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The relationship between insulin resistance, metabolic syndrome and nonalcoholic fatty liver disease in non-obese non-diabetic Turkish individuals: A pilot study

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Original Article

ABSTRACT

Background/Aims: Nonalcoholic fatty liver disease is related to obesity, metabolic syndrome, and insulin resistance. Nonalcoholic fatty liver disease and metabolic syndrome may also be encountered in non-obese, non-diabetic individuals, and there are no published data about the prevalence of these conditions in non-obese, non-diabetic Turkish subjects. We aimed to determine the difference between non-obese, non-diabetic nonalcoholic fatty liver disease patients and healthy controls in terms of insulin resistance and metabolic syndrome in Turkish subjects.

Materials and Methods: Non-obese, non-diabetic individuals (n=219) were enrolled. The cohort was divided into two groups according to presence of steatosis in ultrasonography: nonalcoholic fatty liver disease group (n=143) and healthy control group (n=76). Insulin resistance and metabolic syndrome were analyzed and compared between the two groups.

Results: The prevalences of metabolic syndrome (32.2% vs. 5.3%, respectively; p<0.001) and insulin resistance (46.2% vs. 9.2%, respectively; p<0.001) were significantly higher in the nonalcoholic fatty liver disease group. According to multiple logistic regression analysis, age (odds ratio 1.534; p=0.0032), insulin resistance (odds ratio 1.074; p<0.001), and serum ALT levels (odds ratio 1.102; p<0.001) were independently associated with nonalcoholic fatty liver disease.

Conclusion: Insulin resistance and metabolic syndrome are not rare in non-obese, non-diabetic Turkish subjects with nonalcoholic fatty liver disease. Ultrasonographically detected fatty liver was independently associated with insulin resistance, irrespective of the presence of metabolic syndrome.

Keywords: Nonalcoholic fatty liver disease, non-obese non-diabetic individuals, insulin resistance, metabolic syndrome

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological entity that displays histological features similar to those observed in alcohol-induced liver injury; nevertheless, it is encountered in individuals with no recent or present significant alcohol intake (1). NAFLD is closely related to obesity and insulin resistance (IR), and it is generally agreed upon that NAFLD is the hepatic manifestation of metabolic syndrome (MetS) (2). MetS is an insulin resistance syndrome comprising glucose intolerance, insulin resistance, central obesity, dyslipidemia, and hypertension, all of which are well-established risk factors for cardiovascular disease (CVD) (3).

Obesity and diabetes mellitus are known to contribute to the development of NAFLD (1). Nevertheless, NAFLD may also occur in non-obese, non-diabetic individuals (4-6). Kim et al. reported that NAFLD is associated with metabolic disorder in non-obese, non-diabetic Asian populations (4). Musso et al. reported that NAFLD is associated with IR in non-obese, non-diabetic Caucasians (5).

Despite the evidence connecting NAFLD to IR, it remains to be elucidated whether a diagnosis of NAFLD can improve cardiometabolic risk stratification beyond current diagnostic criteria, thus enabling identification of non-obese, non-diabetic individuals who are actu-

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ally at risk. The Adult Treatment Panel (ATP) III criteria for MetS are quite robustly correlated with IR (sensitivity of 46% and specificity of 76% for IR) in the general population, albeit with a weaker correlation in the absence of obesity and diabetes (7-9).

There are few studies concerning the clinical significance of ultrasonographically detected NAFLD in non-obese, non-diabetic individuals. To the best of our knowledge, no such study has been performed in the Turkish population.

In this study we aimed to determine:

1. Whether there is a difference between non-obese, non-diabetic NAFLD patients and healthy controls in terms of IR and MetS in Turkish subjects.

2. The differences in demographic and biochemical findings between non-obese, non-diabetic NAFLD patients and healthy controls.

3. Whether ultrasonographically detected NAFLD is more closely correlated with IR than MetS in non-obese, non-diabetic subjects.

