Original Article

Biochemical markers and lipid profile in nonalcoholic fatty liver disease patients in the PERSIAN Guilan cohort study (PGCS), Iran

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Abstract

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) is a global epidemic that is often asymptomatic and silent, and progresses slowly. This study aimed to determine the biochemical markers and lipid profile among NAFLD patients and their possible relationship with degrees of fatty liver. **Methods:** This is analytical cross-sectional study, in which, 950 individuals referred to the PERSIAN Guilan cohort study were included through sequential sampling method. The demographic information and blood pressure of the subjects were taken and the blood sample was prepared to investigate the biochemical markers and lipid profile. Also, abdominal ultrasonography was performed to investigate NAFLD and its grades. For data analysis, independent sample *t*-test, one-way ANOVA, and logistic regression model were used, where $P < 0.05$ was considered significant. **Results:** The systolic blood pressure (SBP) ($P < 0.001$), diastolic blood pressure (DBP) ($P < 0.001$), hepatic enzymes (aspartate aminotransferase [AST], $P < 0.001$, alanine aminotransferase [ALT], $P < 0.001$; gamma-glutamyle transferase [GGT], $P < 0.001$; AST/ALT ratio, $P < 0.001$), lipid profile (triglyceride [TG], $P < 0.001$; total cholesterol [TC], $P = 0.008$; high density lipoprotein [HDL], $P < 0.001$; LDL-C/HDL-C (ratio), $P = 0.003$; TC/HDL-C (ratio), $P < 0.001$); and fasting blood sugar [FBS], $P < 0.001$ correlated with NAFLD. However, there was no relationship between age ($P = 0.34$), alkaline phosphatase [ALP] ($P = 0.26$) and low-density lipoprotein [LDL] ($P = 0.72$). Further, a significant relationship was observed between AST ($P < 0.001$), ALT ($P < 0.001$), and GGT ($P = 0.004$) and NAFLD degrees based on the ultrasonography. **Conclusion:** Biochemical markers and lipid profile are associated with NAFLD. Thus, it is recommended to investigate NAFLD in clinical settings in cases in which their changes are observed in patients through ultrasonography.

Keywords: Biochemical markers, lipid profile, nonalcoholic fatty liver disease

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a global epidemic which is mostly asymptomatic and progresses slowly.[1] NAFLD involves a whole spectrum of liver pathologies from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[2]

Prevalence of NAFLD has doubled over the past 20 years, while prevalence of other chronic diseases of the liver has remained constant and even diminished.[3] Prevalence of NAFLD in the world is about 25%,[4] in non-obese Asian-Pacific individuals, it is 15–21%,[5] in American adults, it is 30%, and in Italy, it has been reported to be 25%.[6] In the Iranian general population,

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prevalence of NAFLD and NASH ranges between 2.9 and 7.1%, and in the south of Iran, it has been reported as 21.5%.[7] Also, a systematic review studies reported a prevalence of 33.95% for NAFLD in Iran.[8]

NAFLD is identified by abnormal liver tests, imaging studies, and liver biopsy, and has the potential to become the most common cause of liver transplantation in the future.[1] Ultrasonography of the liver is the most common technique for screening fatty liver in the general population.[6]

One of the common reasons for patients' visit to gastroenterology or hepatology clinics is the high levels of aminotransferase tests. Thus, currently, special attention is paid to transaminase values and in many studies, NAFLD diagnosis is based on abnormal aspartame transaminase (AST) and alanine transaminase (ALT) values.[9,10] Accordingly, in clinical settings, to detect NAFLD, measurement of aminotransferases, blood lipids, and insulin resistance (IR) are often used.[11,12] Several indicators such as lipid profile, AST, ALT, fasting blood sugar (FBS), CRP, and fasting insulin level play a significant role in NAFLD. These indicators assist in understanding the severity and prognosis of the disease, and also results in early intervention, which is a good alternative to liver biopsy.[2,13]

This study aimed to determine biochemical markers and lipid profile in patients with and without NAFLD, and also examine their possible relationship with degrees of NAFLD.

