Original Article

Nonalcoholic Fatty Liver Disease in a Cluster of Iranian Population: Thyroid Status and Metabolic Risk Factors

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Abstract

Aim: This study aimed to investigate the prevalence, metabolic risk factors, and thyroid dysfunction among a healthy urban population.

Methods: In a cross-sectional study, the patients were evaluated for nonalcoholic fatty liver disease (NAFLD) using ultrasonography. The participants' characteristics such as age, sex, weight, height, body mass index (BMI), waist circumference, hip circumference, waist-to-hip ratio, systolic and diastolic blood pressure, and history of diabetes, ischemic heart disease (IHD), hypertension, and hyperlipidemia were recorded using a data gathering form. The patients were compared to those without NAFLD in terms of metabolic factors and thyroid abnormalities.

Results: From 832 participants, 127 (15.3%) individuals had NAFLD. Metabolic syndrome was detected in 39 participants (30.70 %) with NAFLD and in 85 participants (12.05%) without NAFLD ($P < 0.001$) (OR: 3.22; 95 % CI: 2.07–5.01). In multivariate logistic regression analysis BMI, waist-to-hip ratio, and higher serum ALT levels were independent predictors for NAFLD ($P < 0.001$). There was no statistically significant difference in serum TSH, free T4, and free T3 levels between the participants with NAFLD and the participants without NAFLD ($P > 0.05$). Neither hypothyroidism nor markers of thyroid autoimmunity were associated with NAFLD in our study population ($P > 0.05$). Serum TSH was categorized according to 25th, 50th, and 75th percentile to <1.29 mIU/L, 1.29–1.91 mIU/L, 1.91–2.77 mIU/L, and >2.77 mIU/L. Compared with non-NAFLD participants, the diagnosis of NAFLD was significantly higher in the low TSH group ($P = 0.004$).

Conclusion: Central obesity as reflected by waist-to-hip ratio is one of the major risk factors for NAFLD. However, thyroid dysfunction was not correlated with NAFLD and the observed alterations in thyroid hormones are due to sick euthyroid syndrome.

Keywords: Central obesity, nonalcoholic fatty liver, metabolic syndrome, thyroid disease, waist- to-hip ratio

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is now considered as a hepatic feature of metabolic syndrome and is a clinical spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) that can progress to liver cirrhosis and hepatocellular carcinoma (HCC).[1] NAFLD is a rapidly growing disease in both developed and developing countries and is probably the most common cause of abnormal liver function tests worldwide.[2] Scientists now believe that a considerable proportion of patients diagnosed with cryptogenic liver cirrhosis have NAFLD/NASH as underlying disease.[3] NAFLD is estimated to affect nearly 30% of general population in western countries.[4] The prevalence in Asian countries seems to be lower but is increasing secondary to an increase in burden of diabetes mellitus (DM), metabolic syndrome, and changing in lifestyle.[5,6] The exact pathogenesis is not still clear, however, several risk factors including advanced age, obesity, insulin resistance, and hyperlipidemia have been proposed.[7]

Thyroid gland is thoroughly involved in cell metabolism, energy homeostasis, regulation of body weight, thermogenesis, lipid and carbohydrate metabolism, and adipogenesis.[8,9] Subclinical hypothyroidism has been reported to be associated with metabolic syndrome, cardiovascular mortality, and disturbance of lipid metabolism.[10] Considering these evidences, some studies were conducted to investigate the association between thyroid dysfunction and NAFLD/NASH. In a recent cross-sectional study, hypothyroidism was more prevalent in patients with NAFLD compared to healthy controls.[11] However, the role of thyroid dysfunction in NAFLD is still a new issue that needs further investigations.

The prevalence of NAFLD and its risk factors has not been well studied in our region. This study was conducted to investigate the prevalence of NAFLD, its related risk factors, and association between NAFLD and thyroid dysfunction in a healthy urban Iranian population.

