient and healthy groups. The average ages and BMIs of the participants were 42.71 ± 5.76 years (32–62 years) and 29.79 ± 3.39 kg/m^2 (25.0–39.90 kg/m^2), respectively (mean ± SD and range). There were no significant differences in the age and marital status between the groups. We found significant differences in sex ($P = 0.020$), weight ($P < 0.001$), and BMI ($P = 0.001$) between the groups in the study (Table 1).

Serum Biochemical Factors

Serum AST concentration was higher in NAFLD participants compared to healthy ones (26.37 U/L vs. 19.80 U/L, respectively; $P < 0.001$). The mean concentrations of ALT were significantly different between NAFLD

Table 1. Demographic and Anthropometric Data of the Study Subjects

Variables	Patient (n = 45)	Healthy (n = 25)	Total(n = 70)	*P* Value
Sex, No. (%)				
Male	34 (75.6)	12(48)	46 (65.7)	0.020[ab]
Female	11 (24.4)	13(52)	24 (34.3)	
Marital status, No. (%)				0.534[d]
Single	2 (4.4)	0	2 (2.9)	
Married	43 (95.6)	25 (100)	68 (97.1)	
Age (y)	43.20 ± 6.33	41.84 ± 4.55	42.71 ± 5.76	0.348[c]
BMI (kg/m^2)	30.75 ± 3.41	28.06 ± 2.64	29.79 ± 3.39	0.001[ac]
Weight (kg)	87.04 ± 10.63	78.39 ± 7.78	83.95 ± 10.52	<0.001[ac]

Abbreviation: BMI, body mass index.
Data are expressed as mean ± SD before and after intervention.
[a] *P*<0.05 considered as significant,
[b] *P* values for differences between groups derived through Pearson Chi-squared test.
[c] *P* values for differences between groups derived through independent-samples *t* test.
[d] Fisher exact test.

and healthy participants (41.91 U/L vs. 27.96 U/L, respectively; $P<0.001$)). Moreover, mean AST/ALT ratio was significantly different between NAFLD and healthy participants (0.67 vs. 0.78, respectively; $P=0.025$). There were no significant differences in FBS, TC and TG between the groups (Table 2).

Association Between BMI and Risk of NAFLD

Among 39 overweight subjects (BMI = 25-29.9), 48.55% had NAFLD. Among 24 class I obese participants (BMI = 30-34.9), 79.2% had NAFLD and among 7 subjects with obesity class II (BMI = 35-39.9), 100% had NAFLD. There were significant differences between the groups in the frequency of subjects in a different classification of over normal BMI ($P=0.001$, Table 3). In other words, there was a direct relationship between the increase in BMI and NAFLD.

Association of Fatty Liver Grade With BMI and Some of Biochemical Factors

Among patients with NAFLD, the mean BMI in patients with NAFLD grade 1, grade 2, and grade 3 were 29.37, 33.63, and 35.25 kg/m^2 respectively, indicating that there were significant differences in mean BMI between the patients with NAFLD grades 1 and 3. However, the mean weight in patients with NAFLD grade 1, grade 2, and grade 3 was 82.80, 91.37, and 94.12 kg respectively. There were significant differences in mean BMI between the patients with NAFLD grades 1 and 3. The mean AST and ALT levels in patients with NAFLD grade 1 were 23.66 U/L and 35.29 U/L, grade 2 were 30.76 U/L and 52.58 U/L, and grade 3 were 24.00 U/L and 36.25 U/L respectively, showing significant differences in mean AST and ALT levels in patients with NAFLD grades 1 and 3. Furthermore, the mean AST/ALT ratio between the patients with NAFLD grade 1, grade 2, and grade 3 were 0.72. 0.60, and 0.68 respectively, confirming significant differences in mean AST/ALT ratio between the patients with NAFLD grades 1 and 3. However, there were no significant differences in mean FBS, TC, and TG levels between the patients with NAFLD grades 1, 2, and 3.

