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Thyroid-stimulating hormone is associated with nonalcoholic steatohepatitis in patients with chronic hepatitis B

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Abstract

The relationship of thyroid function parameters with nonalcoholic steatohepatitis (NASH) in patients with chronic hepatitis B (CHB) remains unknown. Hence, we assessed the impact of thyroid function parameters on NASH in patients with CHB.

Consecutive patients with CHB with concurrent nonalcoholic fatty liver disease (NAFLD) were recruited. Liver histology and baseline examinations were carried out in each patient. The associated risk factors for NASH were evaluated.

A total of 361 patients with CHB with biopsy-proven NAFLD were included. There was a significant difference in the serum thyroid-stimulating hormone (TSH) level between patients with NASH and non-NASH (3.24 ± 2.00 vs 2.05 ± 1.35 mIU/L, $P < .01$). Moreover, the NASH prevalence in patients with euthyroidism was significantly higher than in the subclinical hypothyroidism (SCH) patients ($P < .001$). In multivariate analyses, higher serum concentration of TSH was significantly correlated with NASH (odds ratio [OR]: 1.69, 95% confidence interval [CI]: 1.24–2.31; $P = .001$). In particular, patients suffering from SCH had a higher risk of having NASH (OR: 4.28, 95% CI: 1.18–15.53; $P = .027$).

Elevated serum TSH level was the independent predictive factor of incident NASH in patients with CHB. Whether the thyroid function parameters should be integrated into future diagnostic scores predicting advanced diseases requires further study.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CHB = chronic hepatitis B, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, SCH = subclinical hypothyroidism, TC = total cholesterol, TG = triglyceride, TSH = thyroid-stimulating hormone, WC = waist circumstance.

Keywords: chronic hepatitis B, liver biopsy, nonalcoholic steatohepatitis, thyroid-stimulating hormone

1. Introduction

Chronic hepatitis B (CHB) is associated with increased liver-related and all-cause mortality. The serum positive rate of hepatitis B surface antigen in the Asia-Pacific region is over 7%, especially in China.[1,2] In parallel with the recent rise in obesity, the incidence of nonalcoholic fatty liver disease (NAFLD) is increasing.[3,4] Extensive experimental and epidemiological evidence suggests that CHB and NAFLD are common chronic liver diseases with a high epidemic proportion worldwide.[5,6] It is estimated that 25% to 30% of patients with CHB have coexisting NAFLD.[7,8] Thus, CHB combined with NAFLD has become common form of chronic liver disease in China.

Nonalcoholic steatohepatitis (NASH) can develop into advanced fibrosis and cirrhosis.[5,9] Moreover, there was no approved therapy for NASH and it could only be diagnosed by liver biopsy. NASH could increase liver-related morbidity and mortality in patients with CHB, so it is urgent to develop new treatment strategies and find noninvasive assessment methods. However, the potential mechanisms of NASH are still relatively unclear. Hence, the studies to enhance our comprehension of NASH-related risk factors are needed.

In the general population, the variations of thyroid function parameters could be related to the incidence of atherosclerosis and cardiometabolic diseases.[10] Thyroid hormones act a critical role in the regulation of energy homeostasis and insulin resistance.[11] NAFLD and NASH are closely related to the dysregulation of energy homeostasis and insulin resistance.[12] Thus, thyroid hormones may be involved in the pathogenesis of NAFLD and NASH. However, the conclusions of the studies on the relationship of hypothyroidism with NASH are controversial.[13–15] Besides, the results of the recent meta-analyses regarding the association of subclinical/overt hypothyroidism with NAFLD were also inconsistent.[16,17] To date, the relationship of thyroid function parameters with biopsy-proven NASH in patients with CHB is not explored. Therefore, this study aimed to investigate the relationship of thyroid function parameters with biopsy-proven NASH in patients with CHB.

