Association between Thyroid Hormones and Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis in Obese Individuals Undergoing Bariatric Surgery

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Abstract

Background:
Non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and hepatic fibrosis have emerged as one of the leading causes of chronic liver disease. The prevalence of the NAFLD spectrum has increased, which can be attributed to the rise in obesity. As NAFLD can ultimately lead to liver cirrhosis, it is imperative to identify modifiable risk factors associated with its onset and progression to provide timely intervention to prevent potentially disastrous consequences. Considering the pivotal role of the endocrine axis in several metabolic pathways such as obesity and insulin resistance, thyroid hormones are crucial in the pathophysiology of NAFLD. The study is focused on the identification of an association between thyroid function and radiographic and histological parameters of NAFLD in patients with severe obesity.

Methods:
Ninety patients were recruited for this study and underwent initial assessments, including demographic profiles, anthropometric measurements, hepatic biopsy, and basic laboratory tests. Liver stiffness was evaluated using two-dimensional shear wave elastography (2D-SWE) at least 2 weeks before liver biopsy.

Results:
Among the 90 participants, 80% were women. The mean age was 38.5±11.1 years, and the mean body mass index (BMI) was 45.46±6.26 kg/m^2. The mean levels of serum T3 and free T4 in patients with positive histology were not statistically significant compared with patients with negative histology. Furthermore, there was no statistical significance in the mean T3 and free T4 levels between patients diagnosed with hepatic steatosis or fibrosis (on ultrasonography and elastography) and those with negative hepatic imaging. Serum levels of thyroid-stimulating hormone (TSH) were negatively correlated with ultrasonography (P=0.007). Binary logistic regression analysis revealed that none of the thyroid hormones was a predictive factor for liver histology in both adjusted and crude models.

Conclusion:
The results from our analysis did not suggest an association between thyroid hormones and NAFLD, which is in line with several previously published studies. However, the authors note that there are published data that do propose a link between the two entities. Therefore, well-designed large-scale clinical studies are required to clarify this discrepancy.

Keywords:
Obesity, Bariatric surgery, Fatty liver, Thyroid

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the main causes of chronic liver disease around the world, and although viral hepatitis remains the most common cause of death from liver disease, NAFLD is the most rapidly growing cause of mortality from liver disease.[1] The term NAFLD encompasses a range of chronic liver conditions from non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), which can progress to hepatic fibrosis and, ultimately, cirrhosis. In clinical practice, NAFLD and NASH are often diagnosed incidentally or in advanced stages as they tend to be asymptomatic.[2-6] NAFLD is the hepatic manifestation of metabolic syndrome, while its risk factors include obesity and type 2 diabetes mellitus (T2DM), with insulin resistance almost always present.[7-9] Obesity renders patients at an increased risk of a multitude of significant comorbidities, including cardiovascular disease, T2DM, osteoarthritis, and dyslipidemia, to mention a few.[10] Particularly, severe obesity is believed to carry a higher risk of comorbidities.

As we know, the endocrine axis plays an important role in the pathophysiology of NAFLD. Indeed, thyroid hormones are important regulators of several metabolic pathways, such as lipid status, adipogenesis, and insulin resistance.[11]

We have previously demonstrated that high levels of parathyroid hormone (PTH) were strongly associated with the NAFLD spectrum in patients with severe obesity undergoing bariatric surgery.[12,13] As thyroid hormones are involved in lipid metabolism and regulation of body weight,[14] it is possible that disturbances in thyroid hormone levels may contribute to the pathogenesis of NAFLD. Despite the fact that the pathophysiology of NAFLD has been thoroughly researched, there is still more to learn. The role of metabolic pathways and endogenous chemicals in obesity and NAFLD should be investigated, as this will help us better understand the disease mechanism. In this study, we explore the association between thyroid hormones and NAFLD in obese individuals undergoing bariatric surgery.

Materials and Methods

The study participants were patients with severe obesity who were referred to our outpatient clinic between December 2016 and September 2017. Finally, among the volunteers, 90 patients with severe obesity were enrolled based on the following inclusion criteria: males and females with alcohol consumption of less than 30 g/d and 20 g/d, respectively, no chronic use of hepatotoxic drugs, no hepatitis B (HBV) or C virus (HCV) proved by specific antibodies. Moreover, as in our previous studies, a comprehensive medical and preoperative psychological assessment was performed to exclude patients with any contraindication, and written informed consent was obtained from all subjects.

Two-dimensional shear wave elastography

To detect liver stiffness, two-dimensional shear wave elastography (2D-SWE) technology, a novel imaging technique, was used 14 days prior to liver biopsy. Elastographic measurements were performed on an Aixplorer ultrasound-based system (Supersonic Imagine, France) with a convex broadband probe (SC6-1, 1–6 MHz) according to the manufacturer's instructions. After 6-hour fasting, measurements were obtained via the intercostal spaces while patients were placed in a supine position with the right arm in maximum abduction. For each patient, 10 valid measurements were acquired, and the result of liver stiffness evaluation was stated as the mean (M) of valid measurements in kilopascals (kPa). Liver stiffness measurement was performed by experienced operators who were blinded to all data and patient diagnoses.