Methods

In this analytical-cross-sectional study, 950 individuals aged 35–60 years referred to the PERSIAN Guilan Cohort Study (PGCS), part of the Prospective Epidemiological Research Studies in Iran (The PERSIAN Cohort Study)[14] (from April 2017 to September 2017), were included through sequential sampling method. Not having chronic and acute liver disease including viral hepatitis C, B, chronic or acute kidney disease, cancers, alcohol consumption (men, more than 20 g/day, and women, more than 10 g/day), pregnancy, taking medications affecting the liver such as steroids, amiodarone, tamoxifen, and patients with proven hemochromatosis, were considered as the exclusion criteria for this study, and identification of the subjects was conducted based on the file created in the cohort plan.[14]

Instruments

After receiving consent form and explaining the research objectives, the personal information of the subjects (age, gender, and level of education, occupation, place of residence, marital status and smoking) was completed face-to-face. Blood pressure (mmHg) was measured by cuff pressure gauge (MTM Munich, Germany) and based on the PERSIAN cohort protocol.[14] Systolic blood pressure equal to or above 140 mmHg or diastolic blood pressure equal to or above 90 mmHg were considered as hypertension.[15]

Venous blood sample was taken from all participants after 12 h of fasting, and then sent to the laboratory of the unit on the same day. Parameters including hepatic enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamy ltransferase (GGT) as well as the lipid profile including triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood sugar (FBS) were examined by quantitative diagnostic kit (Parsazmoon Co., Tehran, Iran) and investigated through photometric method. Abdominal ultrasonography was performed by ultrasonix device from sonix SP series using a deep probe of 3.5-5 MHz to detect fatty liver and confirmed by two radiologists residing in the cohort center. Based on the sonography findings, fatty liver was categorized into three grades: Grade 1 (mild): elevated echogenicity of liver paranchyma with visible periportal and diaphragm; Grade 2 (moderate): elevated echogenicity of liver paranchyma with obstruction of the walls of the portal vein branches, without diaphragm blockage; Grade 3 (severe): elevated echogenicity of liver paranchyma with undetectable periportal echogenicity and diaphragm obstruction.[16] The subjects in this study were considered as NAFLD group with any degree and severity of liver disease.

Data analysis

For all analyses, SPSS 18 was used. The numerical variables were expressed as mean ± standard deviation (SD), while the classification variables were expressed by number (%). Statistical analysis was done by independent sample *t*-test, one-way ANOVA and logistic regression model. *P* value less than 0.05 was considered significant.

Ethics

This study has been registered in the committee of research and ethics of the Research Center for Gastroenterology and Hepatology of Guilan University of Medical Sciences (registration code: IR.GUMS.REC.1394.499). Written consent form was obtained from all the subjects and at any stage of the research, they were free to withdraw from the study.

Results

Of 950 cases, 587 (61.8%) were female, out of which 154 (42.4%) had NAFLD. The minimum age was 35 and the maximum was 60 years, and 382 (40.2%) were within the age range of 35-44 years. The demographic information of the subjects per NAFLD and non-NAFLD is reported in [Table 1].

In this study, the mean age of the subjects was 47.14 ± 7.2 years, and the mean FBS, systolic blood pressure (SBP), and diastolic blood pressure (DBP) was 102.59 ± 31.7, 120.62 ± 16.84 and 80.70 ± 11.35, respectively. The total mean of the results of lipid profile and level of hepatic enzymes is presented in [Table 2].

The results of this study showed no significant relationship between age and NAFLD (P = 0.34, OR: 1.009; 95% CI:

Table 1: Demographic characteristics of participants

Variables	Total *n* (%)	Subjects without NAFLD *n* (%)	Subjects with NAFLD *n* (%)
Gender			
Male	353 (38.2)	325 (55.4)	262 (44.6)
Female	587 (61.8)	209 (57.6)	154 (42.4)
Residence			
City	677 (71.3)	375 (55.4)	302 (44.6)
Village	273 (28.7)	159 (58.2)	114 (41.8)
Job			
Farmer	108 (11.4)	72 (66.7)	36 (33.3)
Housewife	310 (32.6)	172 (55.5)	138 (44.5)
Employed	160 (16.8)	92 (57.5)	68 (42.5)
Worker	130 (13.7)	64 (49.2)	66 (50.8)
self-employed	242 (25.5)	134 (55.4)	108 (44.6)
Education			
Illiterate	61 (6.4)	30 (49.2)	31 (50.8)
Elementary	204 (21.5)	112 (54.9)	92 (45.1)
High school	545 (57.4)	317 (58.2)	228 (41.8)
Academic	140 (14.7)	75 (53.6)	65 (46.4)
Age (years)			
35-44	382 (40.2)	218 (57.1)	164 (42.9)
45-54	366 (38.5)	199 (57.4)	167 (45.6)
55-60	202 (21.3)	117 (57.9)	85 (42.1)
Smoking			
Yes	290 (30.5)	143 (49.3)	147 (50.7)
No	660 (69.5)	391 (59.2)	269 (40.8)
Marital status			
Single	29 (3.1)	17 (58.6)	12 (41.4)
Married	921 (96.9)	517 (56.2)	404 (43.9)

