Original Article

Assessment of Lean Patients with Non-alcoholic Fatty Liver Disease in a Middle Income Country; Prevalence and Its Association with Metabolic Disorders: A Cross-sectional Study

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Abstract

Background: Recent data has proven that the WHO (world health organization) cut-off for obesity is not applicable to the Asian population. This study aims to estimate the prevalence of lean NAFLD (non-alcoholic fatty liver disease) in the capital of Iran and extract probable predictors for this growing health issue in this population.

Methods: This is a population-based cross-sectional study on apparently healthy subjects over 18 years of age. The participants were interviewed for baseline demographic and clinical information. They were subsequently referred for physical examination and blood sampling. NAFLD was diagnosed using abdominal ultrasonography by a single expert radiologist.

Results: Of 927 eligible participants who entered the study, 314 were lean; BMI (body mass index) <25 kg/m^2. The prevalence of NAFLD was 17.52% (95% Exact CI: 13.48%–22.18%). BMI, SBP (systolic blood pressure), DBP (diastolic blood pressure), total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein) and triglyceride were significantly different in patients with NAFLD. In the final multiple analysis, higher levels of triglyceride, upper SBP and higher BMI even in the range of less than 25 kg/m^2 were independent predictors of NAFLD in lean participants. In lean participants with more components of metabolic syndrome, the prevalence of NAFLD increased significantly (all $P < 0.01$). BMI cut-offs in men and women along with waist circumference cut-off in men could significantly predict the presence of NAFLD in lean patients. After comparing these values, McNemar test showed that BMI cut-offs are more robust than waist circumference cut-offs for predicting the presence of NAFLD in lean subjects ($P < 0.01$).

Conclusion: The prevalence of NAFLD in lean subjects in a sample of Iranian population is 17.52%. Hypertriglyceridemia, higher SBP, and higher BMI especially over 23.2 are independent factors associated with the presence of NAFLD in lean subjects.

Keywords: Cut-off, lean, metabolic syndrome X, Non-alcoholic fatty liver disease, non-obese

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Introduction

Prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide, mainly as a result of the global pandemic of obesity.[1] Recent data has proven that the World Health Organization (WHO) cut-off for obesity (body mass index (BMI) > 30 kg/m^2) is not applicable to the Asian population, as they have more body fat at any level of BMI.[2–4] Some Asian studies have focused on the prevalence and severity of NAFLD among subjects with normal BMI and found that the prevalence of NAFLD is of great importance.[5–10] Different studies show identical prognosis of NAFLD among lean patients in comparison with obese subject.[5,7,11] but some reports indicate that the severity of nonalcoholic steatohepatitis (NASH) and liver fibrosis is more prominent in non-obese subjects.[12,13] Some studies have shown that human genome has an influence on lean NAFLD and its severity. In this regard, polymorphism in PNPLA3[14,15] and TM6SF2[16,17] genes have been recognized to affect both disease severity and progression in lean patients with NAFLD. These genes accumulate triglyceride in the liver but do not affect the metabolic panel and thereby, result in NAFLD in lean subjects who do not suffer from the metabolic syndrome.

Several studies have estimated the prevalence of NAFLD among Iranian general population,[18–22] but few have measured the prevalence and predictors of NAFLD in lean (BMI < 25kg/m^2) subjects.[23,24] This study aims to assess the prevalence of lean NAFLD in the capital of Iran and extract probable predictors for this growing health issue in this population.

Materials and Methods

Study design

This is a population-based cross-sectional study conducted on apparently healthy subjects over 18 years of age in Tehran, the

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capital of the Islamic Republic of Iran, between January 2015 and January 2016. Participants were selected using a random approach. To have a representative sample of the population, family registries of public health centers were considered as the sampling frame, while two samples with an average size of 30 were recruited from each public health center registry using computer-generated random numbers.

Subjects with any of the following were excluded:

1) Positive serum level for hepatitis B surface antigen (HBsAg) (using enzyme-linked immunosorbent assay, Enzygnost, Siemens);
2) Positive serum level for hepatitis C virus antibody (HCVAb) (using enzyme-linked immunosorbent assay, Hepanostika, Beijing United Biomedical);
3) Alcohol use more than 20 grams per day;
4) Active malignancy, and
5) History of chronic liver diseases including Wilson's disease, hemochromatosis, and autoimmune hepatitis.