Histologic analysis of the liver

During bariatric surgery, biopsy samples were collected from the left hepatic lobe under direct surgeon visualization using a 16-gauge Tru-Cut needle. Biopsy indications were abnormal liver function tests, hepatic steatosis/dysmorphism approved through ultrasound, or macroscopically abnormal liver tissue recognized by the surgeon, who was blinded to the 2D-SWE results. Specimens were fixed in paraffin wax and stained with hematoxylin-eosin-saffron, Masson's trichrome, and picrosirius red for histological assessment.[15,16] The expert pathologist who studied the biopsy samples was also blinded to all data. For staging and grading of NASH, NASH Clinical Research Network Modified

Brunt methodology and NASH Activity Score (NAS) were applied, respectively.[17]

According to 2D-SWE results, a scoring system was used for each hepatic disorder: five stages from 0 to 4 for hepatic fibrosis, four stages from 0 to 3 for steatosis-based on the percentage of steatosis (0, < 5%; 1, 5–33%; 2, 34–66%; 3, > 66%), four stages from 0 to 3 for lobular inflammation-based on the number of inflammatory foci per field of view at a magnification of × 20, and three stages from 0 to 2 for hepatocellular ballooning-according to the number of ballooned hepatocytes. Moreover, based on the total score, patients were divided into two groups: no NASH (score 1 or 2) and definite NASH (score 3 or more).[17,18]

Statistical analysis

Statistical analysis was performed using SPSS software (version 25). The normality of the data was checked using the one-sample Kolmogorov-Smirnov test. To present the results of parametric and non-parametric variables, mean (standard deviation [SD]) and median (interquartile range [IQR]) were calculated, respectively. Spearman's rank correlation coefficient was applied to indicate the association between ordinal variables. Receiver operating characteristic (ROC) curves were drawn to discover the optimal thyroid markers cut-off point and its sensitivity and specificity. Finally, binary logistic regression was utilized to control for confounding factors and to determine the predictive variables.

Results

Patient characteristics

Among the 90 participants, 80% were women. The mean age was 38.5 ± 11.1 years, and the mean body mass index (BMI) was 45.46 ± 6.26 kg/m^2. Approximately a quarter of patients had type 2 diabetes and/or hypertension, and more than half (51.9%) had metabolic syndrome. Severe steatosis (> 66%) was observed in 8.9% of patients, while fibrosis (F ≥ 1) and NASH were detected in more than half (Table 1).

Table 1. Patient characteristics

Variable	Total
Male, No. (%)	18 (20)
Age (y)	38.5 ± 11.1
BMI (kg/m^2)	45.46 ± 6.26
Weight (kg)	121.34 ± 20.32
Waist circumference (cm)	133.04 ± 13.6
Height (cm)	1.62 ± 8.87
Diabetes type 2	25 (27.8)
Hypertension	23 (25.6)
Metabolic syndrome	46 (51.1)
Liver stiffness measurement (kPa)	6.1 ± 1.25
Fibrosis stage	
0 = No fibrosis	38 (42.2)
1 = Zone 3 perivenular or pericellular fibrosis	40 (44.4)
2 = Stage 1 plus portal fibrosis	8 (8.8)
3 = Bridging fibrosis, focal or extensive	4 (4.4)
4 = Residual pericellular fibrosis	-
Steatosis status	
S0 = < 5%	39 (43.3)
S1 = 5–33%	31 (34.4)
S2 = 34–66%	12 (13.3)
S3 = > 66%	8 (8.9)
NASH status	
No NASH (0–2)	39 (43.3)
NASH (3–8)	51 (56.7)

BMI, body mass index; NASH, Non-alcoholic steatohepatitis. Data presented as mean ± standard deviation and No. (%).

Thyroid hormone concentration based on fatty liver disease

The comparison of thyroid parameters between study groups is presented in Table 2. The mean levels of serum T3 and free T4 in patients with positive histology for liver fibrosis, steatosis, and NASH were not statistically significant compared with patients with negative histology. In addition, no significant differences were detected in the mean levels of T3 and free T4 between patients who had been diagnosed with fibrosis or steatosis by elastography and ultrasonography, respectively, with patients who had not been diagnosed.

For parameters with non-normal distribution, the results were the same except for TSH, which showed a significant difference between patients with and without steatosis based on ultrasonography.

