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Original Article

Prevalence of non-alcoholic fatty liver disease in patients with diabetes mellitus, hyperlipidemia, obesity and polycystic ovary syndrome: A cross-sectional study in north of Iran

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ABSTRACT

Background and aim: The aim of this study was to describe the frequency of non-alcoholic fatty liver disease (NAFLD) in patients with diabetes mellitus (DM), hyperlipidemia, obesity and polycystic ovaries syndrome (PCOS).

Methods: In a cross-sectional study, 333 patients who had one of the certain diagnosis of DM, hyperlipidemia, obesity or PCOS were enrolled. Information about demographics, anthropometric, nutritional habitude, smoking history, medical history and physical activity were recorded. Liver ultrasound examination and routine biochemistry analysis were performed.

Results: Among 333 patients with one of the four above-mentioned diseases. 199 patients (59.8%) had NAFLD. Male were more likely to have NAFLD than female (72.8% vs. 50.8% respectively, $P < 0.001$). About, 80.7% of patients through 41–50 years age had NAFLD. The frequency of abnormal fasting blood glucose, alanine aminotransferase (ALT), triglyceride, and total cholesterol were significantly higher in patients with NAFLD ($P < 0.05$). Subjects with NAFLD had a higher body mass index than non-NAFLD (33.6 ± 7.9 kg/m^2 vs. 31.1 ± 5.0 kg/m2 respectively, $P = 0.002$). Patients with DM, hyperlipidemia, hypertension, and hypothyroidism were more likely to have NAFLD ($P < 0.05$). Patients with consumption of supper, high-fat diet, enjoy of eating and smoking were more likely to have NAFLD and patients with fruit and vegetable uptake and physical activity were less likely to have NAFLD ($P < 0.05$).

Conclusions: As most patients with NAFLD are asymptomatic, employed individuals with higher education levels, with a history of smoking and unhealthy diet along with DM, hyperlipidemia, PCOS and obesity seriously have to be followed and educated for lifestyle modification.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is depicted as a most prevalent cause of hepatic injury in the world [1,2]. It is characterized by a mass of lipid, primarily triglycerides in hepatocytes. In the absence of excessive alcohol consumption, it exceeds 5% of the liver weight [3,4]. NAFLD represents a spectrum of disease from the earliest stage of steatosis (fat accumulation in the liver tissue without inflammation) to non-alcoholic steatohepatitis (NASH), which is described with steatosis accompanied with hepatocellular injury and inflammation and perhaps fibrosis which has the highest risk for affecting the liver to cirrhosis and even to Hepatocellular carcinoma [5,6].

NAFLD prevalence has been increased primarily because of the increased prevalence of obesity, hyperlipidemia, diabetes mellitus (DM) and polycystic ovary syndrome (PCOS) [7–11]. It has been estimated that NAFLD affects one-third of the US population and approximately 2–5% suffer from NASH [5]. A study reported the NAFLD prevalence is 21.5% in Iran as a developing country [12]. In

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addition, the overall prevalence of NASH has been found 2.9% [13] and 3.3% [14]. Here, we aimed to investigate the presence of NAFLD in diabetic, hyperlipidemic, obese patients or who had PCOS. Also, to compare the demographic and anthropometric data, nutritional habitude, medical history and physical activity among patients with and without NAFLD.

2. Methods

2.1. Setting

In this cross-sectional study, after setting a panel with gastroenterologists, endocrinologists, and gynecologists, it was planned to refer the patients for the diagnosis of DM, hyperlipidemia, obesity or PCOS to the Gastrointestinal and Liver Diseases Research Center (GLDRC) between November 2014 and March 2017. The following criteria were followed to diagnose these diseases:

- DM was diagnosed based on either approved the previous diagnosis of DM, or if FBS ≥126 mg/dl. Pre-diabetic status was defined as a fasting glucose of 110–125 mg/dL [15].
- Hyperlipidemia was defined as a total cholesterol level ≥240 mg/dL or a triglyceride level ≥200 mg/dL. According to Adult Treatment Panel III (ATP III) criteria, high LDL is defined as ≥160 mg/dl and low HDL as <40 mg/dL. Patients who reported current use of anti-hyperlipidemic medications were regarded as having hyperlipidemia.
- Obesity was defined according to the calculated body mass index (BMI) and divided into three categories of normal (19–25 kg/m^2), overweight (25–30 kg/m^2) and obese (>30 kg/m^2).
- PCOS subjects were referred from the residential gynecologist.