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2. Materials and methods

2.1. Participants and study design

We analyzed a cohort of patients with CHB with NAFLD confirmed by biopsy from the Tianjin Second People's Hospital between January 2013 and August 2018. The diagnostic criteria for CHB have been previously reported.[18] Patients who were <18 years old had an excessive alcohol consumption history (more than 30 g/d for men and 20 g/d for women), and were combined with other viral liver diseases, autoimmune liver disease, drug-induced liver disease, primary biliary cirrhosis, and Wilson disease were excluded. Patients who had a history of receiving antiviral therapy were excluded. Participants who were prescribed thyroid agents were excluded. None of the patients had clinical hypothyroidism or hyperthyroidism, and none of the patients had administered any agents that affected thyroid function. This study protocol was approved by the Ethics Committee of Tianjin Second People's Hospital and complied with the ethical guidelines of the 1975 Declaration of Helsinki. The written informed consent was obtained from all patients in our research.

2.2. Assessments and laboratory testing

A complete medical history and physical examination were undertaken. Current weight, height, and waist circumstance (WC) were all measured wearing minimal clothing and without socks. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured by a Hitachi 7600-110 automatic analyzers (Hitachi Co, Tokyo, Japan). Serum hepatitis B virus-DNA (HBV-DNA) was measured by quantitative polymerase chain reaction (light Cycler480 II/96; Roche, Rotkreuz, Switzerland). Serum HBV-DNA level $>10^5$ copies/mL was defined as positive serum HBV-DNA. Thyroid function was detected by immunoassay system (UniCel DxI 800; Beckman Coulter, Brea, CA). The diagnosis of subclinical hypothyroidism (SCH) was established based on the serum thyroid-stimulating hormone (TSH) level over 4.2 mIU/L and normal free thyroxine (FT4) level. Euthyroidism was established based on the normal TSH, FT4, and free triiodothyronine (FT3) level (0.27–4.2 mIU/L for TSH, 12–22 pmol/L for FT4, 3.1–6.8 pmol/L for FT3).

2.3. Liver histology

Each liver specimen was fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin, Masson trichrome, and collagen. Two experienced liver pathologists evaluated the histologic specimen. The diagnosis of NAFLD was established based on the finding of ≥5% macrovesicular steatosis. The diagnosis of NASH was established based on the NAFLD activity score system.[19]

2.4. Statistical analysis

Results are expressed by using mean ± standard deviation for continuous variables and frequencies (percentage) for categorical variables. The differences were evaluated using the *t* test for continuous variables and the Chi-squared test for categorical variables. Binary logistic regression was applied to assess the independent risk factors relating to NASH. $P < .05$ means statistically significant. Statistical analyses were performed using SPSS software (version 22.0; SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics

The demographics of the participants and the results of the laboratory test are shown in Table 1. A total of 361 patients who met the inclusion criteria participated in the study. The age was 37.5 ± 10.98 years and the body mass index (BMI) was 26.55 kg/m^2. The mean serum FT4 level was 15.93 pmol/L and the mean serum TSH level was 2.28 mIU/L. Seventy-one percent of patients were men. The incidence of events in patients with diabetes and hypertension was 13.9% and 19.4%, respectively.

3.2. Comparison of clinical and laboratory features in patients with CHB

The comparison is shown in Table 2. Liver biopsy histology showed that NASH was found in 72 patients among 361 patients with CHB with NAFLD. Patients with NASH had greater BMI, WC, TC, TG, ALT, AST, TSH, lower HDL, FT3, and FT4 as compared to patients without NASH. The prevalence of diabetes was significantly higher in the NASH group compared with the non-NASH group. Furthermore, the results, as shown in Figure 1A, indicate that the prevalence of SCH was significantly higher in the NASH group compared with the non-NASH group ($P < .001$). However, no obvious discrepancies in age, gender, hypertension, and virologic indicators were found between the 2 groups. In addition, as shown in Figure 1B, the incidence of NASH showed a significant difference between the euthyroidism and the SCH group ($P < .001$). When patients were classified by serum TSH levels, we observed that the prevalence of NASH was significantly associated with serum TSH levels in a dose-dependent manner (Fig. 1C).

3.3. Factors independently associated with NASH in patients with CHB

After adjusting for various confounders, the relationship between serum TSH levels and the incidence of NASH events was still

Table 1

General characteristics of patients.