The relationship between thyroid hormones and liver status

The relationship between thyroid hormones and liver

Table 2. The comparison of serum parameters concentration between study groups

	T3	Free T4	T4[a]	TSH[a]
Fibrosis status (biopsy)				
No fibrosis	124.8±23	1.18±0.2	8.7(7-9)	2.1(1-3)
Fibrosis	126.8±22	1.17±0.2	8.8(7-9)	2.3(1-3)
Steatosis status (biopsy)				
No steatosis (<5%)	124.9±22	1.18±0.2	8.7(7-10)	2.2(1-3)
Steatosis (≥5%)	126.7±22	1.17±0.2	8.7(7-9)	2.2(1-3)
NASH status				
No NASH (0–2)	124.9±22	1.18±0.2	8.7(7-10)	2.2(1-3)
NASH (3–8)	126.1±22	1.17±0.2	8.7(7-9)	2.2(1-3)
Fibrosis status (Elasto)				
No fibrosis	126.4±18	1.17±0.2	8.7(7-9)	2.3(1-3)
Fibrosis (Fibrosis cutoff=5.85 kPa)	125.7±25	1.17±0.2	8.7(7-9)	1.9(1-3)
Steatosis status (Sono)				
No steatosis (0-1)	121.4±21	1.17±0.2	8.6(7-9)	2.8(1-4)*
Steatosis (>1)	127.7±22	1.17±0.2	8.7(7-9)	1.9(1-3)

Values are means±SD.
[a] Mann-Whitney test, values are medians±interquartile range.
* $P<0.05$, between two groups.

fibrosis, NASH, liver steatosis, liver elastography, and ultrasonography are presented in Table 3.

As shown in Table 3, serum levels of TSH were negatively correlated with ultrasonography ($P=0.007$). The other parameters did not show any substantial correlation.

Table 3. Correlation coefficient between parameters

CC	r	*P* value
T3		
Fibrosis (biopsy)	0.072	0.512
Steatosis (biopsy)	-0.020	0.855
NASH	-0.018	0.871
Elastography	0.113	0.306
Ultrasonography	0.068	0.537
Free T4		
Fibrosis (biopsy)	-0.043	0.714
Steatosis (biopsy)	-0.118	0.315
NASH	-0.140	0.233
Elastography	0.020	0.866
Ultrasonography	0.161	0.176
T4		
Fibrosis (biopsy)	0.081	0.452
Steatosis (biopsy)	-0.049	0.647
NASH	-0.057	0.600
Elastography	-0.038	0.730
Ultrasonography	0.172	0.112
TSH		
Fibrosis (biopsy)	-0.010	0.928
Steatosis (biopsy)	-0.037	0.734
NASH	-0.015	0.887
Elastography	-0.110	0.315
Ultrasonography	-0.291	0.007

CC, correlation coefficient; NASH, Non-alcoholic steatohepatitis.
Spearman's rank correlation coefficient was used.

Diagnostic yield of thyroid parameters in assessing the liver disease

In the present study, ROC curves were used to evaluate the sensitivity and specificity of thyroid hormones in predicting liver outcomes and optimal cut-off points. The sensitivity and specificity for each NASH CRN-modified BRUNT methodology stage are summed in Tables 4-9.

According to the results of ROC curve analysis, the optimal cut-off value for T3 to identify fibrosis (biopsy), steatosis (biopsy), and NASH (biopsy) was 105 mg/dL, while the optimal cut-off values for identifying fibrosis (elastography) and steatosis (ultrasonography) were 120 and 104 mg/dL, respectively (Table 4 and Figure 1).

As displayed in Table 5 and Figure 2, the optimal cut-off for free T4 level to detect fibrosis (biopsy), steatosis (biopsy), NASH, and fibrosis (elastography) was 1.4 mg/dL, but it was 0.8 mg/dL for detecting steatosis (ultrasonography). Furthermore, based on

Table 4. Diagnostic performance of T3 vs Liver disease

Diagnostic performance		AUC	Cut-off	Sensitivity	Specificity
T3	Fibrosis (biopsy)	0.527	105	83%	27%
	Steatosis (biopsy)	0.523	105	83%	26%
	NASH (biopsy)	0.515	105	83%	26%
	Fibrosis (elastography)	0.525	120	42%	71%
	Steatosis (ultrasonography)	0.558	104	85%	31%

AUC, area under the curve; NASH, Non-alcoholic steatohepatitis.

Table 5. Diagnostic performance of Free T4 vs. Liver disease

Diagnostic performance		AUC	Cut-off	Sensitivity	Specificity
Free T4	Fibrosis (biopsy)	0.519	1.4	88%	16%
	Steatosis (biopsy)	0.519	1.4	88%	16%
	NASH (biopsy)	0.519	1.4	88%	16%
	Fibrosis (elastography)	0.506	1.4	92%	20%
	Steatosis (ultrasonography)	0.507	0.8	3.8%	85%

AUC, area under the curve; NASH, Non-alcoholic steatohepatitis.

