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Research Article

Prevalence of Hypothyroidism in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Aim: We determined the prevalence of hypothyroidism in a cohort of patients with Nonalcoholic Fatty Liver Disease (NAFLD) and analyzed the potential factors associated with hypothyroidism in this patient population.

Methods: Two hundred and forty-six patients with proven NAFLD attending hepatology clinics from October 2012 to June 2017 and 430 age, gender, race and BMI matched control subjects seen in the general internal medicine clinic were included. Patients with a clinical diagnosis of hypothyroidism who were on thyroid replacement therapy were hypothyroid.

Results: Hypothyroidism was more frequent among patients with NAFLD (21% *vs* 9.5%.; P<0.01) compared to controls and was higher in NASH patients than NAFLD patients without NASH (25% *vs* 12.8%, P=0.03). Subjects with hypothyroidism were 2.1 (95% CI: 1.1, 3.9, P=0.02)) and 3.8 (95% CI: 2,6.9, P<0.001) times more likely to have NAFLD and NASH respectively. By Multivariate analysis, female gender (P<0.001) and increased BMI (P=.03) were associated with hypothyroidism. NAFLD with mild alcohol consumption were less likely to have hypothyroidism compared to those who reported complete abstinence (OR 0.37, P=0.008).

Conclusions: This study showed a higher prevalence of hypothyroidism in patients with NAFLD compared to controls. It was also demonstrated that patients with hypothyroidism were more likely to have NASH.

Keywords: Nonalcoholic fatty liver disease; NAFLD; Hypothyroidism

Introduction

Massive collection of triglycerides and free fatty acids in the liver is identified as Nonalcoholic Fatty Liver Disease (NAFLD) [1]. NAFLD is considered as the most widespread liver disorder in developed and developing countries [2,3] and there has been a surge of interest in NAFLD, since it is estimated to be the leading cause of liver associated mortality by 2030. According to preceding research, NAFLD is a multi-system disease and has directly significant impact on both liver and cardiovascular system [4]. Further, there is a strong association between NAFLD and metabolic syndrome [5,6]. Based on last studies, thyroid dysfunction especially hypothyroidism associate with components of the metabolic syndrome include insulin resistance [7,8], dyslipidemia [9] and obesity [10].

Surprisingly, hyperthyroidism has resemblance to NAFLD in some features such as dyslipidemia, decreased fatty acid oxidation, and increased hepatic lipid peroxidation and insulin resistance [11]. Therefore, there is likely to be an association between thyroid abnormality and NAFLD. However, clinical data supporting that this association are incomplete and the pathophysiology is unclear. To date, very little research has been conducted about thyroid function and NAFLD in Iran. This study was conducted to investigate the relationship between nonalcoholic fatty liver disease and thyroid abnormalities to assess its impact on thyroid gland function tests in the Iranian general population.

Material and Methods

Study design and patient population

This study was a descriptive study, which was approved by our ethics committee. Individuals were asked to sign an informed consent form before blood samples obtaining. All the terms of the Helsinki declaration were considered, and the personal information remained anonymous. The study population consisted of 1340 adult patients individuals at least ≥18 years of age with proven Nonalcoholic Fatty Liver Disease (NAFLD) by a gastroenterologist with 10 years of experience, seen in the gastroenterology outpatient clinics October 2012 to June 2017.

Detailed medical history, clinical examination, anthropometric assessment and laboratory tests were evaluated. Height and body weight were measured and Body Mass Index (BMI) was calculated as follows: BMI= body weight (kg)/ height squared (m^2). The normal range of BMI is 19-24.9 kg/m^2, overweight is 25-29.9 kg/m^2, and obesity ≥30 kg/m^2. All routine investigations were done after a 12-hour overnight fast. Baseline thyroid functions (FT4 and TSH) were measured. Other lab tests included liver function tests, lipid profile and serum albumin. NAFLD was diagnosed as presence of fatty liver by ultrasonography in the absence of excess alcohol intake (>20 g/day).

Individuals with significant alcohol use (>14 drinks per week in males or 7 drink/day in females), the patients or those with

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Table 1: Demographic and Clinical Characteristics: NAFLD.

Factor			P Value or N	Factor	N
BMI (kg/m²) †	Normal	149(11%)	<0.001	Hypothyroid	73(5.4%)
	Overweight	580(36%)		Smoking	73(5.4%)
	Fat	564(42%)		Alcohol	16(1.2%)
Grade†	I	507(37.9%)	<0.001	AST (IU/L)	33.5±20.6
	II	515(38.5%)		ALT (IU/L)	50.6±35.4
	III	227(17%)		ALP (IU/L)	196±69
	other	40(3%)		TSH (mU/L)	3.2±12.2
Hyperlipidemia(mg/dL)	550.3.8±8	DM	132(10%)	T4(mU/L)	80±226.05
LDL(mg/dL)	115.8±41.7	HTN	203(15.2%)	T3(mU/L)	5.1±22.4
HDL(mg/dL)	44.3±13.5	Alb(mg/dL)	4.7±3.6	T3RU(mU/L)	29.9±16.2

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphtase and Alb: Albumin. Values presented as N(%) for diabetes, HTN, hyperlipidemia and hypothyoidism and Mean (SD). p-values correspond to univariable conditional logistic regression analyisis to account for †Data not available for all subjects; BMI n=1293; grade n=1249

any laboratory or clinical evidence to suggest certain or probable underlying chronic liver disease including hemochromatosis, viral and autoimmune hepatitis, wilson's disease and chronic cholestatic liver disease were excluded from the study.

