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ORIGINAL ARTICLE

Prevalence of Hypothyroidism in Nonalcoholic Fatty Liver Disease

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Abstract
Background A possible association between nonalcoholic fatty liver disease (NAFLD) and hypothyroidism has been suggested. The recognized link between hypothyroidism and elements of the metabolic syndrome may explain this association.
Aim The purpose of this study was to determine the prevalence of hypothyroidism in a cohort of patients with NAFLD and analyze the potential factors associated with hypothyroidism in this patient population.
Methods Two hundred forty-six patients with biopsy-proven NAFLD attending hepatology clinics at the Cleveland Clinic between October 2006 and June 2009, 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 considered to be 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 ($P = 0.03$) were associated with hypothyroidism. NAFLD subjects who reported mild alcohol consumption were less likely to have hypothyroidism compared to those who reported complete abstinence (OR 0.37, $P = 0.008$).
Conclusions A higher prevalence of hypothyroidism was demonstrated in patients with NAFLD compared to controls. Among subjects with NALFD, female gender, increased BMI and history of abstinence from alcohol were associated with hypothyroidism. Patients with hypothyroidism were also more likely to have NASH.

Keywords Fatty liver · Nonalcoholic steatohepatitis · Hypothyroidism · Insulin resistance

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease with a histological spectrum ranging from steatosis

alone to nonalcoholic steatohepatitis (NASH), the latter having an increased risk for progression to cirrhosis. The prevalence of NAFLD in adults has been reported to be as high as 33%, making it the most common cause of chronic liver disease in the United States [1]. Thyroid dysfunction, particularly hypothyroidism, has been associated with insulin resistance [2, 3], dyslipidemia [4, 5] and obesity [6, 7], all of which are important components of the metabolic syndrome.

Recent data suggest that hypothyroidism may be associated with NAFLD [8]. However, confirmation and further characterization of clinical data supporting this association is needed. This case control study was designed to assess the prevalence of hypothyroidism in consecutive NAFLD patients compared to matched controls while evaluating potential factors that could be associated with hypothyroidism in this patient population.

Methods and Design

Study Design and Patient Population

The study population consisted of 246 adult patients ≥18 years of age with biopsy proven nonalcoholic fatty liver disease (NAFLD) seen in the hepatology outpatient clinic of the Cleveland Clinic Foundation in Cleveland, Ohio between October 2006 and June 2009. All consecutive cases who met inclusion criteria were included. Out of the study population, 233 NAFLD cases were matched by age, gender, race and BMI with 430 controls without any evidence of chronic liver disease attending the general medicine outpatient clinics of Cleveland Clinic Foundation. The controls were identified using the e-Cleveland clinic electronic medical record system. Records of all cases and controls were reviewed by a single physician (MP) and relevant data were abstracted.

Exclusion criteria included subjects with significant alcohol use (>14 drinks per week in males or 7 drink/week in females), or those with any laboratory or clinical evidence suggesting an alternate or coexistent underlying chronic liver disease including viral hepatitis, hemochromatosis, autoimmune hepatitis, Wilson's disease, alpha1 antitrypsin disease or chronic cholestatic liver disease.

Histology

Liver biopsy specimens were reviewed by a single experienced liver pathologist (LY). The histological grading and staging for NAFLD were performed using the modified Brunt classification: steatosis, inflammation, and fibrosis. Steatosis is graded on a scale from 0 to 3 according to the amount of fat present in the lobules: 0, none (<1%); 1, 1–33%; 2, 34–66%, 3, >66%. Inflammation is graded on a scale of 0–3: 0, none; 1, mild (scattered lymphocytes or small clusters within portal tracts and lobules); 2, moderate (increased portal and lobular inflammation with lobular macrophages and/or neutrophils in comparison to grade 1); and 3, severe (same as grade 2 but with more intense inflammation, including several collections of inflammatory cells in the lobules, concentrated around zone 3). Fibrosis was classed as *Stage 1:* Zone 3 perivenular or pericellular fibrosis; *Stage 2:* same as for stage 1 plus focal or extensive portal fibrosis; *Stage 3:* bridging fibrosis, focal or extensive; *Stage 4:* cirrhosis with or without residual perisinusoidal fibrosis. The NASH Clinical Research Network validated histological scoring system, the NAFLD activity score (NAS), was used to distinguish "NASH" and "not NASH" [9].