Written informed consent was obtained from all subjects or their legally authorized representatives (LARs), and they were free to withdraw from the study at any stage.

Data collection

Participants were recruited in an 8-hour fasting status to Farabi Hospital. They were re-interviewed for baseline demographic and clinical information. They were subsequently referred for physical examination, blood sampling and abdominal ultrasonography.

Physical examination

All participants underwent general physical examination. Weight was measured in upright position using a digital well-calibrated scale on hard ground while the participants wore light clothes without shoes. Height was measured to the nearest 0.1 cm with a standard ruler on a wall with the participants standing upright, the feet paired and their back to the ruler. Waist and hip circumference were measured at the level midway between the lower rib margin and iliac crest while the subjects were requested to breathe out and at the widest point over the buttocks to the nearest 0.5 cm, respectively. Waist-hip ratio (WHR) was calculated as waist circumference (cm) to hip circumference (cm).

Blood pressure was measured using a calibrated sphygmomanometer following 10 minutes of relaxation and the measurement was repeated 2 minutes later. The average was documented as the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the participants. Subjects taking antihypertensive medications or those with SBP ³ 140 mmHg or DBP ³ 90 mmHg were considered hypertensive.

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.[25] Also, we added another definition of metabolic syndrome; Joint Interim Statement (JIS), since some studies have shown that definition of metabolic syndrome according to (JIS) is more acceptable for the Mediterranean population.[26]

Blood sampling

Ten milliliters of antecubital venous blood sample was extracted to measure serum levels of fasting plasma glucose (FPG), lipid profile (total cholesterol, high-density lipoprotein (HDL), Low-density lipoprotein (LDL) and triglyceride), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).

Diabetes mellitus was defined as FPG ³ 126 mg/dL or taking antihyperglycemic medications.[27]

Abdominal sonography

NAFL or simple steatosis was diagnosed using abdominal ultrasonography by a single expert radiologist who was blind to previous records of participants. We used 3.5–5 MHz transducers, General Electric Logiq 200 scanner. Steatosis was defined as poor penetration of the posterior segment of the right lobe of the liver, increase in hepatic echogenicity, and poor or no visualization of the hepatic vessels and diaphragm.[28]

Statistical analysis

Data were analyzed using IBM SPSS Statistics (version 22) for windows. All participant with BMI < 25 kg/m^2 were included in the analysis. Data are reported as mean (standard deviation; SD) or number (%) as appropriate. Statistical difference was calculated using student's t test for quantitative and chi-square test for qualitative covariates. Variables with $P < 0.1$ on univariate analysis entered a binary multiple logistic regression model. Stepwise backward and forward analyses were done and compared to identify the independent predictors for NAFLD in subjects with BMI < 25 kg/m^2. In stepwise regression, variables with $P < 0.05$ entered the model and those with $P > 0.1$ were omitted. Also, to obtain the best cut-off for BMI and waist circumference in order to predict the presence of NAFLD in lean patients, we used ROC curve. Best cut-offs were chosen using Youden's J statistic.(29) Sensitivity, specificity, likelihood ratios and diagnostic odds ratio were calculated for the best cut-offs. Overall, $P < 0.05$ was considered statistically significant.

The study protocol was approved by the ethics board of Digestive Disease Research Institute (DDRI) and ethics committee of Tehran University of Medical Sciences (approval letter code IR.TUMS.REC.1394.1927).

Quality control was undertaken in different steps of the study. In various unpredicted time points, we assessed the whole project, from subject recruitment to data collection and data entry.

Results

Of 927 eligible participants who entered the study, 314 were lean (BMI < 25 kg/m^2). The mean age was 41.93 (14.79) years and 44.3% were male (Table 1). The total number of participants with NAFLD was 55, and the prevalence of NAFLD was 17.52% (95% exact confidence interval (CI) 13.48%–22.18%). There were no significant differences in age and sex between participants with or without NAFLD, while BMI, SBP, DBP, total cholesterol, HDL, LDL and triglyceride were significantly different in patients with NAFLD. Interestingly, waist circumference in men and hip circumference in women were higher in patients with NAFLD. The prevalence of metabolic syndrome according to ATP III or JIS definitions was not statistically higher in patients with NAFLD than those without NAFLD.