NASH Clinical Research Network validated histological scoring system was used to histological grading and staging for NAFLD [12].

Definitions

Hypothyroidism was defined as serum TSH ≥4.1 mIU/L and FT4 level less than 0.7 ng/dL. Ultrasound criteria for Non-alcoholic fatty liver disease**:**

Grade I: Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.

Grade II: Increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm.

Grade III: Increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm.

Statistical analysis

For continuous variables and frequencies and percentages for categorical variables Mean and standard deviations were calculated. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. P value < 0.05 considered statistically significant. The qualitative data were expressed as numbers (%). To evaluate associations between continuous variables and presence of hypothyroidism student's tests or Wilcoxon rank sum tests were used. Pearson's chi-square for categorical variables and for steatosis, fibrosis, inflammation and ballooning Mantel-Haenzel tests were used. In addition, a multivariable logistic regression analysis was performed to evaluate factors associated with presence of hypothyroidism.

Theory

Patients with hypothyroidism are seemed to have NASH. Female gender, increased BMI and history of abstinence from alcohol are associated with hypothyroidism among patients with NALFD.

Results

Table 1 summarizes clinical and demographical information of the subjects. The mean age among NAFLD cases was 44.75±11.27 years, 838(62.5%) were males versus 502(37.5%) females and the mean BMI was 31.16±14 kg/m^2. There was a significant different between the four class of BMI, so that the most individuals were overweight. (P<0.001)

Prevalence of hypothyroidism in NAFLD

The prevalence of hypothyroidism was 5.4% among patients with NAFLD. The prevalence of hypothyroidism was also higher in patients with NASH in comparison to those with no NASH (5.3 % *vs* 5.5%, P= 0.52). In multivariate analysis subjects with hypothyroidism were 0.92 (95% CI: 0.22, 3.96) and 0.96 (95% CI: 0.51, 1.82) times more likely to have NAFLD and NASH respectively. After adjusting for diabetes mellitus, dyslipidemia and hypertension, this association remained statistically significant.

According to Table 2, NAFLD patients with hypothyroidism were more males, in older age and with higher BMI compared to NAFLD patients without hypothyroidism.

Additionally, hypothyroidism was more frequent in NAFLD patients who reported alcohol consumption compared to those who reported no alcohol consumption. (5.4% *vs* 6%, P=0.59)

Female gender (OR, 5.2; P< 0.001) was associated with increased risk of hypothyroidism in NAFLD. In contrast higher BMI (OR, 1.1; P=0.7) was associated with increased risk of hypothyroidism in NAFLD. Alcohol consumption was not associated with a reduced risk of developing hypothyroidism compared to those who reported complete abstinence (OR, 0.86; P=0.88). Though patients with hypothyroidism had increased risk of NASH it was not statistically significant. (OR 0.96; P=0.9).

Discussion

Perhaps the most striking finding of the recent study is that, hypothyroidism patients are more likely to have NAFLD and NASH respectively. It was also revealed that hypothyroidism is more common among old and highly BMI level men. Higher rates of hypothyroidism in men in our study may be related to environmental factors that increase autoimmunity in our population, such as iodine supplementation. The prevalence of hypothyroidism in patients with NAFLD 5.4 as observed in a recent study. In another study,

Table 2: Univariable analysis of factors associated with hypothyroidism in NAFLD.

Factor	Hypothyroidism		No Hypothyroidism		P Value
	Count	Percent	Count	Percent	
Female	54	10.8%	448	89.2%	<0.001
Age (mean)	50.96±8.26		44.3858±11.32		<0.001
BMI (kg/m^2)	31.21±15.20		30.34±4.08		0.18
Alcohol use†	1	6.3%	15	93.8%	0.595
ALT† (IU/L)	40.48±20.94		51.2±36.04		0.012
TSH† (mU/L)	5.57±16.39		3.09±11.91		0.1
DM †	11	8.3%	121	91.7%	0.296
HTN †	20	9.9%	183	90.1%	0.006
Hyperlipidemia †	44	7.8%	522	92.2%	0.005
Metabolic Syndrome	27	8%	309	92%	0.054
Ferritin†	158.06±386.98		140.33±167.36		0.478
NASH	12	5.3%	215	94.7%	0.902

Values presented as Mean ± SD for continuous factors and (count – percent) for categorical factors

p-values correspond to independent-samples T-test for continuous factors, Fisher's Exact tests for alcohol and Pearson's chi-square for all other categorical factors.

