

Association of Sensitivity to Thyroid Hormones and Non-Alcoholic Fatty Liver Disease and the Severity of Liver Fibrosis in Euthyroid Adults: A Retrospective Study

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Purpose: The relationship between non-alcoholic fatty liver disease (NAFLD) and thyroid function is controversial. A mild acquired thyroid hormone resistance may exist and explain these contradictions. This study aims to investigate the associations of thyroid hormone sensitivity with NAFLD and the severity of liver fibrosis in euthyroid populations.

Patients and Methods: Twenty-nine thousand three hundred and eighty-six adult subjects were recruited from the medical examination center of the Beijing Chao-Yang Hospital. Free triiodothyronine (FT3)/free thyroxine (FT4), thyroid feedback quartile-based index for FT4 (TFQI_{FT4}) and for FT3 (TFQI_{FT3}), thyroid stimulating hormone index (TSHI), thyrotropin thyroxine resistance index (TT4RI), and thyrotropin triiodothyronine resistance index (TT3RI) were calculated. Logistic regression analysis was used to analyze the associations of thyroid hormone sensitivity indices with the risks of NAFLD and related metabolic disorders. The correlation between thyroid hormone sensitivity and the severity of liver fibrosis evaluated by noninvasive fibrosis indices was analyzed through ordinal logistic regression.

Results: Euthyroid adults with NAFLD had elevated levels of serum FT3 and FT4, reduced TSH, and impaired sensitivity to thyroid hormones. Compared with participants in the first quartile group, the risk of NAFLD was higher in the fourth quartile of TFQI_{FT3} (OR 1.25, 95% CI 1.13–1.39, $P < 0.001$) and FT3/FT4 (OR 1.45, 95% CI 1.32–1.60, $P < 0.001$) after adjusting for metabolic confounders. Among NAFLD patients, higher FT3/FT4 positively correlated with increased severity of liver fibrosis, with ORs per SD of 10.80 (95% CI 4.12–28.53, $P < 0.001$) for aminotransferase-to-platelet ratio index, 4.74 (95% CI 1.56–14.38, $P = 0.006$) for NAFLD fibrosis score and 3.21 (95% CI 1.02–10.08, $P = 0.046$) for fibrosis-4 index.

Conclusion: Impaired central sensitivity to FT3 and higher FT3/FT4 were associated with increased risks of NAFLD and related metabolic disorders. In patients with NAFLD, higher FT3/FT4 correlated with its progression to liver fibrosis. These findings might provide novel insight into the monitoring and evaluation of the risk of NAFLD and the severity of liver fibrosis.

Keywords: sensitivity to thyroid hormones, NAFLD, liver fibrosis, metabolic disorders, euthyroid adults

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder, with a global prevalence of 25.24%¹ and 29.81% in China.² NAFLD is often paralleled with extrahepatic comorbidities, including obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia.¹ However, the pathogenesis of NAFLD is not clearly understood. Emerging studies focused on the relationship between thyroid dysfunction and NAFLD.^{3,4}

Thyroid hormones play important roles in the regulation of lipid and glucose metabolism and insulin resistance. Both overt and subclinical hypothyroidism have been associated with higher risks of NAFLD, possibly due to decreased lipid

utilization, secondary hepatic lipid accumulation, and insulin resistance.^{5,6} However, other studies reported no association between hypothyroidism and NAFLD.^{7,8} Recent animal experiment found that mice developed NAFLD when thyroid hormones were mildly decreased but not when they were severely decreased.³ In euthyroid populations, higher-normal free triiodothyronine (FT3) and lower-normal thyroid-stimulating hormone (TSH) levels were linked to increased NAFLD risks,⁹ and elevated FT3 and TSH increased the risk of NAFLD in those with T2DM.¹⁰ All these studies indicated that thyroid hormone resistance-like manifestation might exist in patients with NAFLD.