Table 6. Diagnostic performance of T4 vs. liver disease

Diagnostic performance		AUC	Cut-off	Sensitivity	Specificity
T4	Fibrosis (biopsy)	0.520	11.2	11%	97%
	Steatosis (biopsy)	0.500	12.4	8%	100%
	NASH (biopsy)	0.508	12.4	91%	0%
	Fibrosis (elastography)	0.511	7.8	36%	74%
	Steatosis (ultrasonography)	0.548	10.6	17%	100%

AUC, area under the curve; NASH, Non-alcoholic steatohepatitis.

Table 7. Diagnostic performance of TSH vs. liver disease

Diagnostic performance		AUC	Cut-off	Sensitivity	Specificity
TSH	Fibrosis (biopsy)	0.517	3.5	82%	31%
	Steatosis (biopsy)	0.527	3.1	76%	35%
	NASH (biopsy)	0.529	3.2	77%	35%
	Fibrosis (elastography)	0.533	3.6	85%	28%
	Steatosis (ultrasonography)	0.678	3.4	82%	45%

AUC, area under the curve; NASH, Non-alcoholic steatohepatitis.

the ROC curve results, the optimal cut-off for T4 in liver fibrosis (biopsy), liver steatosis (biopsy), NASH score, liver fibrosis (elastography), and liver steatosis (ultrasonography) were 11.2 ($P=0.752$), 12.4 ($P=0.997$), 12.4 ($P=0.901$), 7.8 ($P=0.861$), and 10.6 ($P=0.505$) mg/dL, respectively (Table 6 and Figure 3).

As presented in Table 7 and Figure 4, the optimal cut-off values for LDL to detect fibrosis (biopsy), steatosis (biopsy), NASH, fibrosis (elastography), and steatosis (ultrasonography) were 3.5, 3.1, 3.2, 3.6 and 3.4 mg/dL, and P values were 0.796, 0.673, 0.646, 0.607, and 0.007, respectively.

The binary logistic regression analysis between thyroid parameters and study parameters

Binary logistic regression analysis for thyroid

Table 8. The binary logistic regression analysis between T3 and study parameters

Parameters		*P*	OR	95% CI for OR	
				Lower	Upper
Crude model	Fibrosis (biopsy)	0.678	1.004	0.985	1.024
	Steatosis (biopsy)	0.708	1.004	0.985	1.023
	NASH	0.812	1.002	0.983	1.002
	Fibrosis (elastography)	0.879	0.998	0.979	1.018
	Steatosis (sono)	0.247	1.014	0.991	1.037
Adjusted model	Fibrosis (biopsy)	0.152	1.023	0.992	1.056
	Steatosis (biopsy)	0.223	1.019	0.988	1.052
	NASH	0.223	1.019	0.988	1.052
	Fibrosis (elastography)	0.937	1.001	0.975	1.028
	Steatosis (sono)	0.168	1.023	0.990	1.056

OR, odds ratio; NASH, Non-alcoholic steatohepatitis.

Table 9. The binary logistic regression analysis between FT4 and study parameters

Parameters		*P*	OR	95% CI for OR	
				Lower	Upper
Crude model	Fibrosis (biopsy)	0.847	0.816	0.104	6.421
	Steatosis (biopsy)	0.847	0.816	0.104	6.421
	NASH	0.847	0.816	0.104	6.421
	Fibrosis (elastography)	0.970	0.962	0.125	7.406
	Steatosis (sono)	0.900	1.158	0.118	11.325
Adjusted model	Fibrosis (biopsy)	0.768	1.541	0.088	27.054
	Steatosis (biopsy)	0.768	1.541	0.088	27.054
	NASH	0.768	1.541	0.088	27.054
	Fibrosis (elastography)	0.791	0.686	0.042	11.113
	Steatosis (sono)	0.686	1.803	0.104	31.358

OR, odds ratio; NASH, Non-alcoholic steatohepatitis.

hormones was done after adjustment for age, sex, waist circumferences, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and homeostatic model assessment for insulin resistance (HOMA-IR) on subject groups (Tables 8-11). Binary logistic regression analysis revealed that none of the thyroid hormones was a predictive factor for liver histology in both adjusted and crude models.

Discussion

In this study, from our analysis of 90 participants with severe obesity undergoing bariatric surgery, we found no association between thyroid hormone levels and the presence or absence of NAFLD on radiographic and histological parameters. Similar results were obtained for parameters with non-normal distribution except for thyroid-stimulating hormone (TSH), which was significantly different between patients with and without steatosis based on ultrasonography. Binary logistic regression analysis revealed that none of the thyroid hormones was a predictive factor for liver histology in both adjusted and crude models.