Definitions

Subjects were defined as having "hypothyroidism" if they carried a clinical diagnosis of hypothyroidism and were on thyroid replacement therapy. Controls were required to have normal liver tests (ALT ≤ 45 IU/L, AST ≤ 40 IU/L, bilirubin ≤1.5 mg/dl and alkaline phosphatase ≤150 IU/L), and have absence of any acute or chronic liver disease, and the absence of fatty liver on at least one radiographic imaging study.

Ethical Considerations

This study was designed as a retrospective case–control study and was conducted in accordance with the ethical guidelines of the Helsinki declaration of 1975 and approved by the Institutional Review Board at the Cleveland Clinic, Cleveland, Ohio.

Statistical Analysis

Descriptive statistics were computed for all factors. Mean and standard deviations were calculated for continuous variables and frequencies and percentages for categorical variables. Propensity score matching was used to match NAFLD subjects to controls without liver disease. A propensity score (PS) was created using age, gender, ethnicity and BMI and up to two control subjects were matched to each NAFLD patient within a caliper of PS ±0.03 using the greedy algorithm. Out of a pool of 246 NAFLD patients and 1,455 controls, depending on the availability of controls, a total of 197 NAFLD subjects were matched 1:2 and an additional 36 were matched 1:1. Conditional logistic regression was used to compare the two groups.

All 246 NAFLD patients were used to assess prevalence of hypothyroidism in subjects with NAFLD and what factors were associated with hypothyrodism in these

patients. Student's *t* tests or Wilcoxon rank sum tests were used to evaluate associations between continuous variables and presence of hypothyroidism. Pearson's chi-square was used for categorical variables and Mantel-Haenzel tests for steatosis, fibrosis, inflammation and ballooning. In addition, a multivariate logistic regression analysis was performed to evaluate factors associated with presence of hypothyroidism. An automated stepwise variable selection was performed on 1,000 bootstrap samples to choose the final model; variables with more than 10% missing values were not considered for inclusion and factors that appeared in ≥30% of replications were kept in the final model. A $P < 0.05$ was considered statistically significant. SAS version 9.2 software (The SAS Institute, Cary, NC) and R version 2.10 software (The R Foundation for Statistical Computing, Vienna, Austria) were used to perform all analyses.

Results

Table 1 summarizes clinical and demographic information of the subjects. The two groups were matched for age, BMI, gender and ethnicity. The mean age among NAFLD cases was 50.4 years, 56.2% were females and the mean BMI was 35.7 kg/m^2. Diabetes mellitus, hypertension and hyperlipidemia were more frequent in the NAFLD group ($P < 0.001$) compared to controls. In addition, the mean levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and thyroid stimulating hormone (TSH) were higher in NAFLD compared to controls ($P < 0.01$).

Table 1 Demographic and clinical characteristics: NAFLD versus controls

Factor	NAFLD ($n = 233$)	Controls ($n = 430$)	*P* value
Female	131 (56.2)	243 (56.5)	0.86
Ethnicity			0.62
Caucasian	219 (94.0)	401 (93.3)	
Black	8 (3.4)	20 (4.7)	
Hispanic	3 (1.3)	3 (0.7)	
Other	3 (1.3)	6 (1.4)	
Age	50.4 (11.1)	51.0 (14.1)	0.76
BMI	35.7 (8.6)	34.7 (8.1)	0.86
DM[a]	99 (42.7)	95 (22.1)	*<0.001*
HTN[a]	137 (59.1)	188 (43.7)	*<0.001*
Hyperlipidemia[a]	174 (86.1)	183 (42.6)	*<0.001*
AST (IU/L)[a]	41.5 (27.0, 65.0)	21.0 (17.0, 25.0)	*<0.001*
ALT (IU/L)[a]	48.0 (29.0, 85.0)	19.0 (14.0, 24.0)	*<0.001*
ALP (IU/L)[a]	80.0 (63.5, 103.5)	76.0 (63.0, 93.0)	*0.001*
Bilirubin (mg/dL)[a]	0.8 (3.1)	0.9 (5.5)	0.97
TSH (mU/L)[a]	2.2 (1.4, 3.2)	1.7 (1.1, 2.6)	*0.013*
Hypothyroidism	49 (21.0)	41 (9.5)	*<0.001*

NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension

NAFLD subjects were matched to controls using propensity score matching using gender, ethnicity, age and BMI. 197 NAFLD patients had two matches and 36 had one match

Values presented as *n* (%) for gender, ethnicity, DM, HTN, hyperlipidemia and hypothyroidism and mean (SD) otherwise