In the final multiple analysis, the results of backward and forward stepwise regression were similar. Higher levels of triglyceride, upper systolic blood pressure and higher BMI even in the range of less than 25 kg/m^2 were independent predictors of NAFL in lean participants (Table 2).

The prevalence of NAFL did not increase according to age in

Table 1. Characteristics of the Lean Participants by the NAFL status.

	Total (n = 314)		Non-NAFLD (n = 259)		NAFLD (n = 55)		*P*-Value*
Age, mean (SD)	41.93	(14.79)	41.63	(14.89)	43.29	(14.38)	.45
Gender, *n* (%)							.91
Male	139	(44.30)	115	(36.60)	24	(7.60)	
Female	175	(55.70)	144	(45.90)	31	(9.90)	
Weight, mean (SD)							
Male	62.03	(10.21)	61.56	(10.60)	64.36	(7.74)	.24
Female	59.50	(9.54)	59.35	(9.87)	60.33	(7.53)	.64
Total	60.64	(9.91)	60.34	(10.24)	62.26	(7.82)	.23
Height, mean (SD)							
Male	165.89	(11.32)	165.85	(11.59)	166.09	(10.08)	.92
Female	163.37	(10.38)	163.72	(10.44)	161.37	(10.06)	.30
Total	164.51	(10.87)	164.67	(10.99)	163.63	(10.24)	.55
BMI, mean (SD)							
Male	22.40	(2.01)	22.23	(2.09)	23.28	(1.24)	<.01
Female	22.22	(2.27)	22.05	(2.33)	23.14	(1.67)	.03
Total	22.30	(2.15)	22.13	(2.22)	23.21	(1.46)	<.01
Waist Circ. , mean (SD)							
Male	80.65	(9.36)	79.54	(9.38)	86.27	(7.08)	<.01
Female	78.80	(8.99)	78.75	(8.66)	79.08	(10.88)	.86
Total	79.64	(9.19)	79.10	(8.98)	82.52	(9.85)	.02
Hip, mean (SD)							
Male	97.32	(7.06)	97.20	(7.47)	97.95	(4.55)	.64
Female	96.66	(6.18)	96.30	(6.26)	98.71	(5.35)	.07
Total	96.96	(6.59)	96.70	(6.83)	98.35	(4.95)	.12
WHR, mean (SD)							
Male	.83	(.08)	.82	(.08)	.88	(.06)	<.01
Female	.82	(.08)	.82	(.08)	.80	(.11)	.39
Total	.82	(.08)	.82	(.08)	.84	(.10)	.10
SBP, mean (SD)	112.07	(16.94)	110.59	(15.91)	119.15	(19.89)	<.01
DBP, mean (SD)	76.20	(8.70)	75.63	(8.29)	78.94	(10.09)	.01
Hypertension, n (%)	28	(8.9)	16	(5.1)	12	(3.8)	<.01
Diabetes Mellitus, n (%)	19	(6.1)	11	(3.5)	8	(2.5)	<.01
Metabolic Syndrome (ATPIII), n (%)	19	(6.1)	13	(4.1)	6	(1.9)	.09
Metabolic Syndrome (JIS), n (%)	27	(8.6)	20	(6.4)	7	(2.2)	0.22
Total Cholesterol, mean (SD)	163.46	(37.14)	159.32	(34.80)	182.84	(41.71)	<.01
HDL, mean (SD)	47.82	(10.96)	47.90	(10.73)	47.44	(12.06)	<.01
LDL, mean (SD)	96.10	(30.22)	93.34	(28.45)	108.91	(34.84)	.03
TG, mean (SD)	101.66	(53.99)	95.07	(43.52)	132.45	(81.46)	<.01
FPG, mean (SD)	85.31	(27.94)	84.00	(28.74)	91.40	(23.13)	.07
AST, mean (SD)	20.83	(6.27)	20.67	(6.30)	21.62	(6.11)	.31
ALT, mean (SD)	18.35	(6.79)	17.98	(6.64)	20.11	(7.24)	.03
ALP, mean (SD)	171.01	(63.86)	169.66	(66.88)	177.44	(46.89)	.42

* *P* value for the difference between subjects with and without NAFLD.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATPIII = adult treatment panel III; BMI = body mass index; FPG = fasting plasma glucose; HDL = high-density lipoprotein; JIS = Joint Interim Statement; LDL = low-density lipoprotein; NAFL = nonalcoholic fatty liver; SE = standard error of mean; TG = triglyceride; WHR = Waist to hip ratio.

