

Association between Thyroid-Stimulating Hormone Levels and Non-Alcoholic Fatty Liver Disease Is Not Independent from Metabolic Syndrome Criteria

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Keywords

Thyroid function · Obesity · Non-alcoholic fatty liver disease · Metabolic syndrome · Thyroid-stimulating hormone

Abstract

Introduction: Thyroid hormones are involved in the regulation of body composition, lipid metabolism, and insulin resistance. Thus, it is possible that they might play a role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). However, the role of thyroid function on NAFLD is not well defined. In this study, we evaluated the relationship between thyroid-stimulating hormone (TSH) levels, within the reference range, and presence of NAFLD in asymptomatic individuals. **Study Design:** We included all individuals evaluated at a preventive clinic of the Hospital Israelita Albert Einstein, between 2014 and 2015. The prevalence of NAFLD (analyzed by abdominal ultrasound), according to TSH quartiles, within the reference range, was determined. The association between TSH quartiles and NAFLD was analyzed by logistic regression adjusted for possible confounders. **Results:** We evaluated 10,539 individuals (73% male, age

43.4 ± 9.4 years). The prevalence of NAFLD was 34, 38, 38, and 39% in the first to the fourth TSH quartiles (0.46–1.44, 1.45–1.97, 1.98–2.68, and 2.69–4.68 mUI/L, respectively, *p* for trend <0.001). At univariate analysis, higher TSH levels were associated with the diagnosis of NAFLD. When data were adjusted for the metabolic syndrome characteristics (waist circumference, HDL-cholesterol and triglycerides levels, presence of diabetes, and systemic arterial hypertension), the association was no longer significant. **Conclusions:** Although the TSH variability within the reference range is associated with NAFLD in univariable models, once adjusted for metabolic syndrome factors no significant association is noted.

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Introduction

Thyroid hormones are involved in the regulation of body composition, lipid metabolism, and insulin resistance [1–6]. It is well known that hypothyroidism is associated with high levels of LDL-cholesterol and triglyc-

erides secondary to a decrease in LDL receptor's activity and clearance of triglyceride-rich lipoproteins [7–9].

Excessive triglyceride accumulation in the liver is manifested through the diagnosis of steatosis, a component of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis [10, 11]. In fact, NAFLD has long been recognized as the hepatic feature of the metabolic syndrome [12]. This condition may lead to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma if not treated in the long term [13–16], and might be considered an independent risk marker for cardiovascular disease [17–19].

Previous studies have sought to evaluate the association between hypothyroidism and NAFLD [20–25]. Most of them showed that hypothyroidism, in its overt or subclinical type, is independently associated to NAFLD [26, 27], suggesting that hypothyroidism may directly result in NAFLD irrespective of other common metabolic risk factors. In a recent prospective study, lower thyroxine (T4) levels were associated with a higher risk for NAFLD [26]. Nevertheless, though this association has been demonstrated for subclinical hypothyroidism, the thyroid function is a continuum and the association between thyroid-stimulating hormone (TSH) levels within the normal range and NAFLD has not been well established. In the present study, we aimed to evaluate the association between thyroid function within the normal range and the presence of NAFLD in asymptomatic individuals.

Methods

All individuals evaluated at a routine health check-up at the Hospital Israelita Albert Einstein, between 2014 and 2015, were included. This evaluation comprised several clinical and laboratory tests, as well as abdominal ultrasound. The Ethical Committee of the Hospital Israelita Albert Einstein approved this study, and the consent form was waived as the research is based on database analysis and no additional patient contact was needed.

Individuals between 20 and 80 years, whose TSH levels were within the normal range, were evaluated, excluding those with previously known liver or thyroid disease, using thyroid-related medication (levothyroxine, methimazole or propylthiouracil), and with a score of more than 8 points in the Alcohol Use Disorders Test [28].

