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Predictors of Nonalcoholic Fatty Liver Disease Among Middle-Aged Iranians

Abstract

Background: The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide. Therefore, we sought to determine the most important predictors of NAFLD among middle-aged men and women in Isfahan, Iran. **Methods:** A total of 413 individuals (163 men and 250 women) aged 30–60 years were selected by stratified random sampling. The participants had safe alcohol consumption habits (<2 drinks/day) and no symptoms of hepatitis B and C. NAFLD was diagnosed through ultrasound. Blood pressure, anthropometric, and body composition measurements were made and liver function tests were conducted. Biochemical assessments, including the measurement of fasting blood sugar (FBS) and ferritin levels, as well as lipid profile tests were also performed. Metabolic syndrome was evaluated according to the International Diabetes Federation (IDF) criteria. **Results:** The overall prevalence of ultrasound-diagnosed NAFLD was 39.3%. The results indicated a significantly higher prevalence of NAFLD in men than in women (42.3% vs 30.4%; $P < 0.05$). Binary logistic regression analysis was performed to determine the significant variables as NAFLD predictors. Overall, male gender, high body mass index (BMI), high alanine aminotransferase (ALT), high FBS, and high ferritin were identified as the predictors of NAFLD. The only significant predictors of NAFLD among men were high BMI and high FBS. These predictors were high BMI, high FBS, and high ferritin in women ($P < 0.05$ for all variables). **Conclusions:** The metabolic profile can be used for predicting NAFLD among men and women. BMI, FBS, ALT, and ferritin are the efficient predictors of NAFLD and can be used for NAFLD screening before liver biopsy.

Keywords: Metabolic syndrome, nonalcoholic fatty liver disease, ultrasonography

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most important public health concerns and a major cause of chronic liver disease worldwide.^[1,2] The annual direct medical costs of NAFLD in the United States and in the Europe-4 countries (Germany, France, Italy, and the United Kingdom) is about \$103 billion and €35 billion, respectively.^[3] NAFLD is strongly related to cardiovascular risk factors such as dyslipidemia, hypertension, diabetes, insulin-resistance, and obesity. Recent studies have suggested an association between NAFLD and increased risk of cardiovascular diseases.^[4,5] The disease may also be an early mediator of atherosclerosis.^[6,7] Today, the term NAFLD covers a wide spectrum of patterns from simple FLD without inflammation (steatosis), as the earliest stage of fat deposition in the liver, to progressive

nonalcoholic steatohepatitis (NASH) with hepatocellular injury and inflammation with or without cirrhosis and hepatocellular carcinoma.^[8,9] Although NAFLD was first described in adults, the growing prevalence of overweight and obesity has turned it into a serious problem in not only adults but also in children. NAFLD generally occurs in nondrinkers; men who drink less than two standard drinks per day (140 g ethanol/week) and women who drink one standard drink per day (70 g ethanol/week).^[10] The global prevalence of NAFLD in the adult population was estimated at about 25%. The Middle East has the highest prevalence of NAFLD in the world with a rate of about 32%.^[11]

The patients with NAFLD are usually asymptomatic.^[12] Since the screening of individuals using imaging methods such as ultrasound and computed tomography (CT) does not appear to be cost-effective, the knowledge of predicting factors would help

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identify the patients at high-risk of NAFLD. Therefore, this study evaluated anthropometric and laboratory exams to predict NAFLD in middle-aged adults in Isfahan, Iran.

Methods

Subjects

In a cross-sectional study from November 2011 to October 2012, multistage random sampling was applied to select 467 individuals. The sample size was calculated based on the Cochran formula, the percentage of population picking a choice, expressed in decimals 0.5 used for sample-size needed. Considering the dropout rate during the study, the sample size was further marked by up to 20%. Hence, the minimum sample number required for this study was 461 subjects. Subjects were selected from 18 health centers in Isfahan Province, Iran. These health centers were randomly selected from a total of 79 health centers in the province. All patients aged 30–60 years, lived in Isfahan, and had no history of severe illnesses, physical disability, alcohol consumption over 20 g/day (1–2 drinks per day), infection with hepatitis B and C viruses, drug-induced hepatotoxicity (corticosteroids, amiodarone, methotrexate), genetic and metabolic diseases (e.g., Wilson's disease and lipodystrophy), and autoimmune liver disease. All of the information for excluding subjects was collected by interview. After random selection, an invitation letter containing project information and the name, age, and identity number of the patient was sent to each selected individual. The subjects were asked to fast for at least 12 h on the day of their visit.