Characteristics	Standard value (range)	All (n = 361)
Age, yr	NA	37.5 ± 10.98
Male gender, n (%)	NA	256 (71)
Body mass index, kg/m^2	NA	26.55 ± 3.97
Waist circumference, cm	NA	92 ± 8.85
Diabetes, n (%)	NA	50 (13.9)
Hypertension, n (%)	NA	70 (19.4)
Serum hepatitis B e antigen hepatitis B e antigen (HBeAg)' positive, n (%)	NA	240 (66.5)
Serum HBV-DNA positive, n (%)	NA	239 (66.2)
Total cholesterol, mmol/L	2.4–5.2	4.53 ± 0.98
Triglyceride, mmol/L	0.38–2.3	1.35 ± 0.69
High-density lipoprotein, mmol/L	1.16–1.6	1.11 ± 0.27
Low-density lipoprotein, mmol/L	2.07–3.37	2.67 ± 0.69
ALT, IU/L	9–50	77.75 ± 64.40
AST, IU/L	15–40	49.47 ± 47.30
FT3, pmol/L	3.1–6.8	4.88 ± 0.78
FT4, pmol/L	12–22	15.93 ± 2.18
TSH, mIU/L	0.27–4.2	2.28 ± 1.57

ALT = alanine aminotransferase, AST = aspartate aminotransferase, FT3 = free triiodothyronine, FT4 = free thyroxine, NA = not applicable, TSH = thyroid-stimulating hormone.

Table 2

Comparison of anthropometric and laboratory features of patients with CHB with NASH and without NASH.

Factors	With NASH (n = 72)	Without NASH (n = 289)	*P*-value
Age, yr	37.97 ± 11.97	37.38 ± 10.74	.685
Male gender, n (%)	52 (72.2)	195 (67.5)	.438
Body mass index, kg/m^2	29.36 ± 3.98	25.85 ± 3.65	<.001
Waist circumference, cm	103.2 ± 8.55	89.21 ± 6.38	< .001
Diabetes, n (%)	19 (26.4)	34 (11.8)	.002
Hypertension, n (%)	17 (23.6)	53 (18.3)	.311
Serum HBeAg positive, n (%)	46 (63.9)	194 (67.1)	.602
Serum HBV-DNA positive, n (%)	41 (56.9)	198 (68.5)	.063
Total cholesterol, mmol/L	4.86 ± 0.86	4.44 ± 0.99	.001
Triglyceride, mmol/L	1.77 ± 0.82	1.25 ± 0.61	<.001
High-density lipoprotein, mmol/L	1.01 ± 0.23	1.13 ± 0.27	<.001
Low-density lipoprotein, mmol/L	2.78 ± 0.68	2.64 ± 0.7	.111
ALT, IU/L	100.95 ± 72.56	71.97 ± 60.98	.001
AST, IU/L	62.06 ± 44.83	46.33 ± 47.45	.011
FT3, pmol/L	4.66 ± 0.82	4.94 ± 0.76	.007
FT4, pmol/L	15.23 ± 1.91	16.11 ± 2.21	.002
TSH, mIU/L	3.24 ± 2.00	2.05 ± 1.35	<.001

ALT = alanine aminotransferase, AST = aspartate aminotransferase, FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid-stimulating hormone.

robust in our study (Table 3). According to the logistic regression analysis, serum TSH level was related to a 69% increment in the hazard for NASH (odds ratio [OR]: 1.69, 95% confidence interval [CI]: 1.24–2.31; $P = .001$). In addition, we also evaluated the link between the status of thyroid function and the incidence of NASH events (Table 4). Logistic regression model adjusted for BMI, WC, diabetes, TC, TG, HDL, LDL, ALT, AST, FT3, and FT4 showed an independent association between SCH and NASH (OR: 4.28, 95% CI: 1.18–15.53; $P = .027$). It means that the risk of NASH events in SCH was 4.28 times that of euthyroid patients.

4. Discussion

We observed the strong correlation of serum TSH levels with NASH confirmed by biopsy in patients with CHB. The mean concentration of serum TSH in patients with NASH was markedly higher than in patients with non-NASH. Interestingly, the NASH prevalence in the patients with SCH was significantly higher than in the euthyroid patients. Besides, our findings also indicate that SCH is more closely associated with the presence of NASH, regardless of BMI and metabolic syndrome components.