The check-up protocol comprised anthropometric evaluation, laboratory measures, physical activity questionnaire, and abdominal ultrasound for NAFLD evaluation, as previously described [29]. Waist circumference was measured by a trained nutritionist and was considered abnormal when above 94 cm for men and 80 cm for women. Body mass index (BMI) was measured using the weight/height² (kg/m²) formula. Plasma concentrations of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides were determined by using automated equipment VITROS 5600[®] Ortho Clinical Diagnostics by dry chemical colorimetric method. Serum TSH was measured by a chemo luminescence

method. Individuals were then divided into 4 groups according to quartiles of TSH levels within the reference range (0.46–1.44, 1.45–1.97, 1.98–2.68, and 2.69–4.68 mUI/L). The international physical activity questionnaire (IPAQ) was used to evaluate the physical activity level in the last week [30]. The presence of NAFLD defined as hepatic steatosis in the absence of excessive alcohol consumption or previous liver disease was based on the ultrasound evaluation, according to standardized criteria [31]. Steatosis was diagnosed by certified radiologists after at least a 6-h fast using an ACUSON XP-10 device (Mountain View, CA, USA) and was identified by the presence of an ultrasonographic pattern of a bright liver, with evident contrast between hepatic and renal parenchyma.

Statistical Analysis

Continuous variables were presented as means and standard deviations or medians and quartiles, as appropriate, and compared using one-way ANOVA or Kruskal-Wallis test. Categorical variables were presented as absolute numbers and proportions, and compared using chi-square test. Triglycerides and TSH were log-transformed for inclusion in the multivariable models as these variables are known to have a skewed distribution.

The association between TSH levels and presence of NAFLD was analyzed using logistic regression models. Initially, we performed a univariable model followed by additional multivariable models adjusted as follows:

- Model 1: adjusted for gender and age;
- Model 2: adjusted for gender, age, smoking, and metabolic syndrome criteria (abdominal circumference, triglycerides, HDL-C, blood pressure, fasting glucose as continuous variables);
- Model 3: adjusted for gender, age, smoking, metabolic syndrome criteria (as in model 2), and physical activity levels.

We first performed those models using TSH as a log-transformed continuous variable. Additionally, we categorized TSH levels in quartiles (0.46–1.44, 1.45–1.97, 1.98–2.68, and 2.69–4.68 mUI/L).

To better understand the role of each metabolic syndrome factors (waist circumference, HDL levels, triglyceride levels, blood pressure, and fasting glucose), as well as other possible confounders such as BMI, physical activity, and smoking, we performed additional models for each of those predictors individually after adjustment for age and gender.

A level of significance of 0.05 was used. All analyses were performed using Stata version 13.0 (StataCorp, USA).

Results

We included 10,539 individuals, 73% male, with mean age of 43.4 ± 9.4 years and mean BMI of 26.4 ± 4.2 kg/m². Baseline characteristics, according to normal range TSH quartiles, are shown in Table 1. Due to the large sample size, almost all variables were statistically different among the groups, though the absolute differences were small.

The overall prevalence of NAFLD was 37.3%. Compared to individuals without NAFLD, those with the condition were older and with more metabolic abnormalities (Table 2).

Table 1. Baseline characteristics of subjects stratified according to TSH quartiles

	TSH 0.46–1.44 mUI/L	TSH 1.45–1.97 mUI/L	TSH 1.98–2.68 mUI/L	TSH 2.69–4.68 mUI/L	Total	<i>p</i> value
Subjects, <i>n</i>	2,672	2,613	2,620	2,634	10,539	
Gender, male, %	71	74	73	72	73	0.04
Age, years	43.04±9.25	43.20±9.14	43.36±9.25	43.85±10.02	43.36±9.43	0.01
BMI, kg/m ²	25.86±3.89	26.26±3.93	26.69±4.42	26.72±4.39	26.38±4.18	<0.01
Waist circumference, cm	90.43±20.70	91.48±12.31	92.23±13.06	92.20±12.91	91.58±15.19	<0.01
SBP, mm Hg	115±12	116±12	117±12	116±12	116±12	<0.01
DBP, mm Hg	76±8	76±8	77±8	77±8	76±8	<0.01
Total cholesterol, mg/dL	180±34	188±35	189±35	190±35	189±35	0.04
LDL-c, mg/dL	116±31	116±32	116±32	116±32	116±32	0.92
HDL-c, mg/dL	49±14	47±13	48±14	48±14	48±14	<0.01
Triglycerides, mg/dL*	98 (72–140)	107 (75–150)	109 (78–156)	112 (81–161)	108 (77–153)	<0.01
Glucose, mg/dL	87±12	88±13	88±15	88±15	88±14	0.08
HbA1c, %	5.4±0.5	5.4±0.5	5.5±0.6	5.5±0.6	5.4±0.6	0.05
Diabetes, <i>n</i> (%)	61 (2.28)	67 (2.56)	59 (2.25)	72 (2.73)	259 (2.46)	0.62
Hypertension, <i>n</i> (%)	340 (12.72)	378 (14.47)	403 (15.38)	387 (14.69)	1,508 (14.31)	0.04
Smoking, <i>n</i> (%)	244 (9.13)	209 (8.00)	179 (6.83)	147 (5.58)	779 (7.39)	<0.01

* Triglycerides expressed as median (interquartile range); other variables expressed as mean ± SD or *n* (%).

BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

Table 2. Baseline characteristics of subjects stratified according to the presence or absence of NAFLD (mean ± SD)

	NAFLD		<i>p</i> value
	absent	present	
Patients, %	6,607 (62.7)	3,932 (37.3)	
Male, %	4,196 (63.51)	3,452 (87.79)	<0.01
Age, years	41.73±9.20	46.11±9.18	<0.01
BMI, kg/m ²	24.75±3.20	29.12±4.19	<0.01
Waist circumference, cm	86.13±10.36	100.74±17.43	<0.01
SBP, mm Hg	113±11	121±12	<0.01
DBP, mm Hg	74±8	80±8	<0.01
Total cholesterol, mg/dL	186±33	193±37	<0.01
LDL-c, mg/dL	114±30	119±33	<0.01
HDL-c, mg/dL	52±14	42±10	<0.01
Triglycerides, mg/dL*	91 (68–126)	141 (104–194)	<0.01
Glucose, mg/dL	85±8	93±19	<0.01
HbA1c, %	5.3±0.4	5.6±0.7	<0.01
Diabetes, <i>n</i> (%)	59 (0.89)	200 (5.09)	<0.01
Hypertension, <i>n</i> (%)	487 (7.37)	1,021 (25.97)	<0.01
Smoking, <i>n</i> (%)	474 (7.17)	305 (7.76)	0.03

* Triglycerides expressed as median (interquartile range); other variables expressed as mean ± SD or *n* (%).

BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; NAFLD, non-alcoholic fatty liver disease.

Table 3. Logistic regression for NAFLD outcome using TSH as continuous and categorical variable

	Univariate		Model 1*		Model 2 [#]		Model 3**	
	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value
<i>TSH quartiles</i>								
0.46–1.44	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
1.45–1.97	1.19	<0.01	1.15	0.02	1.01	0.94	1.01	0.94
1.98–2.68	1.18	<0.01	1.15	0.02	0.86	0.04	0.86	0.04
2.69–4.68	1.25	<0.01	1.22	<0.01	0.90	0.15	0.90	0.15
<i>lnTSH (per one unit)</i>								
0.46–4.68	1.25	<0.01	1.22	<0.01	0.93	0.20	0.93	0.20

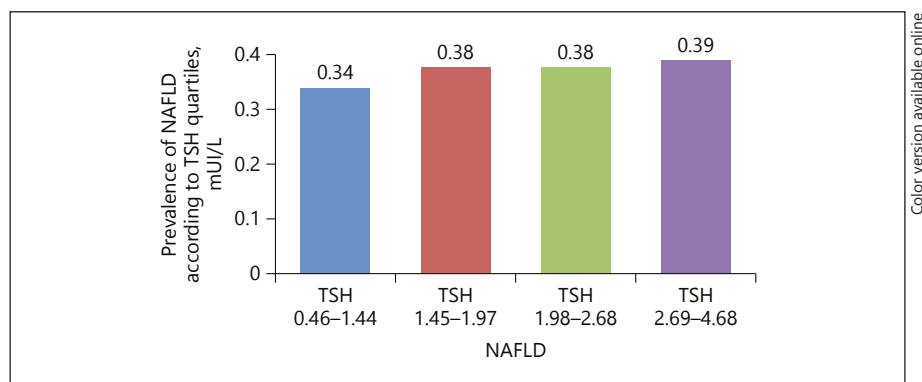
* Model 1: adjusted for age and gender.

[#] Model 2: adjusted for 1 + metabolic syndrome criteria + smoking.

** Model 3: adjusted for 2 + physical activity level + smoking.

lnTSH, log-transformed TSH (continuous variable); TSH, thyroid-stimulating hormone (mU/L); Ref, reference; NAFLD, non-alcoholic fatty liver disease.

Fig. 1. Prevalence of non-alcoholic fatty liver disease, according to thyroid-stimulating hormone quartiles (mUI/L).