Table 2. Result of the Stepwise Multiple Logistic Regression Analysis of Predictors of Nonalcoholic Fatty Liver in Lean Participants.

	Odds Ratio	SE	Z	P Value	[95% Conf. Interval]	
Increase 10 mg/dL in TG	1.101	.0300	3.490	<.010	[1.043	1.162]
Increase 10 mmHg in SBP	1.212	.116	2.000	0.045	[1.004	1.436]
BMI	1.278	.137	2.290	0.022	[1.036	1.576]

TG = triglyceride; SBP = systolic blood pressure; BMI = body mass index

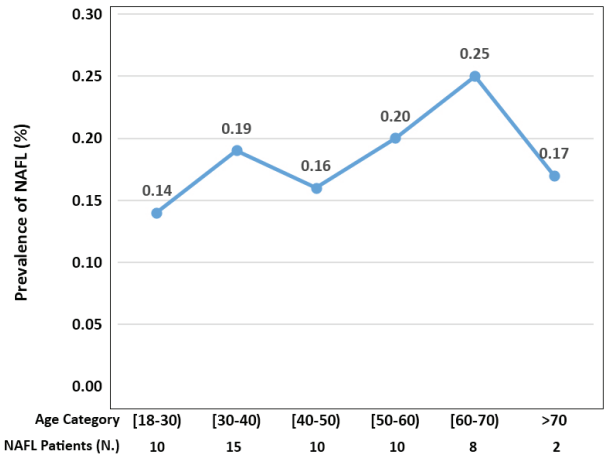

Figure 1. Prevalence of NAFL in Lean Subjects According to Different Age Categories.

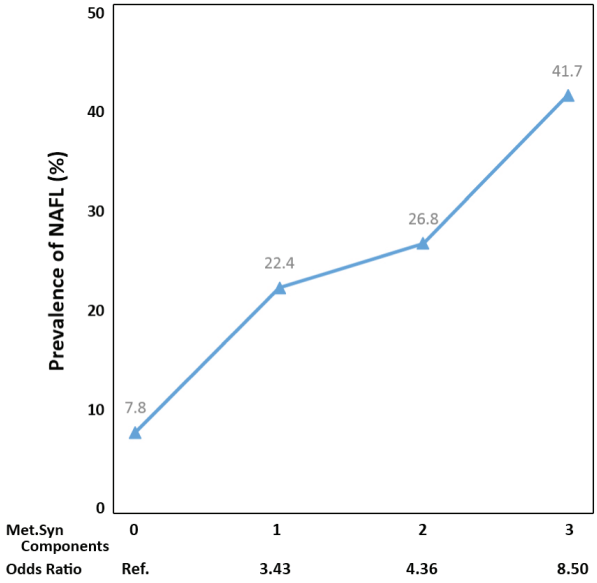

Figure 2. Prevalence of NAFLD in Lean Subjects According to the Number of Components of Metabolic Syndrome.

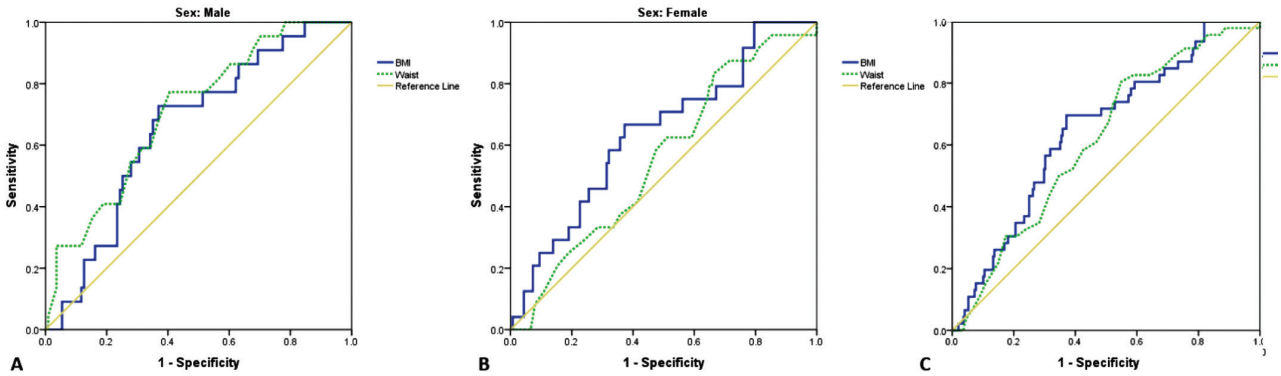

Figure 3. Receiver Operating Characteristic (ROC) Curve for Different Cut-Offs of BMI and Waist Circumference in Predicting the Presence of NAFL.