Materials and Methods

Study population

A cross-sectional study was conducted among adult (>18 years) healthy population form Kavar, a town near Shiraz City, Fars Province, Iran between September 2011 and September 2012. Clustered random sampling was used to select the study population. The town was divided into 20 distinct geographic areas

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and 50 participants were selected from each area according to the postal code. Individuals with a history of liver cirrhosis, underlying liver disease such as autoimmune or viral-induced hepatitis, hepato-billiary cancers, those with >20g/day alcohol consumption, and individuals receiving antithyroid medications were excluded from the study.

Clinical and laboratory assessment

The participants' characteristics such as age, sex, weight, height, body mass index (BMI), waist circumference, hip circumference, waist-to-hip ratio, systolic and diastolic blood pressure, and a history of diabetes, ischemic heart disease (IHD), hypertension, and hyperlipidemia were recorded using a data gathering form. BMI was calculated as follows: body weight (kg)/square of height (m^2). Waist circumference was measured at the midpoint between the lower costal margin and the anterior superior iliac crest by a well-trained examiner using a tape. Hip circumference was similarly obtained at the widest point between the hip and the buttock. Systolic and diastolic blood pressure of brachial artery was measured using appropriate cuffs. Blood samples (10 mL) were collectd in standard tubes and were send to the Endocrinology Research Center, Nemazee Hospital, Shiraz, Iran. All tests were performed with the same commercial kits. Laboratory tests including thyroid hormone profiles: thyroid stimulating hormone (TSH) (IRMA, Immunotech, Czech Republic), free T4, free T3 (RIA, Immunotech, Czech Republic), antithyroid peroxidase (anti-TPO) antibody, and antithyroglobulin (anti-Tg) (competitive RIA, Immunotech, Czech Republic) were measured after obtaining 5 mL blood samples from each individual after 12 hours of fasting. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglyceride, high- density lipoprotein (HDL) cholesterol, and glucose were also measured.

Definition

NAFLD was defined as presence of hepatorenal echo contrast and liver brightness of these four ultrasonographic criteria for fatty liver: hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring [12] and absence of 1) seropositivity for hepatitis B surface antigen or antibody to hepatitis C virus, 2) alcohol consumption (>20 g/day), 3) history of other causes of liver disease, and 4) medications known to produce fatty liver disease during the last six months prior to the study.

Metabolic syndrome was defined as presence of three or more of the following metabolic components according to the National Cholesterol Education Program and Adult Treatment Panel III (NCEP: ATPIII) criteria: 1) central obesity: waist circumference >102 cm for men and >88 cm for women, 2) hypertriglyceridemia: triglyceride ≥150 mg/dL or taking specific medication, 3) low HDL cholesterol: <40 mg/dL in males and <50 mg/dL in females or taking specific medication, 4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking specific medication, 5) fasting plasma glucose ≥100 mg/dL or taking specific medication or previously diagnosed as type II diabetes.

Euthyroidism was defined as serum TSH level between 0.2 and 5.2 mIU/L with normal free T4 levels (11.5–23 pmol/L). Subclinical hypothyroidism was defined as a serum TSH level above 5.2 mIU/L and a normal free T4 concentration. Overt hypothyroidism was described as a free T4 level less than 11.5 pmol/L and TSH level over 5.2 mIU/L. Hyperthyroidism was defined as a free T4 level over 23 pmol/L and TSH level below 0.2 mIU/L. Subclinical hyperthyroidism was defined as serum TSH level below 0.2 mIU/L and a normal free T4 concentration. An ALT level over 40 IU/L was considered abnormal. DM was defined as fasting plasma glucose ≥126 mg/dL or taking glucose lowering agents. Participants were considered hypertensive if taking antihypertensive medications or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Ultrasonographic examinations were performed by two expert radiologists who were unaware of laboratory tests and clinical evaluations of the participants (interobserver agreement value (κ) = 0.90).

Ethics and consent

The study protocol was confirmed by local Ethics Council of Shiraz University of Medical Sciences. The study protocol, benefits, and harms of the study were described to all participants and a written informed consent was obtained. The study was performed in accordance to Helsinki Declaration as revised in Seoul 2008.