The proportion of individuals with NAFLD was higher among those with higher TSH levels (Fig. 1; $p < 0.001$). Indeed, at univariate analysis, higher TSH quartiles were associated with the diagnosis of NAFLD. This association remained significant when the model was adjusted for age and gender. However, when the data were adjusted for metabolic syndrome characteristics, the association was no longer significant, as well as when adjusted for physical activity level (Table 3). When TSH was modeled as a continuous log-transformed variable, the results remained unchanged (Table 3).

When further exploring the role of each individual predictor individually, the association between TSH and NAFLD lost significance after adjustment for waist circumference, BMI, and triglyceride levels, but not for other predictors (Table 4).

Discussion

This study shows an association between TSH levels within the reference range and NAFLD presence. However, this association seems to be mediated by the characteristics of metabolic syndrome (waist circumference, HDL-C levels, triglycerides levels, diabetes, and systemic arterial hypertension), as no significant association was seen after adjustment for those variables.

Many studies have investigated the role of thyroid dysfunction in the genesis of NAFLD [23, 32]. In 2012, a Korean study showed that NAFLD was statistically significantly associated with hypothyroidism and subclinical hypothyroidism in a dose-dependent manner, independently of metabolic syndrome risk factors [27]. Recently, a publication from the Rotterdam group has also found a positive association between the prevalence of NAFLD

Table 4. Logistic regression for NAFLD outcome with individual risk factors

	Waist circumference		BMI, kg/m ²		HDL		lnTg		SBP		Glucose		Physical activity [#]		Smoking	
	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value	OR	<i>p</i> value
lnTSH	1.03	0.60	1.00	0.97	1.18	<0.01	1.04	0.43	1.19	<0.01	1.20	<0.01	1.22	<0.01	1.23	<0.01
<i>TSH quartiles</i>																
1	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
2	1.07	0.32	1.08	0.26	1.11	0.11	1.06	0.38	1.12	0.07	1.15	0.03	1.14	0.03	1.16	0.02
3	0.95	0.47	0.92	0.24	1.12	0.08	1.00	0.94	1.09	0.15	1.14	0.03	1.14	0.03	1.16	0.02
4	1.00	0.96	0.98	0.78	1.17	0.01	1.02	0.81	1.19	0.01	1.20	<0.01	1.22	<0.01	1.23	<0.01

All data were adjusted for gender and age.

[#] Measured by International Physical Activity Questionnaire.

BMI, body-mass index; HDL, high density lipoprotein levels; lnTg, log-transformed triglycerides levels; SBP, systolic blood pressure; ref, reference; NAFLD, non-alcoholic fatty liver disease.

and TSH levels [26]. The group was able to demonstrate that the risk of NAFLD progressively decreased from a hypothyroid to a hyperthyroid state [26]. However, in both studies, there was no analysis within the normal reference range.

In 2014, a Chinese group analyzed the prevalence of NAFLD in euthyroid subjects and found a positive association between TSH levels, even within the reference range, and NAFLD, independent of known metabolic risk factors, evaluated through multiple logistic regression [33]. However, this study evaluated less than 1,000 subjects. Our analysis has the strength of including more than 10,000 subjects and we could not demonstrate this independent association.

NAFLD is the most common liver disorder in Western industrialized countries and shares the same risk factors as type 2 diabetes, dyslipidemia, obesity, and metabolic syndrome [34]. Indeed, it may often be recognized as one of the metabolic syndrome features. Also, TSH levels have been associated with increased body fat and BMI, as well as increased cardiovascular risk [35], although the studies are still controversial [36, 37]. Within the reference range, it was already acknowledged that TSH levels seem to increase the BMI proportionally [38]. The upsurge in BMI could lead to the metabolic syndrome if other features are present and this could justify our finding of the influence of normal thyroid function and its spectrum in the prevalence of NAFLD.

The main limitation of this study is its cross-sectional design, as we cannot exclude the possibility of different results if a similar analysis was conducted consider-

ing the variation of TSH levels along the time. Another point for discussion is that we only included TSH levels within the reference range, what could mitigate the expected effect of overt hypothyroidism in NAFLD. Also, as the individuals included were patients from a preventive clinic, only TSH values were available and not thyroxine levels.

Overall, our study suggests that thyroid function, even within the normal range, is associated with metabolic syndrome, through which it may play a role in NAFLD. This is an important finding because it opens a discussion if the adequacy of the TSH level to a lower reference could prevent the metabolic syndrome risk factors and, thus, the emergence of NAFLD.

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