There is still little consensus on the relationship between NAFLD/NASH and hypothyroidism. A study revealed a relationship between hypothyroidism and NASH.[15] However, the limitation of this study was that the diagnosis of hypothyroidism was established based on receiving thyroid hormone replacement. Therefore, the specific laboratory results on thyroid function were lacking. Similarly, another study revealed that there was a higher prevalence of hypothyroidism in patients with NAFLD.[13] However, they use thyroid replacement therapy as a surrogate for diagnosis. In contrast, in a retrospective study which included 103 patients with NAFLD conformed by biopsy, investigators revealed no direct connection between hypothyroidism, and the severity of NAFLD. However, the sample size of the study was small and it did not detect the levels of FT3, FT4, and TSH.[14]

Compared to the patients without NASH, patients with NASH had higher serum TSH levels and lower thyroid hormone levels. Besides, we further divided patients into 3 groups based on serum TSH tertiles. As the elevated level of TSH, we found that the prevalence of NASH also increased gradually. Interestingly, we observed that the association of the serum TSH levels with NASH was still pronounced after adjusting for the confounding factors, such as obesity and metabolic abnormalities. It means that our multivariate analysis showed an independent association between the serum TSH levels and NASH. Importantly, our study did not observe the association between virologic indicators of hepatitis B and NASH. This might be mainly attributed to sample size and the inherent flaw of observational design. Yan et al reported that increased serum TSH levels could accelerate the development and progression of NASH.[20] Several studies demonstrated that increased serum TSH levels were significantly related to the presence of NASH.[21,22] A possible account for the relationship is that increased TSH levels are related to metabolic disorders.[10,23] Metabolic syndrome plays an important role in modulating the correlation of thyroid dysfunction with NAFLD by decreasing serum thyroid hormone levels.[24] Recently, several studies have investigated the latent efficacy of thyroid hormones or thyroid hormone analogs on NASH. For instance, MGL-3196, a selective thyroid hormones receptor β agonist, has been developed for the therapy of biopsy-proven NASH in a multicenter clinical trial.[25] On the contrary, a multicenter study from Singapore observed that levothyroxine could decrease intrahepatic lipid content in euthyroid patients with NASH.[26] In our study, the elevated serum TSH levels are associated with NASH, independent of the thyroid hormones. A cross-sectional study showed that serum TSH affected lipid components by acting directly on the hepatocyte cell membranes.[27] In terms of

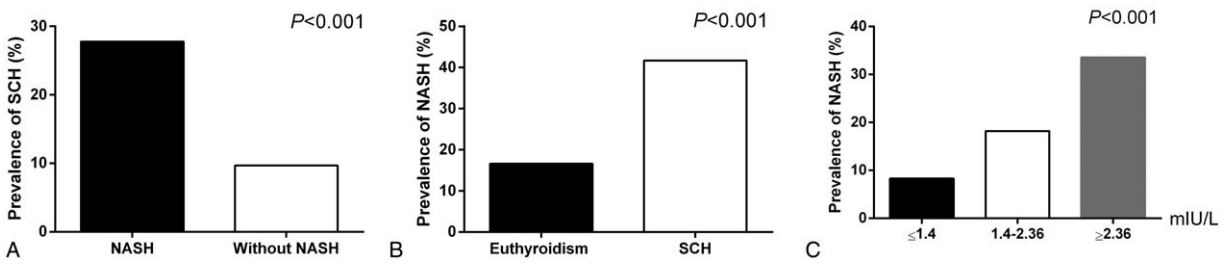

Figure 1. Prevalence of subclinical hypothyroidism (SCH) based on the presence of nonalcoholic steatohepatitis (NASH) (A) and prevalence of NASH based on the status of thyroid function (B) and thyroid-stimulating hormone levels (C).

Table 3

Factors independently associated with NASH based on TSH level.