Statistical analysis

Comparisons of continuous variables were performed with the Student's *t*-test, and categorical variables were compared using the Chi-square test. Variables that were statistically significant by univariate analysis and known risk factors were added to a multiple logistic regression model to identify independent risk factors of NAFLD. Statistical analysis was performed with SPSS 16.0 (SPSS Inc.; Chicago, IL, USA). A *P*-value of < 0.05 was considered statistically significant.

Results

Among 1000 individuals, 168 were exclude (109 individuals did not consent to participate in the study, 32 individuals excluded due to medications, 15 due to viral hepatitis, and 12 individuals due to other liver disease) (Figure 1). From 832 participants who completed the study, 127 individuals (15.3 %) had NAFLD. Five hundred ten participants (61.3%) were females and 322 (38.7%) were males. The mean age of the participants with NAFLD was significantly higher than those without NAFLD, 48.20 ± 12.82 years versus 36.97 ± 18.76 years, ($P < 0.001$). Baseline characteristics and anthropometric indices in patients with and without NAFLD are outlined in Table 1. All measured anthropometric indices including weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio were significantly higher among individuals with NAFLD compared to those without NAFLD in univariate analysis ($P < 0.001$) (Table 1). Higher mean systolic and diastolic blood pressures were associated with presence of NAFLD ($P < 0.001$) (Table1). The mean fasting plasma glucose, triglyceride, total cholesterol, and HDL were not associated with NAFLD ($P > 0.05$) while higher serum ALT and AST levels were associated with NAFLD (Table 1). Metabolic syndrome was detected in 39 participants (30.70%) with NAFLD and in 85 participants (12.05%) without NAFLD ($P < 0.001$; OR: 3.22, 95% CI: 2.07–5.01). Hypertension, DM, hyperlipidemia, and IHD were associated with NAFLD in univariate analysis (Table 2). Multivariate logistic regression analysis of risk factors showed that BMI, waist-to-hip ratio, and higher serum ALT levels were independently associated with presence of NAFLD ($P < 0.001$) (Table 3).

Thyroid dysfunction

Table 1. Baseline characteristics of the patients.

	With NAFLD	Without NAFLD	*P*-value
Age (year)	48.20 ± 12.82	36.97 ± 18.76	<0.001
BMI (kg/m^2)	29.30 ± 5.44	23.5 ± 5.37	<0.001
Weight (kg)	73.67 ± 14.33	58.79 ± 13.72	<0.001
Waist circumference (cm)	94.13 ± 13.59	77.31 ± 12.94	<0.001
Hip circumference (cm)	101.67± 8.02	92.77 ± 9.63	<0.001
Waist/hip ratio	0.92 ± 0.12	0.83 ± 0.08	<0.001
Systolic BP (mmHg)	125.6 ± 23.53	109.56 ± 17.43	<0.001
Diastolic BP (mmHg)	80.67 ± 10.71	71.6 ± 10.94	<0.001
Triglyceride (mg/dL)	141.6 ± 109.35	123.44 ± 82.41	0.092
HDL (mg/dL)	50.65 ± 11.12	51.82 ± 12.35	0.346
Cholesterol (mg/dL)	186.68 ± 44.17	189.8 ± 43.32	0.481
FPG (mg/dL)	98.77 ± 24.74	100.66 ± 29.95	0.526
TSH (mIU/L)	2.02 ± 1.35	2.29 ± 1.47	0.068
Free T4 (pm)	15.84 ± 2.76	16.51 ± 5.63	0.213
Free T3 (pm)	3.80 ± 0.73	4.09 ± 1.64	0.057
ALT (IU/L)	23.41 ± 14.69	17.06 ± 10.86	0.001
AST (IU/L)	22.64 ±13.18	20.35 ± 12.03	0.09
ALK.Ph (IU/L)	145.46 ± 65.53	159.58 ± 96.77	0.17

NAFLD=nonalcoholic fatty liver disease; BMI=body mass index; BP=blood pressure; HDL=high-density lipoprotein; FPG=fasting plasma glucose; TSH=thyroid stimulating hormone; ALT=alanine aminotransferase; ALK.Ph=Alkaline phosphatase, AST=Aspartate aminotransferase.