A structural questionnaire was developed to obtain various information including demographics, socioeconomic status, and health information (e.g., smoking status, alcohol consumption, existing diseases and their durations, history of medications and supplements, hospitalization for liver diseases in the past year, and family history of liver disease).

The patients' blood pressure was measured while they were in a sitting position. Their body composition was examined using a bioelectrical impedance analyzer (BIA). Other anthropometric indices, including body weight, height, waist circumference, and hip circumference, were performed according to the standard protocol described in the National Health and Nutrition Examination Survey.^[13] Bodyweight and height were measured using a digital scale *SECA 761, Hamburg, Germany* while the patients were wearing light underclothing. Body mass index (BMI) was then calculated accordingly.

During data collection, 20 mL fasting venous blood samples were drawn by a trained nurse. Subjects fasted at least 10 h before blood sampling. Subjects were asked to be seated and relax in an arm-chair. Fasting blood sugar (FBS), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), vitamin D, ferritin, and lipid profile, that is, cholesterol (Chol), triglyceride (TG),

low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) levels were measured. Antioxidant and oxidative stress tests were also performed. Metabolic syndrome was evaluated according to the International Diabetes Federation (IDF) criteria.^[14]

Finally, the subjects were invited to visit Noor Hospital for a liver ultrasound by using a transabdominal ultrasonography 3.5 MHz transducers (Siemens SONOLINE G50-Germany). All scans were conducted under similar conditions and by a single expert radiologist to minimize variations in scan interpretation and NAFLD screening and grading. The presence of steatosis was indicated by a marked increase in liver echogenicity compared to the normal renal cortex. The ultrasounds were graded on a scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

The study protocol was consistent with the ethical guidelines of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1975) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This study was approved by the research committee of the Universiti Kebangsaan Malaysia (UKM 1.5.3.5/244/SPP/NN-077-2011, 29 July 2011). Moreover, all subjects were provided with an information sheet about the study and asked to sign a written informed consent form.

All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses of all variables were run to inspect the distribution of the data and check for outliers. The differences between groups with or without NAFLD were compared using independent t-tests for continuous variables (e.g., age and income). Pearson's Chi-square test (χ^2) was applied to identify associations between the presence/absence of NAFLD and categorical variables (e.g., sex and smoking). A multivariate analysis using binary logistic regression was performed to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs). All variables with a *P* value <0.05 in the bivariate analysis were entered into the binary logistic regression model to identify the potential independent factors associated with NAFLD. Variables that were statistically significant were added to binary logistic regression analysis to determine the significant variables as NAFLD predictors. The forward stepwise method was employed to assess the accuracy and stability of the model. When a significant correlation was found between two variables, the higher OR was chosen as the representative variable.

Results

A total of 413 participants, including 163 men (39.47%) and 250 women (60.53%), visited the hospital for a liver ultrasound (response rate = 88.4%) and their data were included in the analysis. The mean age of the

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participants was 45.5 ± 8.6 years. The overall prevalence of ultrasound-diagnosed NAFLD was 39.3% and 60.7% of the subjects had normal liver echogenicity and no evidence of steatosis (non-NAFLD).

NAFLD had a significantly higher prevalence in men than in women. The overall prevalence of NAFLD was not significantly different between different age groups (30–39, 40–49, and 50–60 years old) of men ($P = 0.519$). However, the disease was significantly more prevalent in older women. The BMI was significantly higher in the NAFLD group than in the non-NAFLD group ($P < 0.001$). The differences between the two groups were also significant for WC ($P < 0.001$ for both men and women), HC ($P < 0.001$ for both men and women), and WHR ($P < 0.01$ for men and $P < 0.05$ for women). Blood tests showed significantly higher FBS, TG, Chol, LDL-C, apolipoprotein B, AST, ALT, ferritin, and glutathione levels in patients with NAFLD than in those without the disease. However, the mean HDL-C and superoxide dismutase (SOD) levels were significantly lower in the patients with NAFLD compared to the non-NAFLD group [Table 1]. As shown in Table 2, BMI and WC were significantly higher in women than in men. In contrast, TG,

ALT, AST, and ferritin levels were significantly higher in male patients with NAFLD than in female patients.