The patient with the diagnosis of NASH, hemochromatosis, viral hepatitis, Wilson's disease, autoimmune disorders and significant alcohol consumption (>14 g/day) were excluded. The included patients were interviewed by a trained interviewer. A questionnaire with five sections as demographic and anthropometric data, nutritional habitude, medical history and physical activity was filled for each patient.

2.2. Liver ultrasonography

The entire patient underwent a liver ultrasonography by a who blinded to study for detecting and grading the steatosis. Steatosis was described as zero, mild, moderate and severe [16]. All the participants were asked to come to a morning examination after an overnight fast of ≥8 h. Abdominal ultrasonography was conducted using a scanner equipped with a 2.0–5.0 MHz transducer (Voluson 730, GE Healthcare, Pittsburgh, PA, United States). The ultrasonographer was unaware of the participants' clinical characteristics.

2.3. Blood sampling and measurements

After sonography, 5 ml blood samples from each patient after 12 h of fasting were obtained to test FBS, 2-h postprandial glucose, HbA1C, triglyceride, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), ferritin, c-reactive protein (CRP), albumin, bilirubin, uric acid, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Patients were divided into two groups according to the liver function test (LFT) results as NAFLD with normal LFT and NASH with elevated LFT.

Systolic and diastolic blood pressures were measured by a physician using a standard mercury sphygmomanometer. Hypertension was defined as two seated systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mm Hg. Patients who reported current use of anti-hypertension medications were regarded as having hypertension [17]. BMI was calculated as weight (kg) divided by the square of height (m2) using Seca Scale. Waist circumference (WC) was measured based on WHO guideline which is the midline between the lowest rib and the top of the iliac crest (13).

2.4. Ethical consideration

The study protocol was approved by the Ethics Committee of GLDRC, Guilan University of Medical Sciences, Rasht, Iran and written informed consent was obtained from patients.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 16. Comparisons of continuous variables were performed with the Student's t-test, and categorical variables were compared using the Chi-square test. $P < 0.05$ on the two-tail test was considered as the statistically significant difference.

3. Results

Among 496 patients who had referred to our center and completed the study, 163 (32.9%) patients were excluded due to NASH(86 patients), history of alcohol consumption (67 patients), viral hepatitis (4 patients), hemochromatosis (3 patients), autoimmune disorders (2 patients) and Wilson's disease (1 patient) (Fig. 1). Among NASH patients, 42 (48.85%) patients had the history of alcohol consumption. From 333 included subjects, 199 ones (59.76%) had NAFLD and other 134 (40.3%)patients were normal (non-NAFLD).

The mean age of the participants without NAFLD was significantly higher than those had NAFLD (50.8 ± 16.0 years vs. 45.9 ± 11.3 years). Also, a significant association between age and having NAFLD was detected as 80.7% of patients who were in 41–50 years age group had NAFLD ($P < 0.001$). Among NAFLD group, the mean age of males and females were 45.6 ± 12.6 years and 49.5 ± 12.6, respectively. There were significant differences in sex ($P < 0.001$), age groups ($P < 0.001$), recent BMI ($P = 0.002$), education level ($P < 0.001$), occupation ($P < 0.001$) and smoking ($P = 0.031$) between NAFLD and non-NAFLD groups (Table 1). Near 79% of patients with high education levels and around 70% of employed or self-employed patients had NAFLD (Table 1). Moreover, patients with overweight had significantly more percentage of NAFLD ($P = 0.008$). In NAFLD patients, 113 (57%) patients had normal LFT and 86 patients (43%) patients had risen LFT. The frequencies of high FBS, postprandial glucose, HbA1c, ALT, triglycerides, total cholesterol, LDL, ferritin, total bilirubin, CRP, uric acid and low albumin were significantly higher in patients with NAFLD in comparison to non-NAFLD patients ($P < 0.05$) (Table 2). Furthermore, patients with DM, hyperlipidemia, hypertension, and hypothyroidism were more likely to have NAFLD ($P < 0.05$). NAFLD, non-alcoholic fatty liver disease; FBS, fasting blood sugar; ALT, alanine aminotransferase; LDL, low-density lipoprotein; CRP, c-reactive protein.