MATERIALS AND METHODS

Non-obese, non-diabetic individuals (n=219) who presented to the Gastroenterology and Internal Medicine outpatient clinics due to dyspeptic symptoms or for routine check-up were enrolled. The cohort was divided into two groups according to ultrasonography (USG) findings: NAFLD (n=143) and healthy controls (n=76). The study protocol was approved by the university ethical committee. Informed consent was obtained from all subjects prior to enrollment. The study was conducted according to the declaration of Helsinki.

Inclusion criteria

Body mass index between 18.5 and 25

Hepatosteatosis on USG

Negative for biomarkers of all viral, autoimmune, metabolic liver disorders

No history of ethanol intake

Exclusion criteria

Diabetes mellitus or history of impaired glucose tolerance

History of exposure to drugs known to cause insulin resistance or secondary diabetes mellitus (i.e. steroids)

History of exposure to drugs known to cause hepatic enzyme elevation and/or hepatosteatosis (steroids, oral contraceptives, methotrexate, tetracycline, amiodarone, etc.)
USG findings consistent with chronic liver disease, dilation of the biliary system, hepatic nodule or mass

Healthy controls also needed to have a BMI between 18.5 and 25, with no history of diabetes or impaired glucose tolerance and with no sign of viral, metabolic, or autoimmune liver disease; and normal liver parenchyma and biliary system on USG.

All patients were questioned about their history of diabetes, impaired glucose tolerance, hypertension, cardiovascular disease, ethanol intake, and concomitant medications. The patients' height, weight, and waist and hip circumferences were measured.

Patients receiving antihypertensive drugs or having a resting recumbent blood pressure of 140/90 mmHg or greater on at least two separate measurements were classified as hypertensive. Their height and weight were determined, and their body mass index (BMI) was calculated as weight (kg) divided by height squared (m). Waist circumference (WC) was measured at the mid-point between the lower border of the arcus costarium and the iliac crest. Hip circumference (HC) was measured around the widest point of the buttocks, with the tape parallel to the ground. Waist-to-hip ratio (WHR) was also calculated as the ratio of the circumference of the waist to that of the hips.

Measurement of biochemical parameters

The laboratory assessment of blood samples for all participants included serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, albumin, total cholesterol (T. cholesterol), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (Tg), fasting blood glucose (FBG), and fasting insulin levels.

Definition of metabolic syndrome

MetS was diagnosed in the presence of 3 or more of the criteria listed by the revised Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (9). These criteria include 1) elevated waist circumference (waist circumference ≥102 cm in men or ≥88 cm in women); 2) elevated triglyceride levels (≥150 mg/dL); 3) low HDL levels (<40 mg/dL for men and <50 mg/dL for women); 4) elevated blood pressure (≥130/85 mmHg or the use of medication for hypertension); 5) elevated fasting glucose (≥100 mg/dL or use of medication for hyperglycemia).

Definition of IR

Insulin resistance was determined by homeostasis model assessment index (HOMA-IR), calculated using the computer-based solution of the model provided by the Diabetes Trials Unit, Oxford Center for Diabetes, Endocrinology, and Metabolism, found at http://www.dtu.ox.ac.uk/homa.

The cut-off value was taken as 2.7 for HOMA-IR (10).

The patients were divided into 2 groups according to their HOMA-IR levels: insulin sensitive (HOMA-IR<2.7) and insulin re-

sistant (HOMA-IR≥2.7).

Hepatic ultrasonography

Hepatic ultrasonography was performed by an experienced radiologist. Fatty liver was identified according to standard criteria, including parenchymal brightness, liver to kidney contrast, deep beam attenuation, and bright vessel walls (11).