P values correspond to univariate conditional logistic regression analysis to account for matching. Values in italics are considered statistically significant ($P < 0.05$)

[a] Data not available for all subjects. DM, $n = 662$; HTN, $n = 662$; hyperlipidemia, $n = 632$; bilirubin, $n = 557$; AST, $n = 561$; ALT, $n = 566$; ALP, $n = 546$; TSH, $n = 391$

Prevalence of Hypothyroidism in NAFLD

The prevalence of hypothyroidism was higher among patients with NAFLD compared to the control group (21.1% vs. 9.5%, $P < 0.001$). Hypothyroidism was also more common in patients with NASH when compared to those with no NASH (25% vs. 12.8%, $P = 0.03$). Subjects with hypothyroidism were 2.1 (95% CI 1.1–3.9) and 3.8 (95% CI 2–6.9) times more likely to have NAFLD and NASH, respectively. After adjusting for diabetes, hypertension, BMI and hyperlipidemia, subjects with hypothyroidism were still found to be 2.1 times (95% CI 1.1–3.9; $P = 0.022$) more likely to have NAFLD than those without hypothyroidism.

Univariable Analysis

In the univariable analysis (Table 2), NAFLD patients with hypothyroidism were more likely to be females, have an older age and higher BMI compared to NAFLD patients without hypothyroidism. ALT levels were significantly lower in patients with hypothyroidism (median 37 vs. 49; $P = 0.045$). As expected, hypothyroid patients had higher TSH compared to those without the disease. Steatohepatitis was more frequent in patients with hypothyroidism compared to those without the disorder ($P = 0.03$). Additionally, mild to moderate alcohol consumption, defined as less then 14 drinks per week in males and ≤6 drinks/week in female subjects appears to lower the likelihood of hypothyroidism in NAFLD. There were no differences between individual components of NAS score between the two groups.

Multivariable Analysis

Table 3 represents the results of the multivariable logistic regression analysis. Female gender (OR, 5.9; $P < 0.001$)

Table 2 Factors associated with presence of hypothyroidism in subjects with NAFLD

Factor	Hypothyroidism ($n = 52$)	No hypothyroidism ($n = 194$)	P value
Female	46 (88.5)	94 (48.5)	*<0.001*
Age	53.5 (12.2)	49.5 (10.6)	*0.035*
BMI (kg/m^2)	39.5 (11.8)	35.4 (8.5)	*0.023*
Alcohol use[a]	13 (25.0)	106 (54.9)	*<0.001*
ALT (IU/L)[a]	37.0 (23.0, 73.0)	49.0 (30.0, 88.0)	*0.045*
TSH (mU/L)[a]	3.1 (1.8, 4.8)	2.0 (1.4, 3.0)	*0.008*
DM[a]	26 (50.0)	84 (43.5)	0.4
HTN[a]	30 (57.7)	116 (60.1)	0.75
Hyperlipidemia[a]	39 (86.7)	147 (86.5)	0.97
Metabolic syndrome[a]	36 (80.0)	131 (73.6)	0.38
Ferritin[a]	133.0 (87.0, 285.0)	170.0 (72.0, 276.5)	0.76
NAS score	4.5 ± 1.5	4.0 ± 1.9	0.074
NASH	42 (80.8)	126 (65.0)	*0.03*

NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension

Values presented as mean (SD) or median (P25, P75) for continuous factors and *n* (%) for categorical factors

P values correspond to Student's *t* test or Wilcoxon rank sum tests for continuous factors and Pearson's chi-square for all other categorical factors. Values in italics are considered statistically significant ($P < 0.05$)

[a] Data not available for all subjects. Alcohol use, $n = 245$; HTN, $n = 245$; DM, $n = 245$; metabolic syndrome, $n = 223$; hyperlipidemia, $n = 215$; ALT, $n = 237$; INR, $n = 214$; ferritin, $n = 169$; TSH, $n = 142$

Table 3 Multivariable analysis of factors associated with hypothyroidism in NAFLD

Factor	Odds ratio (95% CI)	P value
Female	5.9 (2.3, 14.8)	*<0.001*
Alcohol use[a]	0.37 (0.18, 0.77)	*0.008*
BMI (1 kg/m^2 increase)	1.04 (1.002, 1.07)	*0.039*
NASH[b]	2.0 (0.90, 4.6)	0.089
Age (5 years increase)	1.1 (0.95, 1.3)	0.16