Data not available for all subjects. Gender n=1338; age n=1325; alcohol n=1338; HTN n=1337; DM n=1336; MS n=1338; Hyperlipidemia n=215; ALT n=1276; Ferritin n=1004; TSH n=1153; Nash n=1338; BMI n=1293; Hyperlipidemia n=1275

Aminorroaya et.al, over a 6-year follow-up, showed that the incidence of hypothyroidism was 3.3 in women and 2.1 in men [13]. Therefore, the prevalence of hypothyroidism in NAFLD patients appears to be higher than in the general population. The National Survey of Health and Nutrition Examinations (NHANES) conducted between 1999 and 2002 showed a prevalence of 3.7% in the United States [14]. The prevalence of thyroid dysfunction has increased in the European population, reported in a 2.59 meta-analysis for hypothyroidism. [15]. The prevalence of subclinical and manifest hypothyroidism in the general population is reported to be 4% -10% and 0.3% -5%. Respectively and 5% in the elderly population [14,16,17].

We found the prevalence of hypothyroidism in patients with NAFLD to be highest in people with NASH. Two other previous studies with smaller sample sizes reported a 15% and 20% prevalence of hypothyroidism in NAFLD, respectively [18,19]. Our study included a large sample size. We also controlled for known factors associated with hypothyroidism (age, sex, and BMI). These current findings confirm the association between hypothyroidism and NAFLD. Eshraghian et al. in their systematic review demonstrated that prevalence of hypothyroidism is roughly 15.2% to 36.3% among patients with NAFLD/NASH [20].

The role of hypothyroidism in the pathogenesis of non-alcoholic fatty liver disease has not been established but a number of possible mechanisms are involved.

Based on studies, hypothyroidism is associated with insulin resistance [7,8], dyslipidemia [21] and obesity [10]; all of which are important components of the metabolic syndrome. It is well known that hypothyroidism is associated with metabolic syndrome, which plays an important role in the development of NAFLD [22].

According to the present results, previous studies show that most NAFLDs have hypothyroidism with fatty liver grade 2. [23]. These results reflect those of Sohrabpour et al. [24] who also showed that the mean BMI in patients with NASH was significantly higher than non-NASH patients and NASH was more common in men than women. This finding is in accordance with that of Kassem et al. [25], which showed a significant increase in Thyroid Stimulating Hormone (TSH) in hypothyroidism patients with NAFLD. However, the ALT result is different from the findings presented here. Damir et al. Found that hypothyroidism can cause NAFLD in rat models and noted that obesity is one of the most important factors in the association between hypothyroidism and NAFLD [26]. As a result of the above metabolic changes in patients with hypothyroidism can lead to the development of NAFLD [27]. Thyroid hormones can regulate lipid metabolism in the liver through the β thyroid hormone receptor and can lower cholesterol and triglyceride levels [28]. Notably, lower levels of thyroid hormones in hypothyroidism can increase cholesterol, low-density lipoproteins, and triglycerides due to the delivery of hepatic fatty acids, but decrease High-Density Lipoprotein (HDL) levels, and As a result, it can affect fat metabolism [29]. Cholesterol deficiency caused by hypothyroidism also plays an important role in the pathogenesis of NAFLD [18].

Up to 90% of hypothyroidism patients have been reported to have abnormal lipid levels. While hypothyroidism primarily raises cholesterol and low-density lipoproteins, it also affects all aspects of fat metabolism [30]. Increased esterification of hepatic fatty acids and decreased lipoprotein lipase activity result in increased triglyceride levels in hypothyroidism. Dyslipidemia is a common anomaly in NAFLD patients and it is likely that hypothyroidism may contribute to dyslipidemia in NAFLD [31]. Because of the antiseptic and triglyceride-selective effects of liver selective thyroid receptor agonists on the liver of live fat animal models, hypothyroidism can impair the lipid abnormalities present in NAFLD [32].

On multivariate analysis females with NAFLD were at a higher risk of hypothyroidism compared to male cases. This gender difference in hypothyroidism is well described [33].

There are many limitations to our study. A retrospective study design cannot define the interval between the progression of hypothyroidism and fatty liver. This limits the ability to establish a temporary causality between these two factors. The use of human-completed charts and questionnaires with human error as well as laboratory error can be another limitation. Alcohol consumption was determined by self-report questionnaire. Therefore, we cannot rule out the possibility of misreporting. Also, no information is available on the timing of the diagnosis of hypothyroidism and the exact results of thyroid function testing.

As FT4 and TSH were measured once, this could be a potential source of bias. More prospective cohort studies are needed to further strengthen the relationship between NAFLD and hypothyroidism.

Conclusion

In summary, our study shows that patients with NAFLD have a higher prevalence of hypothyroidism and are more likely to have NASH than those with no NASH. The high prevalence of hypothyroidism in NAFLD patients suggests that hypothyroidism

can identify a group of patients in the general population who may benefit from screening for the presence of fatty liver disease.

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