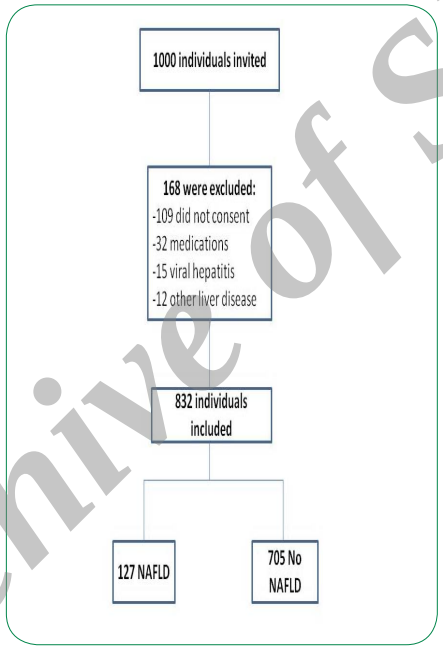

Figure 1. Flow diagram of the study.

There was no statistically significant difference in serum TSH, free T4, and free T3 levels between the participants with NAFLD and the participants without NAFLD (Table 1). In the NAFLD group, 18 participants (14.17 %) had positive anti-TPO compared to 117 participants (16.64 %) in the non-NAFLD group (OR: 0.81, 95 % CI: 0.45–1.43). In the NAFLD group, 17 participants (13.38 %) were anti-Tg positive compared to 129 participants (18.29 %) in the non-NAFLD group (OR: 0.84, 95 % CI: 0.47–1.52). Subclinical hypothyroidism was observed in nine (7.08%) participants with NAFLD and in 43 participants (6.09%) without NAFLD (OR: 1.12, 95% CI: 0.51–2.46). Overt hypothyroidism was detected in seven participants (4.72 %) with NAFLD and in 35 participants (4.96%) without NAFLD (OR: 0.87, 95% CI: 0.33–2.28) (Figure 2). Subclinical hyperthyroidism was present in only one individual (0.78 %) in the NAFLD group compared to 11 individuals (1.56 %) in the non- NAFLD group (P = 0.47) (OR: 0.54, 95% CI: 0.06–4.31). Only four participants in the non-NAFLD group had hyperthyroidism and none of the participants in the NAFLD group had hyperthyroidism (P > 0.05).

Serum TSH was categorized according to 25th, 50th, and 75th percentile to <1.29 mIU/L, 1.29–1.91 mIU/L, 1.91–2.77 mIU/L, and >2.77 mIU/L. Compared with the non- NAFLD participants, the diagnosis of NAFLD was significantly higher in the low TSH group (P = 0.004) (Table 4).

Nine individuals (17.07 %) with overt hypothyroidism found to have metabolic syndrome compared to 113 individuals (14.5 %) without overt hypothyroidism (OR: 1.208, 95% CI: 0.521–2.80, P = 0.3).

Discussion

The prevalence of NAFLD was 15.3% in our population. Metabolic syndrome, higher BMI, waist circumference, hip circum-

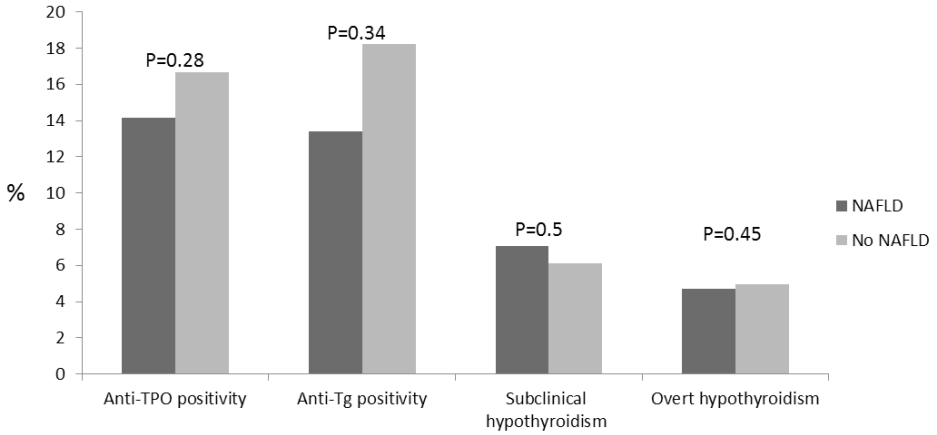

Figure 2. Thyroid autoimmunity and hypothyroidism among NAFLD and non-NAFLD groups.