CI confidence interval, *NAFLD* nonalcoholic fatty liver disease, *BMI* body mass index

P-values in italics are considered statistically significant ($P < 0.05$)

[a] Use of moderate alcohol has a protective effect

[b] Histological diagnosis of NASH

and higher BMI (OR, 1.04; $P = 0.03$) were associated with the presence of hypothyroidism in NAFLD. In contrast, mild to moderate alcohol consumption was associated with a reduced likelihood of developing hypothyroidism compared to those who reported complete abstinence (OR, 0.31; $P < 0.001$). By univariable analysis, hypothyroidism was more common in NAFLD patients with NASH when compared to those with no NASH. After adjusting for diabetes mellitus, dyslipidemia, hypertension, and age, the association remained statistically significant. However, once gender was included in the multivariable model, the association between NASH and hypothyroidism lost statistical significance ($P = 0.08$).

Discussion

The prevalence of hypothyroidism in the United States is 3.7% as reported by the National Health and Nutritional Examination Survey (NHANES) conducted between 1999 and 2002 [10]. Other studies report the prevalence of sub clinical and overt hypothyroidism to be 4–10% and 0.3–5% in the general population, respectively, and 5% in the geriatric population [10–14]. We found an increased prevalence of hypothyroidism among patients with NAFLD compared to age, gender, race and BMI matched controls without known chronic liver disease with the prevalence being highest among subjects with NASH. Two previous studies with smaller sample sizes and incomplete histology reported prevalence rates of 15 and 20% for hypothyroidism in NAFLD [8, 15]. Our study included a large sample size with liver histology read by a single pathologist for all the patients. We also controlled for known factors associated with hypothyroidism (age, gender, ethnicity and BMI). These current findings confirm an association between the presence of hypothyroidism and NAFLD.

The link between hypothyroidism and NAFLD may relate to several underlying mechanisms. Hypothyroidism has been associated with insulin resistance [2, 3, 16], dyslipidemia [4, 5] and obesity [6, 7]; all of which are important components of the metabolic syndrome. In addition, hypothyroidism is also associated with the metabolic syndrome [17], which plays an important role in the development of NAFLD [18].

Insulin resistance in the setting of hypothyroidism has been documented [2] and is associated with decreased responsiveness of glucose uptake in muscle and adipose tissue to insulin, as well as decreased glycogen synthesis in skeletal muscle in both animal and human studies [2, 3, 16, 19, 20]. These effects were alleviated by thyroid replacement [3]. Hypothyroidism is also more common in patients with diabetes than in the general population [21]. If hypothyroidism enhances the degree of insulin resistance in NAFLD patients, it may increase the already elevated lipolysis and free fatty acid delivery to the liver and thereby accelerate liver injury in NAFLD [22].

There is also an increased prevalence of hypothyroidism in the obese population as compared to the general

population [7] with the prevalence of hypothyroidism being 10–20% in obese subjects [6, 7]. On average hypothyroid patients weigh 15–30% more than during euthyroid state [23]. Leptin, an adipocytokine that affects thermogenesis and appetite and is an indicator of body fat content, may have a possible role in hypothyroidism and obesity [24]. Hypothyroidism patients have increased levels of leptin [25] which increases collagen production and insulin resistance in the liver [26, 27]. Hypothyroidism can also increase risk of hypertension [28]. Possible mechanisms responsible for hypertension in individuals with hypothyroidism include increased peripheral vascular resistance and arterial stiffness [29], abnormalities that occur in NAFLD patients [30].

Up to 90% of hypothyroid patients have abnormal lipid values [5]. While hypothyroidism primarily causes elevation in cholesterol and low density lipoproteins, it also affects the synthesis, mobilization and degradation of all aspects of lipid metabolism [4, 31]. There is increased triglyceride levels in hypothyroid subjects due to increased estertification of hepatic fatty acids with diminished lipoprotein lipase activity and decreased hepatic uptake of HDL levels in these subjects [4, 31]. It is possible that dyslipidemia in hypothyroidism may contribute to NAFLD [32]. The antisteatotic and triglyceride reducing effects of a liver-selective thyroid receptor (TR) agonist on livers of animal models with fatty liver have been described [33]. Therefore hypothyroidism may exacerbate preexisting lipid abnormalities in patients with NAFLD.