Thyroid hormones regulate metabolic processes in the human body, and their levels correspond to weight and energy expenditure.[19-21] The role of thyroid hormones in accelerating basal energy expenditure by their action on carbohydrates, proteins, and lipids is well established.[22] Evidence suggests that in addition to the induction of hepatic lipogenesis, thyroid hormones increase the availability of non-esterified fatty acids , which promotes fatty acid oxidation.[18]

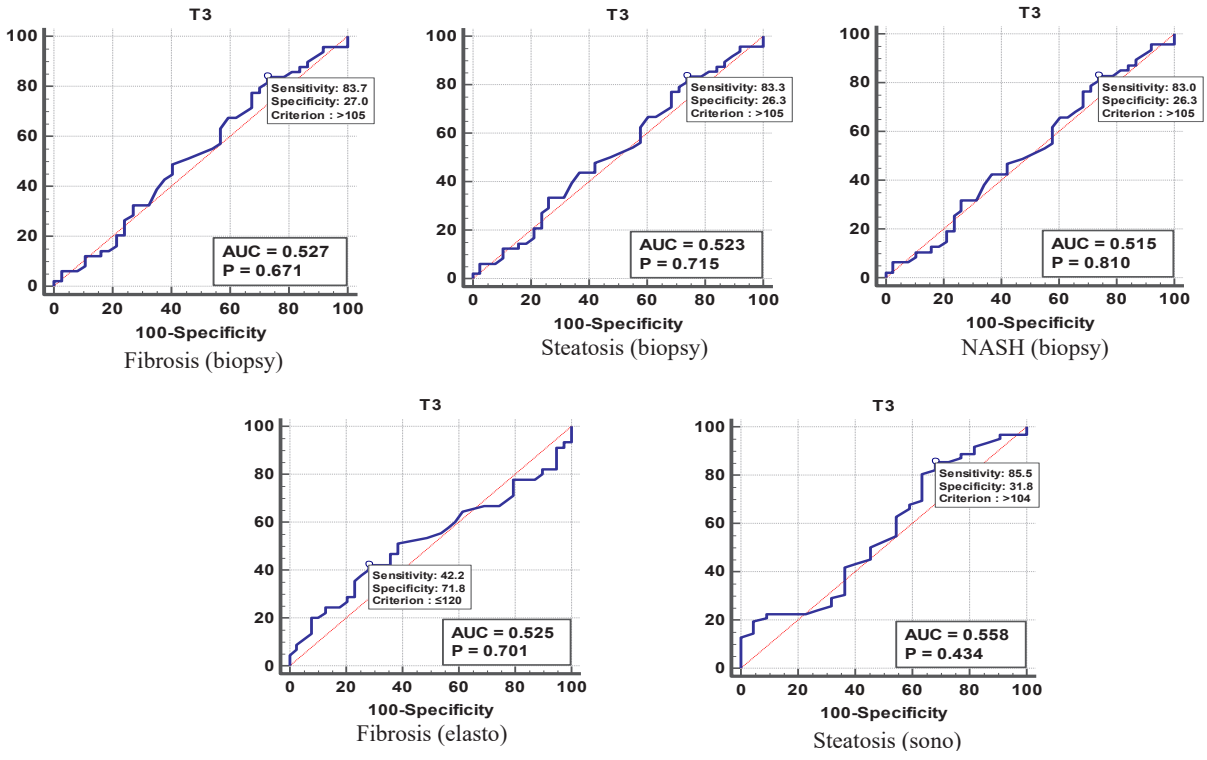

Figure 1. The ROC curve for T3 in the detection of liver disease

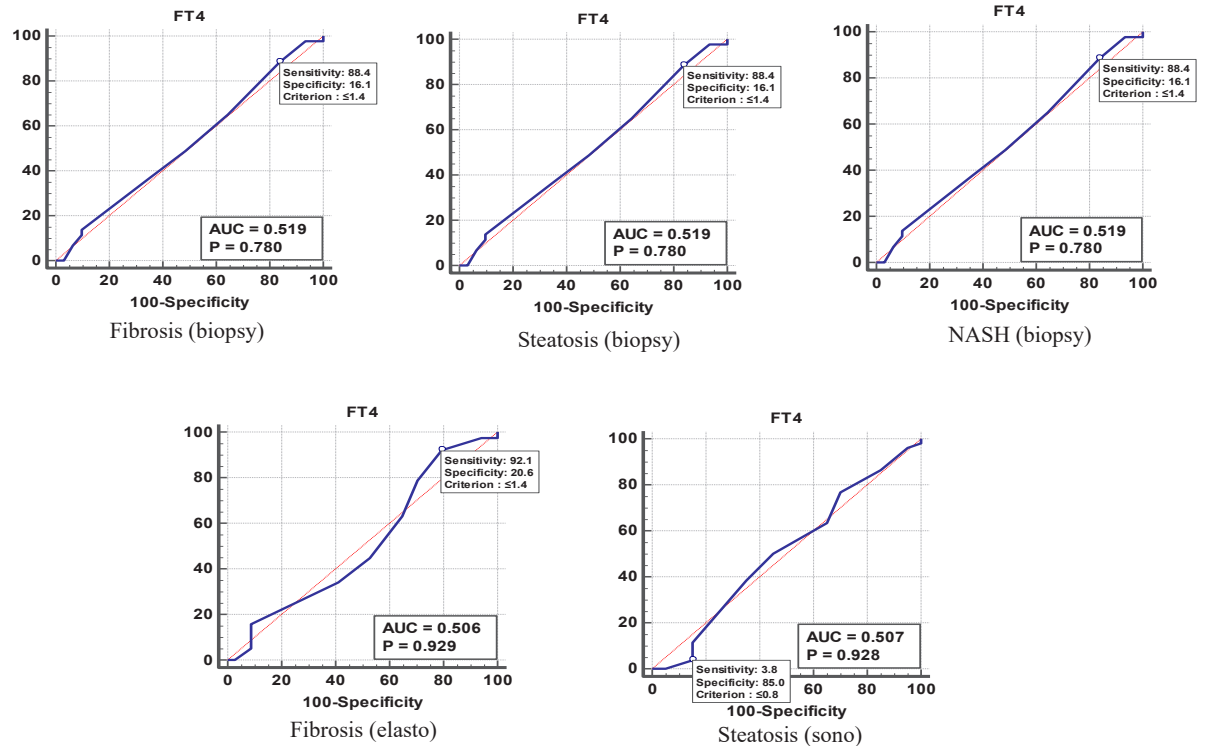

Figure 2. The ROC curve for free T4 in the detection of liver disease

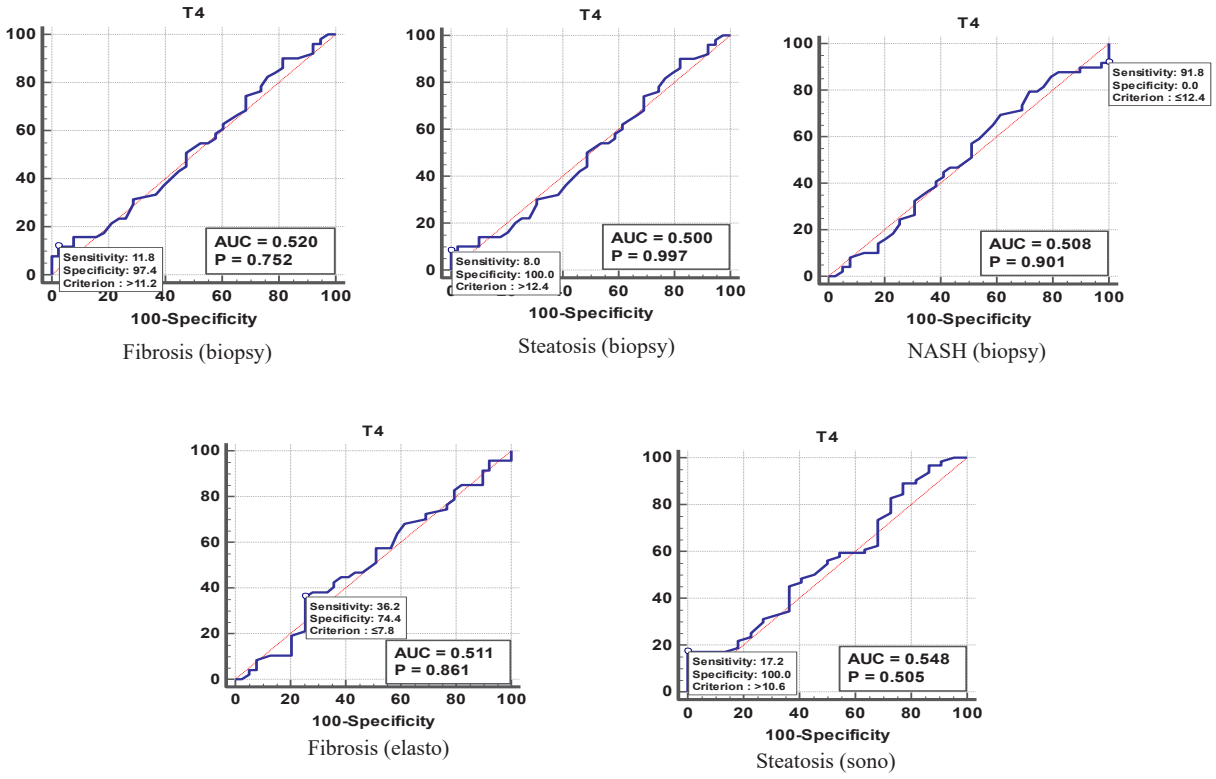