Statistical analysis

Statistical analysis was performed using SPSS for Windows Version 15.0. Continuous variables were expressed as mean ± standard deviation, median, and minimum and maximum values, whereas categorical variables were expressed as numbers and percentages. The normal distribution of continuous variables was verified with the Shapiro •Wilk test, and the homogeneity of group variances was assessed with the Levene test. Comparisons between multiple groups were performed using one-way variance analysis or Welch variance analysis if the parametric test assumptions were verified, and using the Kruskal •Wallis test if the parametric test assumptions were not verified. Following these tests, binary comparisons were made using the Tukey HSD, Games •Howell, and Dunn tests. Comparisons between 2 groups in terms of continuous variables were made using the t test if the parametric test assumptions were verified, and using the Mann •Whitney U test if the parametric test assumptions were not verified. Comparisons between groups with regard to categorical variables were made using the chi-square test. Correlation between continuous variables was assessed using the Spearman correlation coefficient. Factors affecting steatosis were determined using multiple logistic regression analysis. Level of significance was assumed as p<0.05.

RESULTS

Demographic, metabolic, and biochemical findings of the study group

The demographic, metabolic, and biochemical findings of the study population are presented in Table 1. Male sex was significantly more predominant in the NAFLD group than in the control group (58.7% vs. 43.4%, respectively; p=0.03). The prevalences of hypertension (41.3% vs. 9.2%, respectively; p<0.001), metabolic syndrome (32.2% vs. 5.3%, respectively; p<0.001), elevated FBG (32.9% vs. 9.2%, respectively; p<0.001), hypertriglyceridemia (35.7% vs. 21.1%, respectively; p=0.038), and IR (46.2% vs. 9.2%, respectively; p<0.001) were also significantly higher in the NAFLD group. Mean age (49.2±14.6 years vs. 36.4±13.6 years, respectively; p<0.001), BMI (24.1 kg/m^2 vs. 23 kg/m^2, respectively; p<0.001), serum AST (23 IU/L vs. 16 IU/L, respectively; p<0.001), serum ALT (33 IU/L vs. 16.5 IU/L, respectively; p<0.001), serum GGT (34 IU/L vs. 18 IU/L, respectively; p<0.001), HOMA-IR (2.5 vs. 1.4; respectively; p<0.001), and fasting insulin levels (10.5 µu/mL vs. 6.65 µu/mL, respectively; p<0.001) were also significantly higher in the NAFLD group.

Subjects with NAFLD were divided into two subgroups: subjects with normal ALT levels and subjects with elevated ALT levels (ALT>40 IU/L). Male sex was significantly predominant in the high ALT subgroup when compared to the normal ALT subgroup (75.9% vs. 48.3%, respectively; p=0.002). The prevalences of hypertension (31.5% vs. 47.2%, respectively; p<0.094), metabolic syndrome (37% vs. 29.2%, respectively; p=0.43), elevated FBG (35.2% vs. 31.5%, respectively; p=0.78), and hypertriglyceridemia (44.4% vs. 30.3%, respectively; p=0.127) were not significantly different between the high ALT and normal