On multivariate analysis, females with NAFLD were more likely to have hypothyroidism compared to male subjects. This gender difference in hypothyroidism has been well described [11–13]. In this study, hypothyroidism was associated with the presence of NASH compared to no NASH among subjects with NAFLD. Although the association lost statistical significance once gender was added to the multivariate model, a statistical trend remained ($P = 0.08$). This suggests that the association between hypothyroidism and more severe histological disease in patients with NAFLD may be independent of gender but larger studies will be needed to demonstrate that.

A novel observation in this study was the apparent protective effect of mild alcohol intake on hypothyroidism among NAFLD cases. While excessive alcohol consumption is known to suppress peripheral thyroid metabolism in patients with alcoholism and especially those with alcoholic cirrhosis independent of the liver damage [34, 35], we did not find any literature that described the association of alcohol consumption and thyroid disease in the general population. It is unclear why abstinence from alcohol compared to those who drank in moderation resulted in increased hypothyroidism in NAFLD. However, alcohol consumption has been shown to decrease thyroid volume and the prevalence of goiter suggesting a possible protective effect of alcohol on the thyroid gland [36]. In addition there is some evidence of a potential protective role of alcohol in thyroid cancer [37]. Similar benefits of alcohol in cardiovascular morbidity and mortality insulin resistance, type 2 diabetes mellitus and HDL have been demonstrated [38, 39].

Markers of oxidative stress including reactive oxygen species and markers of lipid peroxidation have been reported in patients with hypothyroidism [40, 41], abnormalities that also occur in NASH patients [42]. This may partly explain the increased presence of hypothyroidism in NASH patients. Recently, mitochondrial dysfunction has been implicated in the pathogenesis of NASH [43]. This is of particular interest since thyroid dysfunction alters mitochondrial respiration [44]. Mitochondria abnormalities and dysfunction in skeletal muscle and alteration of cardiolipin (an important phospholipid in the inner membrane of mitochondria) have been described in hypothyroidism [45, 46].

Although the precise cause of the increased prevalence of NAFLD and NASH in hypothyroidism patients remain unclear, insulin resistance in hypothyroidism is likely to exacerbate free fatty acid influx and subsequent hepatic steatosis. Furthermore, hypothyroidism has been reported to modulate mitochondrial nitric oxide synthesis and alter mitochondrial inner membrane composition and permeability which alters respiratory gene expression and mitochondrial oxygen uptake [47]. Such abnormalities would result in increased ADP concentration and generation of reactive oxygen species [48]. The clinical importance of these findings is emphasized by the nascent but important data indicating that fatty liver may improve with liver-specific thyromimetics [49–51].

There are a number of limitations to our study, including all limitations inherent to a retrospective study design. In particular, the retrospective study design cannot define the timeline between the development of hypothyroidism and that of NAFLD. This limits the ability to establish the temporal relationship between these two factors. Data regarding the time of diagnosis of hypothyroidism as well as comprehensive results of thyroid function tests were not available. The use of medical records to make a diagnosis of hypothyroidism could have resulted in some patients being missed in both the NAFLD as well as the control groups. Similar to earlier studies, we had to use thyroid replacement therapy as a surrogate for diagnosis.

Even though we did not study the prevalence of hypothyroidism among other types of chronic liver disease, our data indicates that the prevalence of hypothyroidism is higher in subjects with NAFLD compared to those with other chronic liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and

viral hepatitis, in which prevalence rates of 10, 6 and 7.3%, respectively, have been reported [8, 15].

Hepatocellular carcinoma (HCC) is known to occur in patients with cirrhosis including those related to NASH. A recent study reported an association between the presence of hypothyroidism in patients with cirrhosis and an increased risk of HCC [52]. The prevalence of hypothyroidism among subjects with HCC is 11.7%. Based on this, it may be important to identify those patients with NASH related cirrhosis who have hypothyroidism which may put them at a higher risk for developing HCC.

In summary, our study indicates that patients with NAFLD have a higher prevalence of hypothyroidism when compared to a matched control population and the prevalence of hypothyroidism may be higher among those with NASH compared to no NASH. In addition, moderate alcohol use appears to have a protective effect for hypothyroidism in NAFLD. We recommend that further investigation using prospective designed studies should be undertaken to evaluate the prevalence of hypothyroidism in NAFLD. Furthermore, the utility of using thyroid-related medication to prevent steatosis and development of NASH needs to be explored in animal and cell culture models. Establishing an association between hypothyroidism as a risk factor for NAFLD in future studies may identify a subgroup of patients in the general population who may benefit from screening for the presence of fatty liver disease.

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