Table 2. Serum Biochemical Factors in Patients With Non-alcoholic Fatty Liver and Healthy Subjects

Variables	Patient (n = 45)	Healthy (n = 25)	*P* Value*
AST (U/L)	26.37±6.66	19.80±5.01	<0.001[a]
ALT (U/L)	41.91±15.76	27.96±13.31	<0.001[a]
AST/ALT	0.67±0.15	0.78±0.21	0.025[a]
FBS (mg/dL)	84.64±9.15	82.28±6.34	0.256
TC (mg/dL)	190.64±34.97	197.52±42.44	0.468
TG (mg/dL)	196.00±90.31	177.80±80/74	0.405

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride.
Data are expressed as mean± SD.
* *P* values for differences between groups derived through independent-samples t test.
[a] *P*<0.05

Predictive Factors for NAFLD

In the present study, sex, BMI, and AST were estimated as independent predictors for NAFLD.

The results showed that in male sex, the risk of NAFLD increased; so, for each man versus the woman, the risk of NAFLD increased by 3.8 times ($P=0.053$). Moreover, the results showed that a 1 unit increase in BMI increased the risk of NAFLD by 1.5 times, ($P=0.002$). However, a 1 unit increase in AST increased the risk of NAFLD by 1.2 times ($P=0.002$).

Additionally, there were no significant association between NAFLD and ALT, AST/ALT and FBS serum levels (Table 5).

Discussion

This study intensified the relationship between NAFLD and Obesity, liver aminotransferase, and hyperlipidemia. Present study showed that there were significant

Table 3. Association Between BMI and Occurrence of NAFLD

Classification of BMI		Group		Total	*P* Value
		Patient (n = 45)	Healthy (n = 25)		
1.00	Count	19	20	39	0.001[a]
	% within BMI	48.7	51.3%	100.0%	
2.00	Count	19	5	24	
	% within BMI	79.2	20.8	100.0	
3.00	Count	7	0	7	
	% within BMI	100.0	0.0	100.0	
Total	Count	45	25	70	
	% within BMI	64.3	35.7	100.0	

P Values values for 3 classes of BMI derived from Kruskal-Wallis test. * $P < 0.05$
BMI 1 = Overweight (BMI 25-29.9).
BMI 2 = Obesity class 1 (BMI 30-34.9).
BMI 3 = Obesity class 2 (BMI 35-39.9).

Table 4. Association of Fatty Liver Grade With BMI and Some of Biochemical Factors in Patients With NAFLD

Variables	Grade 1 (n = 24)	Grade 2 (n = 17)	Grade 3 (n = 4)	*P* Value
BMI ((kg/m^2)	29.37±2.95[a]	33.63±2.72[b]	35.25±4.21[ab]	0.001*
Weight (kg)	82.80±8.56[a]	91.37±10.86[b]	94.12±12.24[ab]	0.012*
AST (U/L)	23.66±6.04[a]	30.76±5.67[b]	24.00±4.96[ab]	0.001*
ALT (U/L)	35.29±13.94[a]	52.58±13.53[b]	36.25±11.84[ab]	0.001*
AST/ALT	0.72±0.18[a]	0.60±0.08[b]	0.68±0.10[ab]	0.044*
FBS (mg/dL)	81.75±5.78	87.52±12.15	89.75±5.90	0.066
TC (mg/dL)	192.04±38.35	186.35±30.33	200.50±38.82	0.745
TG (mg/dL)	194.83±78.09	187.35±99.40	196.00±90.31	0.588

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride.
Data are expressed as mean ± SD.
Data with different superscript letters are significantly different ($P<0.05$) from the ANOVA statistical analysis.