Table 1. Demographical, metabolic, and biochemical findings of the study group

	NAFLD (n=143)		Control (n=76)		
	n	%	n	%	p
Sex Female	59	%41.3	43	56.6%	0.030*
Male	84	58.7 %	33	43.4%	
Hypertension	59	41.3%	7	9.2 %	<0.001*
Met S	46	32.2%	4	5.3%	<0.001*
Elevated FBG	47	32.9%	7	9.2%	<0.001*
Low HDL	74	51.7%	32	42.1%	0.174
Elevated TG	51	35.7%	16	21.1%	0.038*
IR Presence	66	46.2%	7	9.2%	<0.001*
	Mean±SD		Mean±SD		p
Age (years)	49.2±14.6		36.4±13.6		<0.001*
WHR	0.86±0.07		0.8±0.1		<0.001*
FBG (mg/dL)	95.1±8.3		87.8±8.7		<0.001*
T. cholesterol (mg/dL)	192.4±37.9		170±31.6		<0.001*
HC (cm)	99.0±4.6		95.9±6.4		<0.001*
LDL (mg/dL)	112.7±32.7		98.1±24.6		<0.001*
	Median (Min-Max)		Median (Min-Max)		p
WC (cm)	87 (65-104)		78 (65-102)		<0.001*
AST (IU/L)	23 (10-89)		16 (8-39)		<0.001*
ALT(IU/L)	33 (8-152)		16.5 (6-38)		<0.001*
BMI (kg/m2)	24.1 (19.7-24.9)		23 (18.6-24.9)		<0.001*
GGT (IU/L)	34 (6-139)		18 (8-49)		<0.001*
HDL (mg/dL)	42 (23-80)		47 (22-88)		0.127
Total bilirubin(mg/dL)	0.6 (0.16-2.1)		0.635 (0.24-2.2)		0.336
Direct bilirubin (mg/dL)	0.2 (0.04-1.2)		0.21 (0.03-0.7)		0.089
Fasting Insulin (µu/mL)	10.5 (0.4-125.1)		6.65 (2.6-23.2)		<0.001*
HOMA-IR	2.5 (0.3-25.0)		1.4 (0.4-5)		<0.001*
TG (mg/dL)	129 (35-331)		85 (32-279)		<0.001*

NAFLD: nonalcoholic fatty liver disease; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; Met S: metabolic syndrome; FBG: fasting blood glucose; HDL: high-density lipoprotein; TG: triglycerides; IR: insulin resistance; BMI: body mass index; HOMA-IR: index of insulin resistance calculated according to the HOMA (Homeostasis model assessment) method; T. cholesterol: total cholesterol; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; Min: Minimum; Max: Maximum; Mean±SD: mean±standard deviation

ALT subgroups. The prevalence of IR (63% vs. 36%, respectively; p=0.003) was significantly higher in the high ALT subgroup. BMI (24.4±0.7 kg/m^2 vs. 23.5±1.3 kg/m^2, respectively; p<0.001), serum AST (33.5 IU/L vs. 19 IU/L, respectively; p<0.001), serum ALT (62 IU/L vs. 22 IU/L, respectively; p<0.001), serum GGT (48.5 IU/L vs. 24 IU/L, respectively; p<0.001), HOMA-IR (3.25 vs. 2.2; respectively; p=0.018), and fasting insulin levels (13.05 µu/ml vs. 9.3 µu/ml, respectively; p=0.016) were also significantly higher in the high ALT subgroup when compared to the normal ALT subgroup (Table 2).

Clinical and laboratory characteristics of the subjects according to IR presence

The patients were also classified as insulin-resistant (n:73) and insulin-sensitive (n:146) according to the HOMA-IR value. Statistically significant differences were found between the insulin-resistant and insulin-sensitive groups with regard to sex (male sex: 63% vs. 48.6%, respectively; p=0.044), hypertension (43.8% vs. 23.3%, respectively; p=0.002), elevated FBG (47.9% vs. 13%, respectively; p<0.001), hypertriglyceridemia (46.6% vs. 22.6%, respectively; p<0.001), BMI (23.9±1.3 kg/m^2 vs. 23.2±1.6 kg/m^2, respectively; p=0.001), WC (87.1±8.3 cm vs. 81.7±8.6 cm, respectively; p<0.001), HC (99.7±4.8 cm vs. 97.1±5.6 cm, respectively; p=0.001), WHR (0.9±0.1 vs. 0.8±0.1, respectively; p=0.003), FBG (97.6±7.9 mg/dL vs. 90±8.7 mg/dL, respectively; p<0.001), serum AST (23 IU/L vs. 18 IU/L, respectively; p<0.001), serum ALT (36 IU/L vs. 19.5 IU/L, respectively; p<0.001), serum GGT (35 IU/L vs. 22 IU/L, respectively; p<0.001), and triglyceride levels (152.6±64.6 mg/dL vs. 114.7±57.4 mg/dL, respectively; p<0.001) (Table 3, 4).