NAFLD: Non-alcoholic fatty liver disease

Table 2: Baseline characteristics

Variables	Mean±SD
Age (y)	47.14±7.2
Systolic BP	120.62±16.84
Diastolic BP	80.70±11.35
FBS (mg/dl)	102.59±31.7
AST (U/L)	20.08±9.8
ALT (U/L)	21.68±16.4
ALP (U/L)	193.75±55.5
GGT (U/L)	27.69±23.3
AST/ALT ratio	1.13±0.49
Triglycerides (mg/dl)	172.83±94.5
Total cholesterol (mg/dl)	201.43±37±0.2
HDL-C (mg/dl)	45.24±9.4
LDL-C (mg/dl)	121.51±30.9
LDL-C/HDL-C (ratio)	2.75±0.7
TC/HDL-C (ratio)	4.59±1.09

FBS: Fasting blood sugar; HDL: C high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase

0.991-1.026). In the NAFLD group, the mean values of TG, GGT, AST, ALT, ALP, and TC were higher, while that of HDL was lower than those of non-NAFLD [Table 3].

The results of this study showed that with elevation of SBP, DBP, FBS, TC, LDL/HDL ratio, TC/HDL ratio, AST/ALT ratio, GGT, ALT, and AST (OR >1), and reduction of HDL (OR <1), the possibility of developing NAFLD increased, whereby, a significant relationship was observed ($P < 0.05$). However, the level of LDL (121.82 ± 32.50 vs. 121.10 ± 29.71; OR: 0.999; 95% CI: 0.995-1.003) and ALP (196.01 ± 53.71 vs. 192.00 ± 56.92; OR: 1.001; 95% CI: 0.999-1.004) was not significant between the groups [Table 3].

When the changes in biochemical parameters were compared with different degrees of NAFLD, the research results showed that there was a relationship between GGT ($P = 0.004$), ALT ($P = 0.007$) and AST ($P < 0.001$), and the severity of fatty liver [Table 4].

Discussion

Since NAFLD does not have any special clinical sign and is a silent disease, this study tries to express the relationship between clinical together with laboratory signs, and NAFLD.

As reported by Pardhe *et al.*[16], there is no significant relationship between age and NAFLD. Similarly, Uppalapti *et al.*[17] provided results in a study on diabetic patients, which is in line with the current study. However, Navokovic *et al.*[18] and Swain *et al.*[10] reported that there is a significant relationship between age and NAFLD.

Dyslipidemia is known as a risk factor for NAFLD. In this study, individuals in the NAFLD group had a higher TC, LDL/HDL

Table 3: The values of assessed clinical and laboratory data (expressed as±SD) of subjects NAFLD and Non- NAFLD

Variables	Non-NAFLD *n*=534	NAFLD *n*=416	Crude OR (95% CI)	*P**
Age (y)	46.94±7.45	47.39±7.06	1.009 (0.991-1.026)	0.34
Systolic BP	118.34±16.50	123.54±16.84	1.019 (1.011-1.027)	<0.001
Diastolic BP	79.03±11.16	82.83±11.25	1.031 (1.019-1.044)	<0.001
FBS (mg/dl)	97.51±24.7	109.11±38.05	1.013 (1.008-1.018)	<0.001
Biochemical markers				
AST (U/L)	18.45±7.75	22.17±11.74	1.049 (1.031-1.068)	<0.001
ALT (U/L)	17.35±12.45	27.25±19.11	1.052 (1.040-1.065)	<0.001
ALP (U/L)	192.00±56.92	196.01±53.71	1.001 (0.999-1.004)	0.26
GGT (U/L)	23.31±18.26	33.31±27.65	1.031 (1.021-1.042)	<0.001
AST/ALT ratio	0.95±0.40	1.27±0.50	0.156 (0.106-0.230)	<0.001
Lipid profiles				
TG (mg/dl)	150.71±85.55	201.22±97.94	1.006 (1.005-1.008)	<0.001
TC (mg/dl)	198.59±35.28	205.07±39.44	1.005 (1.001-1.008)	0.008
HDL-C (mg/dl)	46.61±9.77	43.47±8.65	0.964 (0.950-0.978)	<0.001
LDL-C (mg/dl)	121.10±29.71	121.82±32.50	0.999 (0.995-1.003)	0.72
LDL-C/ HDL-C (ratio)	2.69±0.76	2.84±0.78	1.283 (1.086-1.517)	0.003
TC/HDL-C (ratio)	4.40±1.04	4.84±1.10	1.472 (1.299-1.668)	<0.001

NAFLD: Non-alcoholic fatty liver disease; FBS: Fasting blood sugar; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol *P<0.05 is significant

Table 4: Correlation of biochemical parameters with severity of ultrasound-based grading of NAFLD