Table 2. Associated factors analysis among the participants with NAFLD and those without NAFLD.

	With NAFLD	Without NAFLD	OR (95% CI)	*P*-value
Metabolic syndrome, *n* (%)	39 (30.70)	85 (12.05)	3.22 (2.07–5.01)	<0.001
Diabetes, *n* (%)	16 (12.59)	48 (6.80)	1.97 (1.08–3.59)	0.03
Hypertension, *n* (%)	20 (15.74)	45 (6.38)	2.37 (1.55–4.81)	0.001
Hyperlipidemia, *n* (%)	46 (36.22)	100 (14.18)	3.43 (2.25–5.21)	<0.001
IHD, *n* (%)	10 (7.87)	19 (2.69)	3.08 (1.39–6.79)	0.007
Cigarette smoking, *n* (%)	6 (4.72)	22 (3.12)	1.53 (0.61–3.86)	0.418
NAFLD=nonalcoholic fatty liver disease, OR=odds ratio, CI=confidence interval.				

Table 3. Multivariate analysis for the presence of NAFLD.

	OR	(95% CI)	*P*-value
Age (year)	1.01	1.02–0.98	0.45
BMI (kg/m^2)	1.11	1.17–1.05	<0.001
Weight (kg)	0.99	1.03–0.98	0.56
Waist circumference (cm)	1.00	1.13–0.88	0.37
Hip circumference (cm)	1.06	1.21–0.89	0.44
Waist/hip ratio	3.71	5.10–2.74	<0.001
Systolic BP (mmHg)	1.20	1.70–0.95	0.25
Diastolic BP (mmHg)	1.81	1.08–0.91	0.34
ALT (IU/L)	1.06	1.07–1.02	0.001
Metabolic syndrome	1.52	1.80–0.73	0.42
Diabetes	1.12	1.25–0.87	0.35
Hyperlipidemia	1.18	1.17–0.96	0.39
IHD	1.01	1.01–0.99	0.59
NAFLD=nonalcoholic fatty liver disease; OR=odds ratio; CI=confidence interval; BMI=body mass index; BP=blood pressure; HDL=high-density lipoprotein; ALT=alanine aminotransferase; ALK.Ph=alkaline phosphatase; IHD=ischemic heart disease			

Table 4. NAFLD according to TSH categorization.

	TSH				*P*-value
	<1.29	1.29–1.91	1.91–2.77	>2.77	
NAFLD	48 (37.7)	27 (21.2	25 (19.6)	27 (21.2)	0.004

ference, advanced age, hypertension, diabetes, hyperlipidemia, elevated ALT, and AST levels were all associated with presence of NAFLD in univariate analysis. However, only higher BMI and waist-to-hip ratio as well as elevated serum ALT levels were independent predictors of NAFLD in multivariate regression analysis. Our study failed to demonstrate any association between markers of thyroid dysfunction and presence of NAFLD. Despite lower free T3 levels among the NAFLD group, serum TSH, free T4, free T3, and markers of thyroid autoimmunity were not different in the participants with NAFLD and those without NAFLD. However, NAFLD patients were more likely to have low TSH levels although hypothyroidism and hyperthyroidism were not associated with NAFLD. The observed changes in TSH and free T3 levels may attribute to alterations in thyroid hormones due to sick euthyroid syndrome in NAFLD.