Multiple logistic regression analysis of the clinical and laboratory factors associated with NAFLD

According to multiple logistic regression analysis, age, HOMA-IR, and serum ALT levels were independently associated with NAFLD (Table 5).

DISCUSSION

MetS represents a constellation of metabolic and cardiovascular risk factors including abdominal obesity, IR, dyslipidemia, hypertension, and glucose intolerance. It has been generally agreed upon that NAFLD is the hepatic component of MetS, and IR is considered to be the common pathophysiological mechanism (2,12).

Obesity and type 2 DM are established risk factors for MetS and NAFLD (9,13). Nevertheless, NAFLD may also be encountered in non-obese, non-diabetic patients. Kim et al. reported that NAFLD is closely related to metabolic disorders, even in non-obese, non-diabetic individuals. Multiple logistic regression analysis demonstrated that sex, waist circumference, IR, and triglyceride levels were independently related to NAFLD in non-obese subjects (4). Musso et al. found that NAFLD is more closely associated with IR, oxidative stress markers, and endothelial dysfunction when compared to ATP III criteria in non-obese non-diabetic individuals, and may contribute to the detection of subjects with a high cardiometabolic risk profile in this population (5). Recently, Sinn et al. demonstrated that ultrasonographically diagnosed NAFLD independently predicts IR, regardless of how many components of the MetS are present in middle aged, non-obese, non-diabetic Asian adults. In

Table 2. Demographical, metabolic, and biochemical findings of the NAFLD group

		NAFLD patients with normal ALT (n=89)		NAFLD patients with elevated ALT (n=54)		
		n	%	n	%	p
Sex	Female	46	51.7%	13	24.1%	0.002*
	Male	43	48.3%	41	75.9%	
Hypertension		42	47.2%	17	31.5%	0.094
Elevated WC		18	20.2%	8	14.8%	0.556
Met S		26	29.2%	20	37.0%	0.432
Elevated FBG		28	31.5%	19	35.2%	0.783
Low HDL		47	52.8%	27	50.0%	0.745
Elevated TG		27	30.3%	24	44.4%	0.127
IR Presence		32	36.0%	34	63.0%	0.003*
		Mean±SD		Mean±SD		p
Age (years)		52.5±14.9		43.8±12.3		<0.001*
WC (cm)		85.2±8.3		87±8.5		0.211
WHR		0.9±0.1		0.9±0.1		0.411
FBG (mg/dL)		95.3±8.4		94.8±8.4		0.751
T. cholesterol (mg/dL)		190±38.1		196.3±37.5		0.338
BMI (kg/m2)		23.5±1.3		24.4±0.7		<0.001*
HC (cm)		98.7±4.7		99.5±4.5		0.327
LDL (mg/dL)		109.6±33.8		117.6±30.5		0.156
		Median (Min-Max)		Median (Min-Max)		p
AST (IU/L)		19 (10-37)		33.5 (21-89)		<0.001*
ALT (IU/L)		22 (8-43)		62 (27-152)		<0.001*
GGT (IU/L)		24 (6-75)		48.5 (10-139)		<0.001*
HDL (mg/dL)		43 (26-80)		41.5 (23-72)		0.408
Total bilirubin (mg/dL)		0.6 (0.16-2.1)		0.5 (0.24-1.9)		0.177
Direct bilirubin (mg/dL)		0.2 (0.09-1.2)		0.2 (0.04-0.7)		0.079
Fasting Insulin (µu/mL)		9.3 (0.4-68)		13.05 (2.1-125.1)		0.016*
HOMA-IR		2.2 (0.29-17.6)		3.25 (0.5-25)		0.018*
TG (mg/dL)		123 (35-331)		136 (58-296)		0.111

NAFLD: nonalcoholic fatty liver disease; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; Met S: metabolic syndrome; FBG: fasting blood glucose; HDL: high-density lipoprotein; TG: triglycerides; IR: insulin resistance; BMI: body mass index; HOMA-IR: index of insulin resistance calculated according to the HOMA (Homeostasis model assessment) method; T. cholesterol: total cholesterol; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; Min: Minimum; Max: Maximum; Mean±SD: mean±standard deviation