The relationships between the presence of NAFLD and consumption of supper, high fat diet, nutritional supplements, enjoy of eating, consumption of fruits and vegetables, regular exercise and smoking are stated in Table 3. Having no supper, high enjoy of eating and consumption of high-fat content food were significantly associated with NAFLD ($P < 0.05$).

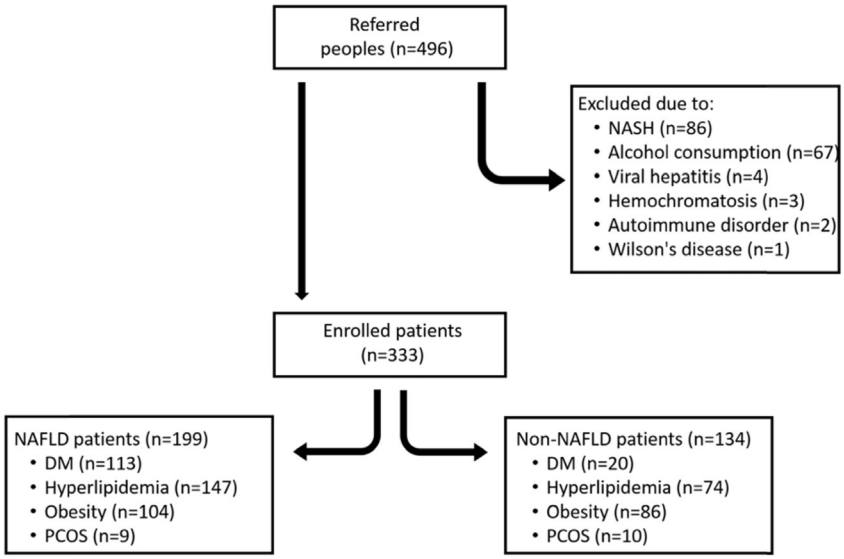

Fig. 1. Flow chart of referred, included and excluded patients.

Table 1
Comparison of demographic and anthropometric status in patients with and without NAFLD.

Variables	Liver status		Total	P value
	NAFLD	Non-NAFLD		
Waist circumference (cm)	105.10 ± 11.48	104.70 ± 12.56	104.90 ± 11.90	0.780
Hip circumference (cm)	109.80 ± 10.94	111.50 ± 11.01	110.50 ± 10.90	0.170
BMI (kg/m2)				
Quantitative	33.60 ± 7.90	31.10 ± 50	32.13 ± 6.50	0.002
Qualitative				0.008
19-25	14 (48.3)	15 (51.7)	29 (100)	
25-30	81 (71.1)	33 (28.9)	114 (100)	
>30	104 (54.7)	86 (45.3)	190 (100)	
Sex				<0.001
Male	99 (72.8)	37 (27.2)	136 (100)	
Female	100 (50.8)	97 (49.2)	197 (100)	
Age (years)				<0.001
<30	17 (41.5)	24 (58.5)	41 (100)	
31-40	41 (67.2)	20 (32.8)	61 (100)	
41-50	71 (80.7)	17 (19.3)	88 (100)	
51-60	53 (58.2)	38 (41.8)	91 (100)	
>60	17 (32.7)	35 (67.3)	52 (100)	
Marital Status				0.054
Single	9 (90)	1 (10)	10 (100)	
Married	190 (58.8)	133 (41.2)	323 (100)	
Education level				<0.001
Illiterate	53 (44.9)	65 (55.1)	118 (100)	
Up to college	94 (63.1)	55 (36.9)	149 (100)	
With degree	52 (78.8)	14 (21.2)	66 (100)	
Occupation				<0.001
Unemployed	90 (50.6)	88 (49.4)	178 (100)	
Employed	69 (71.1)	28 (28.9)	97 (100)	
Self-employed	40 (69)	18 (31)	58 (100)	
Smoking				0.031
Yes	51 (70.8)	21 (29.2)	72 (100)	
No	148 (56.7)	113 (43.3)	261 (100)	
Physical activity				0.525
Yes	143 (58.6)	101 (41.4)	244 (100)	
No	56 (62.9)	33 (37.1)	89 (100)	
Weight loose within 6 months				0.705
Yes	55 (61.8)	34 (38.2)	89 (100)	
No	144 (59)	100 (41)	244 (100)	

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index.