Table 5. Logistic Regression Model for Independent Variables as Predictive Factors for NAFLD

Variables	OR (95% CI)	*P* Value
Sex	3.878 (0.987 to 15.279)	0.053
BMI	1.502 (1.163 to 1.940)	0.002
AST	1.222 (1.075 to 1.389)	0.002
ALT	0.916 (0.744 to 1.127)	0.407
AST/ALT	0.378 (0.011 to 13.376)	0.593
FBS	1.01 (0.911 to 1.119)	0.853

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride.
Hosmer–Lemeshow test: chi-square (8)=14.307, $P = 0.074$

differences in sex, weight, and BMI between the NAFLD and healthy groups, but there were no significant differences in the age and marital status. This result was in line with the result of Loomis et al. They reported that there was a significant and constant association between BMI and NAFLD/NASH diagnosis. They also highlighted the significance of weight loss strategies in NAFLD prevention and management (18). In the study of Cheng et al, it was also reported that female sex is not a risk for NAFLD. According to records, in Asia-Pacific region, men are more affected than women (19).

It is assumed that the differences in the prevalence and severity of NAFLD based on gender is related to differences of central obesity, adipose distribution, adipocytokines, and sex hormones (20).

Inconsistent with our study, in another study, age was shown as an independent risk factor for developing a more severe NAFLD or hepatitis fibrosis, with advancing age linked to an increased risk of death (21). NAFLD is observed in any age and is prevalent in most ethnics. In general, age is directly associated with NAFLD.

The study showed that serum AST and ALT concentrations were higher in NAFLD participants compared to healthy ones, but there were no significant differences in FBS, TC and TG levels between the groups. Similar and contradictory results were seen in the study of Amarapurkar et al. They reported that increase in FBS, AST, and ALT serum levels were the risk factors for NAFLD (22).

Inconsistently previous study based on liver enzymes screening reported a lower prevalence of NAFLD (3%–12%) than other studies (23).

In the present study, sex, BMI, and AST were estimated as independent predictors of NAFLD.

Different results were reported in several studies in this field. Normal levels of liver enzymes were demonstrated

in subjects with the entire spectrum of NAFLD, and therefore, ALT and AST were not very useful in predicting NAFLD (24).

Inconsistent with our study, it was reported in a study that increased fasting blood glucose and serum triglyceride levels were predictors of NAFLD (25).

In a case–control cohort study on the employees of Shanghai Bao-Steel Group, mean ALT values in NAFLD patients were lower in comparison to baseline. Furthermore, no complications of cirrhosis were reported (26). Recently, Adams et al demonstrated that with a significant variability in the rate of development, fibrosis gradually increased among NAFLD patients. Variations in ALT level were not consistent with the stages of fibrosis. Interestingly, diabetic patients with high BMI and lower fibrosis grades were at risk of developing fibrosis (27). Other studies have indicated that the presence of NASH, and mainly fibrosis at initial biopsy, predicts the development of chronic liver disease with NAFLD in the future (28,29).

Limitations

This study was a cross-sectional study with a limited number of subjects, and we did not use a liver biopsy. Large-scale prospective studies are required to validate our results.

Ultrasound is a common screening test used for diagnosing fatty liver; however, it is insensitive, operator-dependent, and unreliable for diagnosing NAFLD. Even with magnetic resonance imaging (MRI), results are variable and not well verified. MRI is expensive and less accessible, and cannot identify steatosis and fibrosis or NASH/ASH (alcoholic steatohepatitis), and cannot stage the disease. In fact, without a liver biopsy, imaging is not able to distinguish NASH from ASH or diagnose fatty liver if it is less than 33%.

Ultimately, NAFLD/NASH is a diagnosis of exclusion, and liver biopsy is required to confirm the assessment and the disease stage, and determine the need for and necessity of invasive therapy. Although liver biopsy is able to identify the severity of the disease, only fibrosis rather than inflammation or necrosis is an accurate predictor of disease prognosis (30).

Conclusion

In conclusion, this study verified the relationship between NAFLD and male gender, obesity (BMI), and liver aminotransferase in NAFLD.

Competing Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The current study was approved by the Ethics Committee of Tabriz University of Medical Sciences.

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