There is lack of data about the prevalence of NAFLD in Iranian healthy adult population. However, the prevalence of NAFLD was reported to be 7.1% among Iranian children. [13] Increased serum ALT and higher waist circumference were independently associated with NAFLD in children. In other Middle Eastern countries, there is also lack of data about NAFLD despite high burden of DM and metabolic syndrome. In a newly published study from

Saudi Arabia the prevalence of NAFLD diagnosed with ultrasonography was 16.6%.[14]

Our study is in accordance with previous studies showing the association between abdominal obesity and NAFLD. In most of previous studies waist circumference has been used as a measure of abdominal obesity.[15,16] However, in our study waist-to-hip ratio was an independent predictor of NAFLD and seems to be a more precise marker of abdominal obesity correlated with development of NAFLD. Waist-to-hip ratio has been reported to have the strongest correlation with hypertension, DM, and dyslipidemia.[17] Waist-to-hip ratio was also a better predictor for type II diabetes rather than BMI and other markers of abdominal obesity.[18]

Several studies have been recently conducted to investigate the association between thyroid dysfunction especially hypothyroidism and NAFLD/NASH. A cross-sectional study showed that increased serum TSH level is an independent risk factor for biopsy-proven NASH.[19] Another cross-sectional study on elderly Chinese population revealed that higher freeT4 level was an independent risk factor for NAFLD.[20] It should be noted that this study population consisted of only elderly participants and did not reflect the status in general population. The other interesting issue is association between thyroid dysfunction in the form of hypothyroidism and severity of nonalcoholic fatty infiltration in the liver. Pagadala, et al. showed that hypothyroidism is more prevalent in patients with NAFLD when compared to healthy controls.[21] They also demonstrated that hypothyroidism is more likely to happen in NASH patients in comparison to patients without NASH. Therefore, hypothyroidism may not only predicts presence of NAFLD but also may occur in more severe pathologic form of NAFLD i.e., NASH. These studies, although valuable, were small in sample size and could not be generalized to all populations. A large population-based study among Korean population has been recently confirmed that hypothyroidism is more prevalent among patients with NAFLD.[11] This study also showed that serum TSH level is an independent risk factor for development of NAFLD. The results of current study were against any association between hypothyroidism or thyroid autoimmunity and NAFLD in our population. Similar to our findings, Mazo, et al. did not find any association between hypothyroidism, simple steatosis, and NASH.[22] Our study is unique in investigating thyroid autoimmunity by checking both anti-TPO and anti-Tg antibodies in patients with NAFLD. Based on our results, there is no association between autoimmune thyroid disorders and NAFLD.

Patients with hypothyroidism have abnormal lipid profiles mostly in the form of elevated serum levels of LDL.[23] Elevated TSH level has been associated with diminished hepatic lipoprotein lipase activity and consequent elevation in serum triglyceride level.[24,25] Elevated serum makers of oxidative stress have been reported in patients with hypothyroidism[26] and oxidative stress is one of the mechanisms involved in NAFLD.[27] Hypothyroid patients were found to have elevated serum leptin levels, a hormone which is increased in obesity and insulin resistance.[28] All of these mechanisms favor association of hypothyroidism with NAFLD. However, in clinical setting evidences are conflicting considering our study results. Our results showed a lower serum free T3 (P = 0.057) and TSH levels (P = 0.068) that can be justified by sick euthyroid syndrome. Although sick euthyroid syndrome has been previously identified in liver cirrhosis,[29] our study is the first that showed sick euthyroid syndrome among patients with NAFLD. Another recently published article showed that low free T4, but not TSH and free T3, level was associated with hepatic steatosis.[30]

Conclusion

Obesity and especially central obesity is an independent predictor for NAFLD. Our study demonstrated that waist-to-hip ratio may be a more precise marker for NAFLD compared to hip and waist circumferences. Our study showed sick euthyroid syndrome as the main pattern of thyroid abnormalities in patients with NAFLD. Although thyroid dysfunction mainly in the form of hypothyroidism has been reported in NAFLD, our study did not show any significant correlation between hypothyroidism, hyperthyroidism, and thyroid autoimmunity and NAFLD. However, the latter issue is relatively a new area of investigation that requires much more studies.

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Competing interest: None.

Conflict of Interest: None declared.

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