	Grade I Mean±SD	Grade II Mean±SD	Grade III Mean±SD	*P**
AST (U/L)	20.37±10.08	26.42±14.56	27.36±9.29	<0.001
ALT (U/L)	24.26±16.59	34.59±23.26	33.09±15.64	<0.001
ALP (U/L)	194.14±54.11	199.45±54.16	211.27±34.65	0.42
GGT (U/L)	30.52±23.65	40.77±36.13	32.59±11.88	0.004
TG (mg/dl)	201.88±99.11	203.85±98.09	157.00±46.63	0.31
TC (mg/dl)	204.71±37.38	206.07±43.95	204.73±48.44	0.95
HDL-C (mg/dl)	43.42±9.08	43.28±7.47	46.73±7.97	0.44
LDL-C (mg/dl)	120.94±31.80	121.00±33,86	126.55±39.69	0.85
FBS (mg/dl)	107.16±35.35	113.76±44.88	114.27±30.34	0.26

*P<0.05 represents statistically significant values NAFLD: Non-alcoholic fatty liver disease; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBS: Fasting blood sugar

ratio and TC/HDL ratio and lower HDL as compared to those in the non-NAFLD group. Further, in the NAFLD group, a significant relationship was observed with TG, but no significant relationship was seen between LDL and NAFLD. In a study conducted by Santhoshakumari *et al.*,[19] patients with NAFLD had higher TC, LDL, and TG, and lower HDL as compared to the control group, and in this study, dyslipidemia was significantly higher in the NAFLD group. In another study, again, mean LDL, and TC was higher than the normal range among NAFLD subjects.[20] Further, Novakovic *et al.*[18] in Serbia, compared chemical parameters with NAFLD and found that there is a significant relationship between TG, LDL, TC, and HDL, and an inverse relationship with HDL in the group. The study by Pardhe[16] as well as Jain *et al.*[2] indicated similar results.

In the present study, the mean DBP and SBP in the NAFLD group was higher than that of non-NAFLD group, where individuals with higher systolic and diastolic blood pressure indicated higher risk for developing NAFLD, and a significant relationship was observed between BP and NAFLD. This result is in accordance with the findings of a number of studies.[2,16,18,19]

The present study showed that with elevation of FBS level, the possibility of developing NAFLD increases (OR = 1.013, CI: 1.008-1.018), and there is a significant relationship between them. Studies by Jain *et al.*,[2] Novakovic *et al.*[18] and Pardhe *et al.*[16] also confirmed this finding.

In this study, the mean levels of hepatic enzymes were higher in the NAFLD group, and apart from ALP (P = 0.26), in other cases, a significant relationship was observed with NAFLD. In the study of Novakovic *et al.*[18] a significant relationship was observed between hepatic enzymes (ALT, GGT, AST/ALT ratio) apart from AST and NAFLD. Most previous studies have shown that there is a significant relationship between NAFLD and AST,[10,16] ALT[10,16,21] and ALP.[16] Zakeri and Karmarat-Panah[21] stated that ALT and dyslipidemia might be involved in the prevalence and development of NAFLD.

For preliminary diagnosis of NAFLD, ultrasonography can be used. It can be posited that sonography with the minimum cost and complications is the cheapest method for identifying NAFLD-associated changes. In this study, a significant relationship was observed between hepatic enzymes GGT (P = 0.004), ALT (P < 0.001), AST (P < 0.001) and NAFLD degrees. In a report by Cuenza *et al.*[20] in Philippine, investigation of FL degrees through sonography indicated that AST (P = 0.00), ALT (P = 0.001), TG (0.047) and

FBS (P = 0.049) had a relationship with NAFLD grades, though it did not have any relationship with age, LDL, HDL and TG. Further, Mahaling *et al.*[22] showed increased degrees of NAFLD with elevation of TC (P = 0.001), LDL (P = 0.000) and VLDL (P = 0.003), and reduction of HDL (P = 0.000), but no significant relationship was observed between TG (P = 0.05) and NAFLD degrees. The study by Pardhe *et al.*[16] in Nepal showed a significant relationship between hepatic enzymes (ALT, ALP) and dyslipidemia (TG, HDL), and different grades of NAFLD.

The limitation of this study was the use of ultrasonography to detect NAFLD. Liver biopsy is a golden standard for diagnosing fatty liver, but because of its invasiveness, risk of complications, and high cost, it is not recommended for the general population. On the other hand, abdominal ultrasonography is a noninvasive, low risk, simple, relatively low-cost and easily available method. In this study, to control this limitation, the comments of two radiologists were used concurrently.

Conclusion

The results of this study indicated that in patients with NAFLD, there are considerable changes in biochemical markers. Thus, it seems essential that in clinical settings in cases in which biochemical and lipid changes are observed, sonography should be performed to examine individuals with NAFLD, since early diagnosis prevents further complications and delays them.

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Conflicts of interest

There are no conflicts of interest.

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