Binary logistic regression analysis was performed to determine the significant variables as NAFLD predictors. In general, high BMI (OR = 6.155; CI = 2.842–13.329; $P < 0.001$), high ALT (OR = 3.588; CI = 1.489–8.646; $P < 0.01$), high FBS (OR = 2.314; CI = 1.344–3.986; $P < 0.01$), and high ferritin (OR = 2.534; CI = 1.271–5.052; $P < 0.01$) were the significant predictors of NAFLD. Among men, high BMI (OR = 6.146; CI = 2.183–17.299; $P < 0.01$) and high ALT (OR = 3.294; CI = 1.288–8.425; $P < 0.05$) were the significant predictors of NAFLD. The significant predictors of NAFLD among women were high BMI (OR = 5.952; CI = 1.751–20.226; $P < 0.01$), high FBS (OR = 2.925; CI = 1.343–6.370; $P < 0.01$), and high ferritin (OR = 3.737; CI = 1.235–11.308; $P < 0.05$) [Table 3].

Discussion

In our study, the overall prevalence of ultrasound-diagnosed NAFLD was 39.3%. The results showed NAFLD to be significantly more prevalent in men than in women.

Table 1: Comparison of baseline characteristics between patients with and without non-alcoholic fatty liver disease (NAFLD)

Characteristics	Total (n=413)	NAFLD (n=145)	Non-NAFLD (n=268)	P
Sex*				<0.01
Men	163 (39.5)	69 (47.6)	94 (35.1)	
Women	250 (60.5)	76 (52.4)	174 (64.9)	
Age groups*				0.134
30-39 years	121 (29.3)	37 (25.2)	84 (31.3)	
40-49 years	139 (33.7)	45 (31)	94 (35.1)	
50-60 years	153 (37)	63 (43.5)	90 (33.6)	
Hypertension*	67 (16.2)	31 (21.4)	36 (13.4)	<0.01
BMI (kg/m ²)**	28.3±5.0	30.9±5.3	26.9±4.3	<0.001
WC (cm)**	97.46±10.87	102.90±10.43	94.52±11.11	<0.001
waist hip ratio**	0.91±0.06	0.93±0.07	0.90±0.066	<0.01
FBS (mg/dl)**	98.1±34.3	107.2±44.7	93.1±25.8	<0.01
TG (mg/dl)**	184.8±101.8	218.9±130.3	166.3±76.5	<0.001
TC (mg/dl)**	176.5±35.9	183.4±35.1	172.7±35.7	<0.01
HDL (mg/dl)**	47±10	45.2±9.8	47.9±10	<0.05
LDL (mg/dl)**	104.5±28.5	110.8±29.6	101.2±27.4	<0.01
Metabolic syndrome*	182 (44.1)	84 (57.9)	98 (36.6)	<0.001
AST (IU/l)**	22.2±8.3	24.4±8.5	21±7.9	<0.001
ALT (IU/l)**	24.3±14.1	31.4±17.3	20.5±10.3	<0.001
Ferritin (ng/ml)**	96.7±104.7	127.7±122.7	79.9±89.4	<0.001
Vit D (ng/ml)**	42.8±20.3	45±21.1	41.6±19.8	0.10
Apo-A (mg/dl)**	107.9±18.6	109±17.2	107.3±19.2	0.37
Apo-B (mg/dl)**	66.2±16.2	70.6±16.6	63.8±15.5	<0.001
SOD (U/ml)**	0.4±1.9	0.2±0.18	0.5±2.3	<0.05
GLU (μM/ml)**	1.3±1.2	1.7±1.5	1.1±0.9	<0.001

*Number (%). **: Mean±standard deviation. NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; FBS: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Vit D: Vitamin D; Apo-A: Apo lipoprotein A; Apo-B: Apo lipoprotein B; SOD: Superoxide dismutase; GLU: Glutathione

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In binary logistic regression analysis, the predictors of NAFLD were BMI and ALT in men and BMI, FBS, and ferritin in women.

NAFLD is the most common liver disorder not only in Western countries but also in Asia. Most patients with NAFLD are not aware of their condition and the disease is usually discovered accidentally during routine laboratory examinations or liver ultrasonography. In fact,

NAFLD symptoms may appear in the severe stage of the disease (liver cirrhosis). Therefore, early diagnosis of the disease is critical.

