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Importance of thyroid-stimulating hormone levels in liver disease

<https://doi.org/10.1515/jpem-2020-0031>

Received January 23, 2020; accepted June 5, 2020; published online August 18, 2020

Abstract

Objectives: Recently, several studies have reported the association between elevation of thyroid-stimulating hormone (TSH) levels and liver disease, especially, non-alcoholic fatty liver disease (NAFLD). We aimed to evaluate the incidence and risk factors of TSH elevation in patients with liver disease.

Methods: We retrospectively reviewed the data of patients aged <18 years who were diagnosed with liver disease between January 2015 and March 2019.

Results: Among the 77 patients, 17 (22.1%) had subclinical hypothyroidism and 3 (17.6%) progressed to overt hypothyroidism. A total of 26 (33.8%) patients had NAFLD, and 6 (23.1%) had subclinical hypothyroidism. The ultrasound grade of liver steatosis was not related to the elevation of TSH levels. The median age was significantly younger in patients with TSH elevation (5 vs. 9 years, $p = 0.017$). Albumin levels were significantly decreased (3.9 vs. 4.3 g/dL, $p = 0.007$), and total bilirubin levels were elevated (2.2 vs. 0.6 mg/dL, $p = 0.001$) in patients with subclinical hypothyroidism.

Conclusions: TSH elevation commonly occurs in patients with liver disease, especially those with younger age. The cause of liver disease was not a risk factor for TSH elevation.

Keywords: hypothyroidism; non-alcoholic fatty liver disease; thyroid-stimulating hormone.

Introduction

The thyroid gland is closely connected to the liver. Thyroid hormones regulate the basal metabolic rate of hepatocytes, and dysthyroidism can cause altered bilirubin metabolism and hepatic circulation [1, 2].

Previous studies have reported an association between hyperthyroidism and liver disease and indicated that the severity of hyperthyroidism is a risk factor for abnormal liver function tests [3, 4]. Previous studies have reported a significant positive association between aspartate aminotransferase (AST) levels and elevated mean levels of thyroid-stimulating hormone (TSH) in patients with liver cirrhosis compared with healthy controls [5, 6].

This association can be explained by the progressive fat accumulation and alteration in lipid metabolism, which are caused by thyroid dysfunction [7–10]. Oxidative stress and lipid peroxidation are other causes of liver cell damage, and this is due to excessive secretion of TSH [11].

Several studies have reported a strong correlation between liver disease and thyroid dysfunction in individuals with non-alcoholic fatty liver disease (NAFLD) [8].

Subclinical hypothyroidism, characterized by an elevated serum TSH level and normal thyroxine (T₄) levels, is considered benign in most cases. However, its effect on the liver is similar to that of overt hypothyroidism, and progression to overt hypothyroidism is possible [12].

In children, subclinical hypothyroidism can affect neurocognitive development and cause growth impairment [13]. In some cases, early atherosclerotic changes are possible with increased cardiovascular risk [14].

Hence, this study aimed to evaluate the incidence of TSH elevation in pediatric patients with liver disease, including those with NAFLD and its risk factors.

Methods

Study patients

We retrospectively analyzed 77 patients aged <18 years who had elevated levels of liver enzymes, between January 2015 and March 2019. After analyzing the results of liver blood test and imaging, patients were divided into two groups, those with NAFLD and those without NAFLD. The exclusion criteria were as follows: (1) positive serologic markers for hepatitis viruses (A, B, and C), Epstein-Barr virus, and cytomegalovirus; (2) autoantibodies indicative of autoimmune hepatitis; (3) previous use of hepatotoxic drugs; and (4) Wilson disease.

Clinical and laboratory evaluation

Body weight and height were measured by a trained technician, and the body mass index (BMI) was calculated by dividing the weight (in

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kilograms) by the square of the height (in meters). Laboratory tests were performed to evaluate the following parameters: AST, alanine aminotransferase (ALT), total bilirubin, albumin, hemoglobin, TSH, and free T4.

Definitions

NAFLD was diagnosed if bright or hyperechoic lesions were observed on liver imaging and when the ALT level was ≥ 30 IU/L [15]. Subclinical hypothyroidism was defined as a serum TSH level higher than the upper limit of normal despite normal levels of serum free T4 [12]. Obesity was defined as a BMI of ≥ 95 th percentile for age and sex [16].

Statistical analysis

Continuous data are expressed as medians or means ($\pm$ standard deviation) and interquartile ranges. These data were further compared using the Mann-Whitney U test or Student's t-test. Discrete data are expressed as numbers and percentages and were compared using Fisher's exact or chi-square tests. To evaluate the factors associated with subclinical hypothyroidism, we used the odds ratio (OR) for logistic regression models. All prognostic variables with a p-value of < 0.1 in the univariate analysis were included in the multivariate analysis. A p-value of < 0.05 was considered significant. Statistical analyses were performed using SPSS (version 24.0; IBM, Chicago, IL, USA).