Table 3. Demographic and metabolic characteristics of study subjects according to HOMA-IR index

		Insulin sensitive (HOMA-IR<2.7) (n=146)	Insulin resistant (HOMA-IR≥2.7) (n=73)	
		n (%)	n (%)	p
Sex (Female/Male)		75(51.4%)/ 71(48.6%)	27 (37%)/ 46(63%)	0.044
Hypertension		34 (23.3%)	32 (43.8%)	0.002
Elevated WC		16 (11.0%)	16 (21.9%)	0.050
MetS		16 (11.0%)	34 (46.6%)	<0.001
Elevated FBG		19 (13.0%)	35 (47.9%)	<0.001
Reduced HDL		64 (43.8%)	42 (57.5%)	0.056
Elevated TG		33 (22.6%)	34 (46.6%)	<0.001
Steatosis on USG	Absent	68 (46.6%)	7 (9.6%)	<0.001
	Mild	35 (24.0%)	14(19.2%)	
	Moderate	32 (21.9%)	27(37.0%)	
	Severe	11(7.5%)	25(34.2%)	
		Mean±SD	Mean±SD	p
Age (years)		44.1±15.7	46.2±15.1	0.334
BMI (kg/m^2)		23.2±1.6	23.9±1.3	0.001
WC (cm)		81.7±8.6	87.1±8.3	<0.001
HC (cm)		97.1±5.6	99.7±4.8	0.001
WHR		0.8±0.1	0.9±0.1	0.003

WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; Met S: metabolic syndrome; FBG: fasting blood glucose; HDL: high-density lipoprotein; TG: triglycerides; IR: insulin resistance; BMI: body mass index; HOMA-IR: index of insulin resistance calculated according to the HOMA (Homeostasis model assessment) method; Mean±SD: mean± standard deviation

their study, subjects with IR that could not be identified by the MetS criteria were identified by the presence of NAFLD (6).

To the best of our knowledge, there are no published data about the metabolic significance of NAFLD in non-obese, non-diabetic Turkish subjects. In the present study, we determined that NAFLD was independently associated with IR regardless of the presence of MetS in Turkish subjects. As the findings of the above-mentioned studies imply, the current diagnostic criteria for MetS including the ATP III may be inadequate for the identification of individuals with IR. Our findings are in line with those reported by Musso and Sinn, who demonstrated that NAFLD is more accurate for the diagnosis of IR than MetS is. In our study, we found a significant difference between the NAFLD and control groups with regard to the presence of IR and MetS. In our study population, 46.2% of the individuals in the NAFLD group and 9.2% of the individuals in the control group had IR. When the groups were compared with regard to MetS, it was seen that 32.2% and 5.3% of the individuals had MetS in the NAFLD group and the control group, respectively.

Table 4. Biochemical findings of the study group according to HOMA-IR index

	Insulin sensitive (HOMA-IR<2.7) (n=146)	Insulin resistant (HOMA-IR≥2.7) (n=73)	
	Mean±SD	Mean±SD	p
FBG (mg/dL)	90±8.7	97.6±7.9	<0.001
ALP (IU/L)	71.1±20.1	80.9±22.6	0.001
LDL (mg/dL)	105.5±30.2	111.8±32.1	0.160
TG (mg/dL)	114.7±57.4	152.6±64.6	<0.001
	Median (Min-Max)	Median (Min-Max)	p
AST (IU/L)	18 (8-77)	23 (11-89)	<0.001
ALT (IU/L)	19.5 (6-152)	36 (8-146)	<0.001
GGT (IU/L)	22 (6-130)	35 (9-139)	<0.001
HDL (mg/dL)	44 (22-88)	42 (23-80)	0.050
Total bilirubin (mg/dL)	0.6 (0.2-2.2)	0.6 (0.16-2)	0.214
Direct bilirubin (mg/dL)	0.2 (0.03-1.2)	0.2 (0.09-0.6)	0.218
Fasting insulin (µu/mL)	6.6 (0.4-12.4)	17.1 (9.8-125.1)	<0.001
HOMA-IR	1.4 (0.3-2.7)	4 (2.7-25)	<0.001
Albumin (mg/dL)	4.3 (3.5-5.2)	4.4 (3.4-5.1)	0.208
T. cholesterol	176 (100-288)	187 (118-276)	0.242