Factors	*P*-value	OR	95% CI
Body mass index, kg/m^2	<.001	1.25	1.15–1.37
Waist circumference, cm	<.001	1.37	1.26–1.48
Diabetes (%)	.118	2.21	0.82–5.96
Total cholesterol, mmol/L	.291	1.40	0.75–2.60
Triglyceride, mmol/L	.273	1.39	0.77–2.51
High-density lipoprotein, mmol/L	.567	0.57	0.08–3.95
Low-density lipoprotein, mmol/L	.468	0.74	0.33–1.67
ALT, IU/L	.066	1.69	0.97–2.96
AST, IU/L	.108	1.02	0.95–1.08
FT3, pmol/L	.692	1.13	0.61–2.09
FT4, pmol/L	.252	0.88	0.71–1.10
TSH, mIU/L	.001	1.69	1.24–2.31

ALT = alanine aminotransferase, AST = aspartate aminotransferase, FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid-stimulating hormone.

mechanism, elevated serum TSH levels may lead to the upregulation of sterol regulatory element binding protein-1c sterol regulatory element binding protein-1c(SREBP-1c) activity by directly stimulating the TSH receptors of hepatocyte cell membranes, subsequently causing the development and progression of NAFLD.[20] Hence, our study further indicated that various putative pathways are probably involved in the development and progression of NASH.

Our findings indicated that the prevalence of SCH was significantly higher in patients with NASH than in patients without NASH. Besides, we further divided into the euthyroidism and the SCH group according to the status of thyroid function. The NASH prevalence in patients with SCH was higher than in those euthyroid patients. After adjusting for the confounding factors, the association between the SCH and NASH was still strong. An observational study from the Netherlands showed that patients with SCH are at increased risk of NASH compared to euthyroid patients.[28] Furthermore, a recent study also showed that hypothyroidism could induce moderate NASH.[29] These findings were similar to our research. Mechanistically, markers of oxidative stress and lipid peroxidation have been revealed in patients with subclinical/overt hypothyroidism.[30] Besides, SCH has an impact on mitochondrial function.[31] Interestingly, a recent study showed that oxidant stress and mitochondrial dysfunction have been involved in the pathogenesis of NASH.[32] Thus, we speculate that thyroid dysfunction may be involved in the pathogenesis of NASH by oxidative stress and mitochondrial dysfunction.

Table 4

Factors independently associated with NASH according to the status of thyroid function.

Factors	*P*-value	OR	95% CI
Body mass index, kg/m^2	<.001	1.28	1.17–1.38
Waist circumference, cm	<.001	1.36	1.26–1.46
Diabetes (%)	.077	2.44	0.91–6.56
Total cholesterol, mmol/L	.336	1.35	0.74–2.46
Triglyceride, mmol/L	.205	1.46	0.81–2.61
High-density lipoprotein, mmol/L	.726	0.72	0.11–4.57
Low-density lipoprotein, mmol/L	.494	0.76	0.34–1.68
ALT, IU/L	.056	1.56	0.99–2.46
AST, IU/L	.104	1.06	0.99–1.13
FT3, pmol/L	.911	0.97	0.51–1.81
FT4, pmol/L	.37	0.91	0.74–1.12
Status of thyroid function			
Euthyroidism	–	1	–
Subclinical hypothyroidism	.027	4.28	1.18–15.53

ALT = alanine aminotransferase, AST = aspartate aminotransferase, FT3 = free triiodothyronine, FT4 = free thyroxine.

The main strength of this study is the inclusion of consecutive patients with biopsy-proven NAFLD, with the assessments of thyroid function markers (e.g., FT3, FT4, and TSH), which allowed us to illustrate the relationship between the serum TSH level and NASH. Besides, our study for the 1st time to our knowledge explored the association of thyroid function parameters with biopsy-proven NASH in patients with CHB. However, our study has several limitations. First, the determination of thyroid autoantibody was absent in our patients due to our study design. But Eshraghian and Hamidian Jahromi have reported no association between thyroid autoantibodies and NAFLD.[33] Second, we could not prove the causality of thyroid function parameters with NASH due to the observational design. Third, we did not explore the association of serum TSH levels with advanced fibrosis or cirrhosis due to the limitation of the disease spectrum. Finally, the participants were all Chinese and our conclusions may not be generalizable to other populations.

In summary, our results indicate the independent role of the serum TSH level for NASH in patients with CHB. The early diagnosis of NASH contributed to the rational selection of antiviral treatment strategies and reduced cancer risk in patients with CHB combined with NAFLD. Further studies are required to develop a new diagnostic score containing TSH levels, which may help to screen patients at high risk of having NASH. In the future, definite conclusions regarding the strong correlation between TSH levels and NASH in patients with CHB deserve further investigation in larger follow-up studies with biopsy-proven NASH.

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