men and women (Figure 1). Overall, changes in age were not associated with increasing or decreasing prevalence of NAFL (P = 0.45). Also, on subgroup analyses, there were no significant associations in either men (P = 0.72) or women (P = 0.50) regarding age or prevalence of NAFLD.

The prevalence of metabolic syndrome in lean subjects with NAFLD was not significantly higher than subjects without NAFLD (Table 1); however, in lean participants with more components of metabolic syndrome, the prevalence of NAFLD increased significantly (all P < 0.01) (Figure 2).

Figure 3 depicts three receiver operating characteristic (ROC) curves for different cut-offs of BMI and waist circumference for predicting the presence of NAFL, in men, women and the overall lean population.

Table 3 shows the best cut-offs for BMI and waist circumference for predicting NAFLD in lean subjects, in both men and women. BMI cut-offs in men and women along with waist circumference cut-off in men could significantly predict the presence of NAFLD in lean patients. After comparing these values, McNemar test showed that BMI cut-offs are more robust than waist circumference cut-offs for predicting the presence of NAFL in lean subjects (P < 0.01).

Discussion

Cho[9] reported almost the same results about the comparison of two subgroups of lean subjects but the prevalence of NAFLD was 12.4%, and lean subjects with NALFD were significantly older and predominantly male. Generally, it has been estimated that the prevalence of lean NAFLD ranges from 20–40% in the United States and Europe[30] to 12–42% in the Asian general population,[8,31–34] which is significantly lower than the prevalence among obese subjects.

There are specific criteria to claim that an individual has

Table 3. Different Cut-offs for BMI and Waist Circumference and Its related determinants in predicting the presence of NAFL.

	Cut-off	Sen.	Spe.	LR+	LR-	DOR	AUC	Confidence Interval		*P. Value*
BMI, **kg/m²**										
Male	**23.12**	0.73	0.63	1.97	0.43	4.56	0.66	0.54	0.77	0.02
Female	**23.19**	0.67	0.63	1.79	0.53	3.38	0.64	0.52	0.76	0.03
Total	-	0.67	0.63	1.82	0.52	3.51	0.64	0.57	0.73	0.02
Waist, **cm**										
Male	**82.50**	0.77	0.60	1.91	0.38	5.00	0.71	0.60	0.82	<0.01
Female	**73.50**	0.83	0.34	1.25	0.50	2.52	0.56	0.44	0.67	0.38
Total	-	0.80	0.45	1.47	0.43	3.38	0.61	0.53	0.70	0.01

Sen. = Sensitivity; Spe. = Specificity; LR = Likelihood Ratio; DOR = Diagnostic Odds Ratio; AUC = Area Under Curve
** We compared the estimated cut-off for BMI and waist circumference using McNemar test. McNemar test showed that obtained cut-offs for BMI are more robust ones (*P*-Value < 0.01).

metabolic syndrome, among which anthropometric measurement is a cornerstone. Recent world health organization expert consultation pronounced that the body-mass index (BMI) criterion is not suitable for Asian populations since the relation between BMI and metabolic syndrome is ethnic-specific.[35] They report that Asians have a higher percentage of body fat compared age, sex, and BMI-matched white individuals. Also, Asians have a greater number of risk factors to develop type 2 diabetes mellitus and cardiovascular disease even when BMI is < 25 kg/m². In this regard, the WHO has indicated that different anthropometric measurements such as waist circumference, which reflects body-fat distribution and measures health in association with BMI, may be more accurate to predict the risk of metabolic diseases.[3]