The prevalence of NAFLD ranges between 25% in Asia.^[15,16] The prevalence of NAFLD in Iran based on a systematic review is 33.95%.^[17] It should be noted that the prevalence of NAFLD has increased during the past decade, basically due to lifestyle changes.^[18] In a cohort population-based study in Japan, the prevalence of NAFLD increased from 13% to 30% over a period of 10–12 years.^[19] The gold standard for diagnosing and staging NAFLD is a liver biopsy. Although liver biopsy is generally safe, it might be associated with a risk of major complications and even death in 1–3% and 0.01% of the cases, respectively. As a result, liver biopsy should be replaced by noninvasive predictors and methods for the prediction of NAFLD and fibrosis.

Since it is not practical to perform a liver biopsy for every patient with suspected NAFLD, some studies have focused on the identification of factors predicting the incidence of NAFLD. Predictive factors are essential for the management of NAFLD as they can facilitate the prediction, diagnosis, treatment, and effective management of the disease especially if the patients are simultaneously examined with an abdominal ultrasound.

This cross-sectional study identified BMI as the best predictor of NAFLD in middle-aged men and women. According to ultrasound, the OR for developing NAFLD was six times (6.1 times in men and 5.95 times in women) higher in overweight and obese subjects (BMI ≥ 25 kg/m²) than in those with BMI < 25 kg/m². The Framingham Heart Study demonstrated that even small increases in body weight (≥ 2.3 kg) during adult life contributed to the development of an abnormal cardiovascular risk profile.^[20] Furthermore, increases in adipose mass led to a rise in adiposity lipid content,

Table 2: Comparison of baseline characteristics between men and women with non-alcoholic fatty liver disease (NAFLD)

Characteristics	Men n=69	Women n=76	P
Age groups*	45.28±8.18	47.96±8.41	0.054
Hypertension**	18 (26.1)	18 (23.7)	0.374
BMI (kg/m ²)*	29.08±3.7	32.60±5.9	<0.001
WC (cm) *	99.6±9.8	105.9±11	<0.001
waist hip ratio*	0.94±0.06	0.92±0.06	<0.05
FBS (mg/dl)*	101.6±35.9	112.3±51.8	>0.05
TG (mg/dl)*	241.7±150.7	198.1±105.2	<0.05
TC (mg/dl)*	178.4±32.8	187.9±36.7	>0.05
HDL (mg/dl)*	42.1±8.8	48.1±9.8	<0.001
LDL (mg/dl)*	106.1±26.3	115.1±32	>0.05
AST (IU/l)*	27.5±8.3	21.6±7.7	<0.001
ALT (IU/l)*	38.4±15.8	25±16.1	<0.001
Ferritin (ng/ml)*	179.6±144.4	80.6±72.7	<0.001
Vit D (ng/ml)*	43.1±15.5	46.7±25	>0.05
Apo-A (mg/dl)*	103.5±14.4	114.1±18.1	<0.001
Apo-B (mg/dl)*	69.4±16.1	71.6±17.1	>0.05
SOD (U/ml)*	0.29±0.21	0.25±0.13	>0.05
GLU (μ M/ml)*	2.1±1.8	1.3±1.2	<0.01

*Mean±standard deviation. **Number (%) NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; FBS: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Vit D: Vitamin D; Apo-A: Apo lipoprotein A; Apo-B: apo lipoprotein B; SOD: Superoxide dismutase; GLU: Glutathione

Table 3: Logistic regression analysis of the predictors of non-alcoholic fatty liver disease (NAFLD) among men and women (n=413)