Figure 3. The ROC curve for T4 in the detection of liver disease

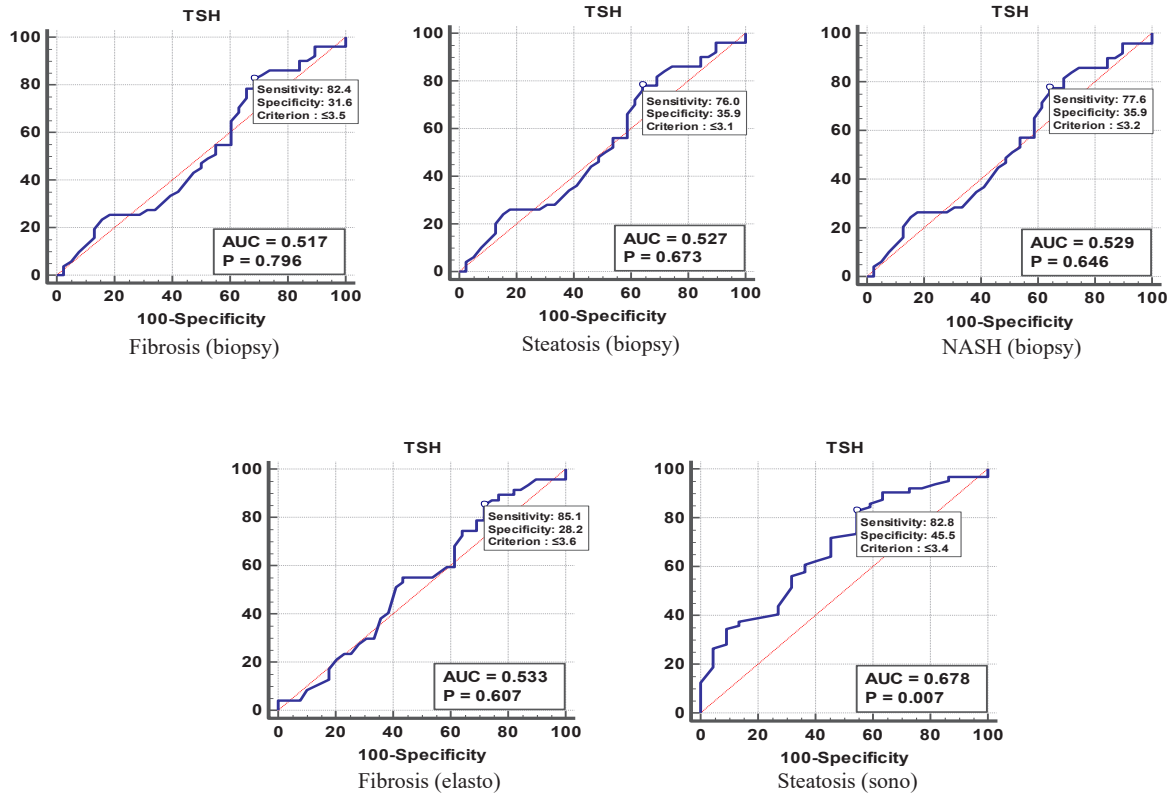

Figure 4. The ROC curve for TSH in the detection of liver disease

Table 10. The binary logistic regression analysis between T4 and study parameters

Parameters		*p*	OR	95% CI for OR	
				Lower	Upper
Crude model	Fibrosis (biopsy)	0.483	1.077	0.875	1.326
	Steatosis (biopsy)	0.496	1.052	0.909	1.217
	NASH	0.494	1.047	0.917	1.196
	Fibrosis (elastography)	0.494	1.037	0.934	1.152
	Steatosis (sono)	0.286	1.169	0.878	1.557
Adjusted Model	Fibrosis (biopsy)	0.471	1.126	0.816	1.554
	Steatosis (biopsy)	0.435	1.070	0.903	1.268
	NASH	0.435	1.070	0.903	1.268
	Fibrosis (elastography)	0.558	1.035	0.923	1.161
	Steatosis (sono)	0.355	1.168	0.840	1.625

OR, odds ratio; NASH, Non-alcoholic steatohepatitis.

Table 11. The binary logistic regression analysis between TSH and study parameters

Parameters		*P*	OR	95% CI for OR	
				Lower	Upper
Crude model	Fibrosis (biopsy)	0.552	1.022	0.951	1.099
	Steatosis (biopsy)	0.542	1.022	0.953	1.095
	NASH	0.539	1.022	0.954	1.095
	Fibrosis (elastography)	0.525	1.020	0.959	1.084
	Steatosis (sono)	0.762	1.006	0.966	1.049
Adjusted model	Fibrosis (biopsy)	0.806	1.027	0.829	1.272
	Steatosis (biopsy)	0.792	1.029	0.830	1.276
	NASH	0.792	1.029	0.830	1.276
	Fibrosis (elastography)	0.847	1.018	0.849	1.221
	Steatosis (sono)	0.346	0.896	0.713	1.126

OR, odds ratio; NASH, Non-alcoholic steatohepatitis.