FBG: fasting blood glucose; HDL: high-density lipoprotein; TG: triglycerides; IR: insulin resistance; BMI: body mass index; HOMA-IR: index of insulin resistance calculated according to the HOMA (Homeostasis model assessment) method; T. cholesterol: total cholesterol; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; ALP: alkaline phosphatase; Min: Minimum: Max: Maximum; Mean±SD: Mean± standard deviation

Table 5. Multiple Logistic Regression Analysis of The Clinical and Laboratory Factors Associated With NAFLD

	Odds ratio (95% CI)	p
Sex (male vs. female)	0.866 (0.361-2.077)	0.746
Age(year)	1.074 (1.035-1.115)	<0.001
Elevated TG (yes vs. no)	0.756 (0.272-2.102)	0.592
Reduced HDL (yes vs. no)	1.481 (0.633-3.466)	0.366
Elevated FBG (yes vs. no)	1.591 (0.456-5.553)	0.467
Met S (yes vs. no)	1.200 (0.251-5.746)	0.820
Hypertension (yes vs. no)	0.961 (0.254-3.628)	0.953
HOMA-IR	1.534 (1.037-2.268)	0.032
ALT(U/L)	1.102 (1.058-1.147)	<0.001

CI: confidence interval; Met S: metabolic syndrome; FBG: fasting blood glucose; HOMA-IR: index of insulin resistance calculated according to the HOMA (Homeostasis model assessment) method; HDL: high-density lipoprotein; TG: triglycerides; BMI: body mass index; ALT: alanine aminotransferase

In our study we did not perform OGTT (Oral glucose tolerance test) and we relied on history of previously documented impaired glucose tolerance and/or diabetes. Likewise, OGTT was not performed in most of the studies on this subject (4,6).

Some authors suggest that NAFLD should be included in the definition of MetS (5,12). In our study group, NAFLD was independently associated with IR irrespective of the presence of MetS. However, considering our relatively small sample size, we conclude that further studies are required to clarify this issue.

There were some limitations to our study. Ultrasonography was utilized to detect fatty liver disease, rather than a liver biopsy. Ultrasonography is currently the most widely utilized method for screening asymptomatic patients with elevated liver enzymes and suspected NAFLD. Nevertheless, ultrasonography cannot provide precise quantitative information about the degree of fat accumulation, or detect inflammation and fibrosis, and thus it cannot be utilized to diagnose NASH and hepatic fibrosis (14). However, the aim of this study was to determine whether ultrasonographically diagnosed NAFLD is more closely associated with IR than MetS is in non-obese, non-diabetic subjects.

Another limitation of our study was the relatively small sample size and that participants were either check-up patients or subjects with dyspeptic symptoms. The predictive value of NAFLD for IR may be different in the general population.

In summary, the findings of our study imply that IR and MetS are not rare in non-obese, non-diabetic Turkish NAFLD subjects. Ultrasonographically detected NAFLD was independently associated with IR, irrespective of the presence of MetS. Ultrasonographically detected NAFLD may be helpful for identifying patients with IR. Early identification of such patients at higher cardiometabolic risk may alert healthcare providers to initiate timely lifestyle and pharmacological interventions. We propose that further studies in larger patient populations are warranted to verify that ultrasonographically detected NAFLD is independently associated with IR, irrespective of the presence of MetS in non-obese, non-diabetic Turkish subjects.

Conflict of Interest: No conflict of interest was declared by the authors.

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