Table 2
Lab findings among NAFLD and non-NAFLD group.

Parameters	Liver status		Total	P value
	NAFLD	Non-NAFLD		
FBS				<0.001
<126 mg/dl	86 (43)	114 (57)	200 (100)	
≥126 mg/dl	113 (84.9)	20 (15.1)	133 (100)	
Post-prandial Glucose				0.009
≤140 mg/dl	55 (46.6)	63 (53.4)	118 (100)	
>140 mg/dl	117 (62.2)	71 (37.8)	118 (100)	
HbA1c				0.003
≤6.5%	31 (37.3)	52 (62.7)	83 (100)	
>6.5%	109 (57.4)	81 (42.6)	190 (100)	
ALT				<0.001
≤40 U/L	116 (52.1)	107 (47.9)	223 (100)	
>40 U/L	83 (75.5)	27 (24.5)	110 (100)	
Triglyceride				0.001
<200 mg/dl	50 (45.5)	60 (54.5)	110 (100)	
≥200 mg/dl	137 (64.9)	74 (35.1)	211 (100)	
Total cholesterol				0.001
<240 mg/dl	74 (48.7)	78 (51.3)	152 (100)	
≥240 mg/dl	113 (66.9)	56 (33.1)	169 (100)	
LDL				<0.001
<160 mg/dl	59 (37.3)	99 (62.7)	158 (100)	
≥1600 mg/dl	125 (78.1)	35 (21.9)	160 (100)	
Ferritin				<0.001
≤200 mg/dl	108 (52.2)	99 (47.8)	207 (100)	
>200 mg/dl	91 (72.2)	35 (27.8)	126 (100)	
Total bilirubin				<0.001
≤1 mg/dl	82 (78.1)	23 (21.9)	105 (100)	
>1 mg/dl	105 (54.4)	88 (45.6)	193 (100)	
CRP				0.008
Negative	143 (55.2)	116 (44.8)	259 (100)	
Positive	49 (73.1)	18 (26.9)	67 (100)	
Uric acid				0.023
≤6.8 mg/dl	105 (54.4)	88 (45.6)	193 (100)	
>6.8 mg/dl	94 (67.1)	46 (32.9)	140 (100)	
Low albumin				<0.001
<3.5 g/dl	74 (77.9)	21 (22.1)	95 (100)	
≥3.5 g/dl	125 (52.5)	113 (47.5)	238 (100)	

Table 3
Comparison of nutritional habitudes patients with and without NAFLD.

Nutritional habitudes	Liver status		Total	P value
	NAFLD	Non-NAFLD		
Breakfast				0.130
Yes	189 (58.9)	132 (41.1)	321 (100)	
No	10 (83.3)	2 (16.7)	12 (100)	
Supper				0.030
Yes	136 (56.2)	106 (43.8)	242 (100)	
No	63 (69.2)	28 (30.8)	91 (100)	
Fruits and vegetables				0.052
Every day	36 (34.0)	70 (66.0)	106 (100)	
Few times per week	42 (37.2)	71 (62.8)	113 (100)	
Few times per month	56 (49.1)	58 (50.9)	114 (100)	
Dairy products				0.220
Every day	37 (61.7)	23 (38.3)	60 (100)	
Few times per week	111 (63.1)	65 (36.9)	176 (100)	
Few times per month	51 (52.6)	46 (47.4)	97 (100)	
Enjoy of eating				<0.001
Low	18 (36.7)	31 (63.3)	49 (100)	
Middle	110 (59.5)	75 (40.5)	185 (100)	
High	71 (71.7)	28 (28.3)	99 (100)	
Having a Meal in restaurant				0.980
<1 time per week	168 (59.8)	113 (40.2)	281 (100)	
≥1 times per week	31 (59.6)	21 (40.4)	52 (100)	
High-fat content foods				<0.001
Yes	74 (83.1)	15 (16.9)	89 (100)	
No	125 (51.2)	119 (48.8)	244 (100)	

NAFLD, non-alcoholic fatty liver disease.