This retrospective analysis was approved by the Institutional Review Board of Chungnam National University Hospital and conducted in accordance with the Declaration of Helsinki (IRB number: 2019-11-029).

Results

Baseline characteristics of all patients

The male-to-female ratio was 1.5:1, while the median age was 8 years (range: 1–17 years). A total of 17 (22.1%) patients had subclinical hypothyroidism, while the condition of 3 (17.6%) progressed to overt hypothyroidism within a follow-up period of three months.

When we analyzed patients based on thyroid function, the median age was significantly younger (5 vs. 9 years, $p = 0.017$) in patients with subclinical hypothyroidism than in those with normal thyroid function. The incidence of NAFLD was similar regardless of thyroid function (35.3 vs. 33.3%, $p = 0.548$).

Albumin levels were significantly decreased (3.9 vs. 4.3 g/dL, $p = 0.007$) and total bilirubin levels were significantly elevated (2.2 vs. 0.6 mg/dL, $p = 0.001$) in patients with subclinical hypothyroidism.

Table 1 shows the baseline clinical characteristics of all patients based on TSH status.

Clinical characteristics of patients with subclinical hypothyroidism as per etiology of liver disease

Of the 17 patients with subclinical hypothyroidism, 6 (35.3%) were diagnosed with NAFLD. The proportion of males was higher in patients with NAFLD (50.0 vs. 36.4%, $p = 0.484$) and the median age was older (9 vs. 3 years, $p = 0.061$).

AST levels were higher in patients without NAFLD (164.4 vs. 66.0 IU/L). The total bilirubin level was significantly elevated in patients without NAFLD (0.4 vs. 3.3 mg/dL, $p = 0.044$).

Table 2 shows the clinical characteristics of patients with subclinical hypothyroidism.

Predictors of subclinical hypothyroidism in patients with liver disease

In the univariate analysis, age below 10 years and elevated total bilirubin levels were significant risk factors for subclinical hypothyroidism. In the multivariate analysis, only younger age was found to be a statistically significant factor (OR: 3.94, 95% confidence interval: 0.97–15.70, $p = 0.045$). Table 3 shows the risk factors for subclinical hypothyroidism.

Discussion

In this study, 22.1% (17/77) of the patients had subclinical hypothyroidism, while 17.6% (3/17) progressed to overt hypothyroidism. Younger age (< 10 years) and elevated total bilirubin levels were risk factors for subclinical hypothyroidism.

The prevalence of subclinical hypothyroidism in our study was much higher than that reported in a previous study (7.7%) [17] and similar to that reported in another study, which reported that subclinical hypothyroidism occurred in 21% of patients with NAFLD, but only in 9.5% of those in the control group ($p < 0.01$) [18]. Subclinical hypothyroidism can result in the dysfunction of other organs and progress to overt hypothyroidism [19]. Therefore, it is important to evaluate the presence of combined dysthyroidism in patients with any etiology of liver disease.

Age was the most significant risk factor for subclinical hypothyroidism. In the adult population, the prevalence of subclinical hypothyroidism increased with aging, and this age-related change was caused by decreased T4 turnover and TSH biological activity, which is due to changes in TSH glycosylation [20, 21]. A similar mechanism may influence

Table 1: Baseline characteristics of patients based on thyroid-stimulating hormone status.

Variable	Total (77)	TSH elevation (17)	TSH normal (60)	p-Value
Male	46 (59.7)	7 (41.2)	39 (65.0)	0.069
Age, years (range)	8 (1–17)	5 (1–17)	9 (1–17)	0.017
Age <10 years	44 (57.1)	13 (76.5)	31 (51.7)	0.023
Presence of NAFLD	26 (33.8)	6 (35.3)	20 (33.3)	0.548
Presence of obesity	35 (45.5)	5 (29.4)	30 (50.0)	0.172
Severity of NAFLD				
Mild	14 (53.8)	4 (66.7)	10 (50.0)	0.395
Moderate	5 (19.2)	0 (0.0)	5 (25.0)	
Severe	7 (27.0)	2 (33.3)	5 (25.0)	
AST, IU/L	119.1 ± 210.3	129.7 ± 190.1	116.1 ± 217.0	0.803
ALT, IU/L	173.8 ± 237.1	183.2 ± 245.4	171.1 ± 236.8	0.858
Albumin, g/dL	4.2 ± 0.3	3.9 ± 0.4	4.3 ± 0.3	0.007
Total bilirubin, mg/dL	0.9 ± 1.6	2.2 ± 3.3	0.6 ± 0.4	0.001
Hb, g/dL	13.1 ± 1.6	12.4 ± 1.6	13.3 ± 1.6	0.078

Data are presented as mean (± standard deviation) or number (%).