The cholesterol-lowering effect of thyroid hormones is achieved via increased expression of hepatic and peripheral LDL receptors, which is regulated by T3, while in a hypothyroid state, as T3 levels are low, LDL cholesterol elimination is reduced due to a decrease in expression of LDL receptors.[23-25] Although there is increased formation and breakdown of lipids in a hyperthyroid milieu, as it is a catabolic state, the net effect is the reduction of plasma cholesterol levels, which in part is also due to weight loss, increased cellular uptake of cholesterol and increased biliary excretion through gut.[23-27]

Numerous studies have been done to explore the association between thyroid hormones and NAFLD; however, the results have been inconsistent. In 2003, Liangpunsakul and Chalasani undertook a case-control study on approximately 600 participants and demonstrated a higher prevalence of hypothyroidism in the NASH group compared with controls.[28] In a retrospective cohort analysis, Lee and colleagues studied 18 544 participants and compared euthyroid controls (n=17 052) with patients with subclinical (n=1303) and overt hypothyroidism (n=189). The median duration of developing NAFLD was 2.92 years. NAFLD group was older, with a higher proportion of males and a higher BMI. However, there was no association between thyroid status and NAFLD, and the incidence of NAFLD did not increase with hypothyroidism.[29] Jaruvongvanich et al conducted a systematic review and meta-analysis of 14 observational studies involving 7191 patients with NAFLD and 30 003 controls and found no difference

in thyroid hormone levels between patients with and without NAFLD. Moreover, they could not uncover a link between NAFLD and subclinical or overt hypothyroidism.[30] These findings are in line with the results presented in our study.

He and colleagues conducted a meta-analysis of 13 observational studies which explored the association between NAFLD and hypothyroidism and found that patients with subclinical and overt hypothyroidism are at a higher risk of development of NAFLD compared with those with normal thyroid function.[31] In a retrospective analysis of 52 histology-proven patients with NAFLD, D'Ambrosio and colleagues reported a high prevalence of hypothyroidism in cases of NAFLD and suggested it was linked to increased NAFLD activity but not with steatosis or fibrosis severity.[32] This evidence suggests that patients with elevated TSH levels are at a higher risk of developing metabolic syndrome and progression of NAFLD.[33,34] Thyroid hormone stimulation increases metabolic rate, which can result in the production of reactive oxygen species, lipid peroxidation, and liver cell injury.[35,36] Hypothyroidism, on the other side, could be responsible for the protection against hepatic fibrosis due to lower levels of oxidative stress.[37] This concept is supported by our findings, which show no association between hypothyroidism and steatosis or NASH.

According to the above mentioned, these results go to show the variability in the results of the published data concerning the association between TH and NAFLD. Understanding the mechanism by which thyroid disease may be linked to NAFLD is not clear, and more research is needed to understand the fascinating interplay between these complex metabolic processes.

By the suppression of lipoprotein lipase activity, hypothyroidism leads to a rise in serum triglycerides.[38,39] Ferrandino et al demonstrated that reduced thyroid hormone levels set off a cascade of events leading to defective insulin secretion, which suppresses lipolysis leading to accumulation of fatty acids. Hepatic deposition of these excess FAs results in NAFLD.[40] Eshraghian and Jahromi have discussed the possibility of hepatic damage from oxidative stress,[41] while the role of fibroblast growth factor-21 has also been explored in the pathogenesis of NAFLD in the context of thyroid dysfunction.[41-43]

In this study, among a population of patients with severe obesity and NAFLD, hypothyroidism was found to play a role in the major elements of metabolic syndrome, namely fat accumulation. However, additional insults, with a focus on oxidative stress and lipid peroxidation, seem to be needed in the progression to NASH. In fact, hypothyroidism could serve as a confounding factor in this regard, halting the progression to NASH and explaining the lack of association seen in our research.[44]

In our study, liver biopsy and elastography were used to investigate this association, which are robust diagnostic techniques adding to the strength of our study. On the other hand, from the collected data, we could not account for levels of physical activity, diet, and any acute illness preceding the investigations, and as such, these parameters could have interfered with the levels of thyroid hormones. TSH showed a significant difference between patients with and without steatosis based on ultrasonography; however, as it was amongst parameters with a non-normal distribution, therefore, the results should be viewed with caution. Nevertheless, our analysis is presented from a fairly large cohort with state-of-the-art investigational techniques to determine the association between thyroid hormones and hepatic pathology.

Conclusion

A growing body of research has explored the association between thyroid hormones and NAFLD with conflicting results. Several studies, including our analysis, have reported no association between thyroid hormones and NAFLD. However, numerous studies have proposed hypothyroidism as a risk factor for developing NAFLD whilst others have demonstrated a high prevalence of it in patients with NAFLD. As thyroid disease is easily treatable, well-designed large-scale prospective studies are required to conclusively demonstrate the association between thyroid dysfunction and the development of NAFLD, and if a link exists, screening and treatment of thyroid disease in this cohort can potentially prevent the onset and progression of NAFLD which in turn will reduce the burden of chronic liver disease.

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Conflict of Interest

The authors declare no conflict of interest related to this work.

Ethical Approval

This investigation was approved by the Ethics Committee of the Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran (serial no. IR.MUMS.fm.REC.1396.312) and was in accordance with the 1964 Helsinki Declaration and its later amendments.

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