Predictors (cut-off)	Total		Men		Women	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
High Body Mass Index (BMI ≥ 25 kg/m ²)	6.155 (2.842-13.329)	<0.001	6.146 (2.183-17.299)	<0.01	5.952 (1.751-20.226)	<0.01
High alanine aminotransferase (ALT ≥ 41 IU/l)	3.588 (1.489-8.646)	<0.01	3.294 (1.288-8.425)	0.013	2.049 (0.576-7.792)	0.268
High fasting blood sugar (FBS > 100 mg/dl)	2.314 (1.344-3.986)	<0.01	1.609 (0.659-3.931)	0.297	2.925 (1.343-6.370)	<0.01
High ferritin (Fe ≥ 248 ng/ml (M) and ≥ 150 ng/ml (W))	2.534 (1.271-5.052)	<0.01	1.744 (0.657-4.632)	0.264	3.737 (1.235-11.308)	0.020
Hypertriglyceridemia (TG ≥ 150 mg/dl)	1.288 (0.716-2.316)	0.399	1.295 (0.545-3.076)	0.558	1.062 (0.369-3.053)	0.912
Hypercholesterolemia (TC ≥ 200 mg/dl)	1.396 (0.816-2.386)	0.223	1.685 (0.465-6.113)	0.427	1.343 (0.402-4.488)	0.632
High low density lipoprotein (LDL ≥ 130 mg/dl)			1.854 (0.445-7.726)	0.397	2.106 (0.648-6.841)	0.215
High waist circumference (≥ 102 cm (M) & ≥ 88 cm (W))	1.398 (0.662-2.953)	0.380	1.095 (0.420-2.855)	0.853	1.030 (0.268-3.959)	0.966
High waist hip ratio (WHR ≥ 0.90 (M) & ≥ 0.85 (W))	1.284 (0.513-3.215)	0.594	1.338 (0.496-3.605)	0.565	3.209 (0.797-12.924)	0.101
Hypertension (Blood pressure $\geq 140/90$ mm Hg)	1.291 (0.699-2.384)	0.415	1.112 (0.433-2.859)	0.825	1.840 (0.768-4.411)	0.171
Metabolic syndrome (IDF ≥ 3 criteria)	1.200 (0.641-2.248)	0.568	1.010 (0.391-2.605)	0.984	1.119 (0.374-3.349)	0.841

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which, in turn, caused a higher release of free fatty acids and possibly other factors, such as tumor necrosis factor- α , that could contribute to insulin resistance. Insulin resistance is a well-established, major component in NAFLD pathogenesis known to increase the serum-free fatty acid uptake by the liver and promote hepatic de novo lipogenesis.

Some studies have highlighted the importance of weight gain in the development of NAFLD. A study in Korea found that 19% of individuals with a normal liver at baseline developed fatty liver after five years and presented more weight gain during the 5-year period (weight gain of 3.5 kg in those who developed NAFLD vs 1.3 kg in those who did not develop the disease).^[19] In another cohort study in Korea, individuals with a very modest weight gain of ≥ 2.3 kg were at significantly elevated risk of NAFLD after adjustments for age, BMI, HDL-C, TG, uric acid, ALT, and homeostatic model assessment of insulin resistance.^[20]

A study in Iran reported that the overall prevalence of obesity increased from 13.6% in 1999 to 19.6% in 2005 and 22.3% in 2007 (OR = 1.08 per year). These rates were respectively 32.3%, 35.8%, and 36.3% for overweight (OR = 1.02 per year).^[21] This indicated a rapid rise in the prevalence of overweight and obesity during recent years in Iran. Based on the high prevalence of overweight and obesity in this study and previous research on NAFLD, the incidence of NAFLD will continue to increase in the future and a higher number of Iranians would, thus, be affected by NAFLD and its complications. This growing incidence of NAFLD may turn it into common chronic liver disease and a critical health concern in Iran. As a result, in order to decrease the high prevalence of NAFLD among Iranians, more attention should be directed to the prevention and treatment of overweight and obesity.

The strengths of this study included its population-based design, its relatively large sample size, and the very good response rate (i.e., the studied individuals represented the general population in Isfahan, Iran). This study highlighted the high prevalence of NAFLD in Iran as about one-third of the general population between 30 and 60 years old had NAFLD. A limitation of the study was the diagnosis of NAFLD merely based on ultrasound. Despite their high sensitivity (up to 89%) and specificity (up to 93%), ultrasound examinations are associated with both false positives and false negatives. Even though liver biopsy is the gold standard for the diagnosis of fatty liver, it was not feasible in this study due to the large sample size and increased risk of mortality. Another limitation of this study was its cross-sectional design which did not allow for the evaluation of cause and effect relationships between the predicting factors and the development of NAFLD.

Conclusions

In conclusion, NAFLD can be sufficiently predicted with some simple anthropometric examinations and laboratory tests. A combination of these predicting factors and liver ultrasound (to exclude normal subjects) can facilitate the early diagnosis, treatment, and management of patients with NAFLD.

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Conflicts of interest

There are no conflicts of interest.

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