Central obesity can be assessed by measuring the visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and is directly associated with metabolic and cardiovascular diseases.[36,37] VAT and SAT are different in terms of anatomical location, endocrine activity, saturation status, and their effect on disturbing glucose and lipid metabolism as well as serum triglyceride level.[38–42] In a longitudinal study of 288 patients with NAFLD, Kim *et al.* showed that an increase in VAT area at baseline is an independent predictor of NAFLD development, while increases in the SAT area are associated with regression of NAFLD in an apparently healthy general population.[43] In our study, multiple analysis revealed that BMI is an independent predictor of NAFLD in the lean population and our data suggest a cut-off of 23 kg/m² for BMI for predicting lean NAFLD. Previous studies support the fact that in lean subjects, those with higher BMI levels are at greater risk of developing NAFLD.[44–46] Furthermore, Ostovaneh *et al.*,[23] emphasized the importance of visceral adiposity and possible correlation between central adiposity indices, including waist circumference and waist to hip ratio, with NAFLD, cardiovascular disorders, and other obesity-related complications. In our study, we demonstrate that a waist circumference cut-off of 82 cm could significantly predict the presence of NAFL in lean male subjects and this cut-off is far from the proposed cut-off points in adult treatment panel III (ATP III) (102 cm)[25] or the Iranian population (94.5 cm).[47]

In this study, both systolic and diastolic blood pressures were higher in NALF subjects. Others have reported this finding and also demonstrated an association between hypertension and a greater risk of NAFLD in the general population.[48,49] In our study, systolic blood pressure was an independent factor of developing NAFLD in lean subjects. Whether hypertension has a causal effect on developing NAFLD remains unknown, but it clearly has a significant effect on development of the metabolic syndrome in both NAFLD and non-NAFLD subjects.

Previous studies have proven a role for dyslipidemia in development of NAFLD.[23,44,46,48–51] In the current study, hypertriglyceridemia was independently associated with lean NALFD subjects. Traditionally, two pathogenetic pathways are described for development of NASH: Visceral fat deposits causing an increased influx of free fatty acids to liver; and insulin resistance causing increased secretion of very low-density lipoprotein (VLDL).[52] More recent studies propose that although dyslipidemia and dysglycemia are two components of fatty liver disease, this condition is independent of fat deposits, including visceral adipose tissue.[53] In light of current findings, regardless of the role of visceral adipose tissue in development of fatty liver, hypertriglyceridemia *per se* should be considered a marker of NAFLD in lean subjects.

Serum insulin level were not measured in our subjects, so we are not able to make comments about the direct role of insulin resistance in the development of NAFLD in lean individuals. Nevertheless, the fact that metabolic syndrome is related to insulin resistance can indirectly connect NAFLD to metabolic irregularities.[54,55] Our study shows that the prevalence of NAFLD increases along with an increase in the number of components of metabolic syndrome in lean subjects. Sinn *et al.*,[56] declared that irrespective of the number of metabolic syndrome components in lean Asian adults, NAFLD is an independent predictor of insulin resistance. One of the frequently used indices for assessing insulin resistance is the homeostasis model assessment of insulin resistance (HOMA-IR).[57] Few studies have assessed the role of HOMA-IR in lean patients with NAFLD and have confirmed higher levels of insulin resistance in lean NAFLD patients.[34,58,59]

Cho *et al.*[9] reported the association between higher HOMA-IR and higher prevalence of NAFLD in lean subjects in their study. They concluded that NAFLD shows better correlation with insulin resistance rather than metabolic syndrome, and suggested current ATP-III diagnostic criteria for the metabolic syndrome to be revised to identify NAFLD in lean subjects accurately.

Ratziu *et al.*[60] suggested that high ALT level is a marker of the progression of NAFLD to steatohepatitis and hepatic fibrosis. Although we found higher ALT level in the NAFLD subgroup, it was not a significant predictor of presence of NAFLD. It seems

that higher levels of ALT in lean NAFL patients are a consequence of this disease while fatty deposition in the liver might cause oxidative damage to the liver and elevate serum ALT.

Our study has some limitations. The cross-sectional nature of the study precludes a conclusion regarding natural course of NAFLD and causal relationships. Although ultrasonography is the main diagnostic modality in epidemiological studies of NAFLD and it has acceptable sensitivity for detection of hepatic steatosis, the fact that it is operator based limits the results.

In conclusion, the prevalence of NAFLD in lean subjects in the capital city of Tehran which might be a representative sample of the whole country is 17.52%. Hypertriglyceridemia, higher SBP, and higher BMI are independent factors associated with the presence of NAFLD in lean subjects. Our results indicate that the Iranian population may develop NAFLD even if they have normal BMI ranges. This is a rather high prevalence, and has implications for health studies in Iranian NAFLD patients.

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