NAFLD, non-alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; TSH, thyroid-stimulating hormone.

Table 2: Baseline characteristics of patients with subclinical hypothyroidism.

Variable	Total (17)	NAFLD (6)	None (11)	p-Value
Male	7 (41.2)	3 (50.0)	4 (36.4)	0.484
Age, years (range)	5 (1–17)	9 (8–17)	3 (1–12)	0.061
Age <10 years	13 (76.5)	4 (66.7)	9 (81.8)	0.034
AST, IU/L	129.7 ± 190.1	66.0 ± 43.8	164.4 ± 230.4	0.197
ALT, IU/L	183.2 ± 245.4	163.1 ± 207.0	194.2 ± 273.0	0.796
Albumin, g/dL	3.98 ± 0.4	4.0 ± 0.6	3.9 ± 0.38	0.864
Total bilirubin, mg/dL	2.2 ± 3.3	0.4 ± 0.1	3.3 ± 3.8	0.044
Hb, g/dL	12.4 ± 1.6	12.5 ± 0.5	12.4 ± 1.9	0.828

Data are presented as mean (± standard deviation) or number (%).

NAFLD, non-alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin.

the association between younger age and subclinical hypothyroidism. A previous study with patients receiving valproic acid therapy showed that younger age (OR: 1.15, cutoff age; 3.9 years) was a significant predictor of subclinical hypothyroidism [22].

Patients with subclinical hypothyroidism had more severe abnormalities in liver function tests than those without this condition. This finding suggests the possibility of more liver cell damage in patients with excessive TSH levels. Similar to our study, significant positive associations between TSH, AST, and total bilirubin levels have been reported previously [5, 6]. A previous study suggested the role of high TSH levels as a cardiometabolic risk marker and that dyslipidemia, hyperglycemia, and liver abnormalities were associated with high TSH levels [23]. In the present study, however, we could not evaluate such laboratory findings.

Elevated TSH levels and hypothyroidism have been associated with the pathogenesis of NAFLD [23–25]. Other factors such as obesity and metabolic syndrome were also

considered risk factors for subclinical hypothyroidism [26]. A previous pediatric study reported that overweight and obese patients had significantly higher serum TSH levels than those with normal weight (7.4 vs. 5.7 IU/mL, respectively) [27]. In this study, NAFLD and obesity were not related to subclinical hypothyroidism. A small portion of these patients and uneven age distribution may have influenced this finding. Hence, an age-matched study with a larger population should be conducted to examine the association between NAFLD and subclinical hypothyroidism.

Our study has several limitations. First, the sample size was too small to allow definitive conclusions. Hence, further well-designed studies are required to confirm the risk factors for subclinical hypothyroidism in patients with liver disease. Second, the retrospective study design may have affected the analysis variables. Laboratory evaluation for dyslipidemia and thyroid antibodies was not performed, and we could not evaluate their association with subclinical hypothyroidism in patients with liver disease.

Table 3: Univariate and multivariate analyses of risk factors of subclinical hypothyroidism in patients with liver disease.

Variable	Univariate analysis OR (95% CI)	p- Value	Multivariate analysis OR (95% CI)	p- Value
Age <10 years	3.04 (0.88– 10.39)	0.024	3.94 (0.97– 15.70)	0.045
Female	2.65 (0.88– 7.98)	0.083		
Severity of NAFLD	0.66 (0.09– 4.88)	0.693		
Presence of NAFLD	1.09 (0.35– 3.37)	0.882		
Bilirubin >1 mg/dL	2.23 (0.21– 20.24)	0.048	2.96 (0.24– 15.66)	0.067

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; CI, confidence interval.

However, we evaluated the incidence of TSH level elevation in pediatric patients with liver disease and its risk factors. Owing to the extremely high incidence of subclinical hypothyroidism, it is important to check thyroid function.

Further research is warranted to explore the reasons for the increased risk of TSH elevation in pediatric patients with liver disease. In conclusion, clinicians may frequently consider thyroid function tests in patients with liver disease, especially younger patients and those with elevated total bilirubin levels.

Acknowledgments: There are no additional acknowledgments associated with this article.

Research funding: None declared.

Author contributions: H.J.K. contributed to the conception and design of the study; acquisition, analysis, and interpretation of data; drafting of the initial manuscript; and critical revision for important intellectual content.

Competing interests: The funding organizations played no role in the study design; collection, analysis, and interpretation of data; writing of the report; or decision to submit the report for publication.

Informed consent: Informed consent was obtained from all individuals included in this study.

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