4. Discussion

Monitoring of patients with DM, hyperlipidemia, PCOS, and obesity about having NAFLD and determining them in the early stages may have a protective role against developing to the advanced stages. NAFLD is a simple hepatic steatosis at most of the time, but a significant number of NAFLD cases develop NASH, which may lead to fibrosis, cirrhosis, or end-stage liver disease [16].

In our study, NAFLD was higher in men which are in accordance with other studies [18–22]. In contrast, He et al. [23] and Eshraghian et al. [24] reported a higher prevalence of NAFLD in women. Probable cause for our far more NAFLD distribution may be this fact that our participants were selected through some disorders definitely. Also, fat distribution in women which is not mainly in the abdomen is a major source of free fatty acids and cytokines for liver would explain the further fat accumulation among women for NAFLD [25]. We found that most of the NAFLD patients had age between 41 and 50 years. Although Castro-Martinez found no age difference between NAFLD and non-NAFLD patients [19], Lankarani and coworkers reported that NAFLD patients were older [22]. Strong relationships between BMI and NAFLD are reported [26–28]. Higher prevalence of NAFLD in our patients with significantly higher BMI would be a great confirmation to emphasize the importance of weight reduction strategies for prevention and management of NAFLD. This can be studied in future interventional prospective researchers. Although no significant differences in the waist and hip circumstances were observed, other studies reported higher values of the waist and hip circumferences in NAFLD patients along with higher BMI [29,30].

NAFLD was significantly higher among higher level educated and employed patients which turn out as the more involvement of these groups with modern lifestyle [31] and more accessibility to the technological facilities by a higher economic status [32]. Opposite to our findings, Zhou and collaborators reported the low education level as one of the risk factors for fatty liver disease [33]. High serum levels of ferritin [34], liver enzymes, triglycerides, LDL, uric acid [35] FBS, and total cholesterol [36] are significantly related with NAFLD as we found in our patients. Moreover, NAFLD patients had significantly lower serum albumin levels which states the alteration of albumin binding capacity to fatty acids. This may be one of the earliest sensitive indicators for liver function evaluation [37].

Fan and colleagues in a review article about possible risk factors of NAFLD in Asia-Pacific region explained that DM may be one the particular risk factors of NAFLD [38]. Similarly, our patients with DM, hyperlipidemia, and hypertension were more likely to have NAFLD. In our study, patients with hypothyroidism were more likely to have NAFLD. Several studies are conducted about the role of thyroid dysfunction and NAFLD which systematically reviewed by Eshraghian and Hamidian Jahromi [39]. They provided controversial results ranged from the significant relationship of hypothyroidism with NAFLD [40] to non-significant associations [41,42]. It has been confirmed that hypothyroidism and small intestinal bacteria overgrowth are linked together in liver dysfunction [43]. However, we did not evaluate the microbiome profile of our patients and this would be interesting to study in future.

We observed significant differences between patients with and without NAFLD with consumption of supper, high-fat content foods, and enjoying the eating. It is proved that macronutrient can have a variety of effects on progression or prevention of NAFLD. Among them, consumption of a low carbohydrate and low saturated fat diet and more fruits and vegetables are the beneficial diets for NAFLD patients [44]. Shi et al. found that nutritional supplements were a protective factor against NAFLD. In addition, they found that consumption of potatoes, vegetables, fruits, coarse

cereals and milk were significantly lower, and consumption of red meat, viscera, candies, pastries and cooking oil was significantly higher in subjects with NAFLD compared with controls [45]. Miele et al. study proved that doing physical activity at least one time per week decrease dramatically the risk of NAFLD. Furthermore, they demonstrated that high consumption of fruit and fat intake have the increased risk and they report a detrimental effect of grilled food on NAFLD risk (37). In contrast, Omagari and coworkers indicated that habitual physical exercise does not independently predict development or regression of fatty liver [46]. The role of smoking in the exacerbation of NAFLD has been confirmed in several studies [47–49] which is related to oxidative stress. We found that NAFLD was significantly more among smokers. The effect of cessation of smoking which is recommended in Zeinet al study [50]could be studied in future.

5. Conclusion

As most patients with NAFLD are asymptomatic, employed individuals with higher education levels, with a history of smoking and unhealthy diet along with diabetes, hyperlipidemia, PCOS, and obesity, we seriously suggested that they have to be followed and educated for lifestyle modification.

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Disclosure statement

The authors declare that they have no competing interests.

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