During the last three years, the association of sensitivity to thyroid hormones with metabolic health has gained increasing attention. Laclaustra et al first proposed the thyroid feedback quantile-based index (TFQI) to assess the central sensitivity to thyroid hormones in 2019 and found that thyroid hormones resistance was associated with increased risks of obesity, diabetes, and metabolic syndrome.¹¹ Subsequently, researchers proposed more indices evaluating sensitivity to thyroid hormones, including thyrotropin thyroxine resistance index (TT4RI)¹² and thyroid-stimulating hormone index (TSHI).¹³ For NAFLD, only one study with relatively small samples investigated its association with thyroid hormone sensitivity.¹⁴ Recently, several studies assessed the association of liver fibrosis in NAFLD with the thyroid function in euthyroid populations. Zhang et al reported correlations between high-normal TSH, impaired sensitivity, and advanced fibrosis in NAFLD with T2DM.¹⁵ Another study highlighted that TFQI combined with factors like age and triglycerides could predict advanced fibrosis in NAFLD patients.¹⁶ However, the sample sizes are relatively small, and the results are partially controversial in these studies. Our previous study has explored the specific lipid profile characteristics of the patients with NAFLD in the health examination cohort.¹⁷ In this large-scale study, we aim to first investigate the associations of thyroid hormone sensitivity indices with NAFLD and related metabolic disorders. Additionally, we explored the relationship between sensitivity to thyroid hormones and the severity of liver fibrosis among NAFLD participants.

Materials and Methods

Study Design and Populations

This retrospective cohort study collected data from the routine health check-up (including hepatic ultrasound and thyroid function) of 39688 subjects aged over 18 years in Beijing Chao-Yang Hospital from April 2016 to August 2020. Participants with missing data, thyroid dysfunction, anti-thyroid therapy, thyroid hormone replacement treatment, a severe hepatic and renal dysfunction, a history of excessive alcohol consumption (≥ 30 g/d for men and ≥ 20 g/d for women), and hepatitis B and C were excluded. Finally, 29386 subjects were included in the data analysis ([Figure S1](#)).

The study was conducted in accordance with the Declaration of Helsinki as revised in 2013 and was approved by the Ethics Committee of the Beijing Chao-Yang Hospital affiliated with Capital Medical University (NO. 2022-KE-517). Individual consent for this retrospective analysis was obtained from all participants.

Diagnosis of NAFLD

NAFLD was diagnosed by three well-trained and experienced clinicians unaware of clinical data via hepatic ultrasound and then the images were reviewed and confirmed by two experts in gastroenterology. The ultrasonic diagnosis for NAFLD included at least the first two of the following criteria: diffuse increases in liver echoes and liver-kidney contrast; liver brightness; vascular blurring; and deep attenuation.¹⁸

Measurements

Body weight, height, and blood pressure were measured according to standard protocols. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the average of three consecutive measurements using a standard sphygmomanometer. Fasting plasma levels of glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), platelet (PLT), creatinine (Cr), and uric acid (UA) were measured by an autoanalyzer. TSH, FT3, and free thyroxine (FT4) were evaluated by electrochemiluminescence immunoassay using an Abbott Architect i2000 (Abbott Diagnostics, Abbott Park, IL, USA).

Calculations and Definitions

Body mass index (BMI) was calculated by body weight in kilograms divided by height in square meters. Obesity was defined as $\text{BMI} \geq 28 \text{ kg/m}^2$. Hyperglycemia was defined as fasting glucose $>5.6 \text{ mmol/L}$.¹⁹ Hypertension was defined as $\text{SBP} \geq 140 \text{ mmHg}$, $\text{DBP} \geq 90 \text{ mmHg}$, or use of antihypertensive medications. Based on the 2016 Chinese guidelines for the management of dyslipidemia in adults,²⁰ dyslipidemia was defined as one of the following conditions: $\text{TC} \geq 5.2 \text{ mmol/L}$, $\text{TG} \geq 1.7 \text{ mmol/L}$, $\text{HDL-C} < 1.0 \text{ mmol/L}$, and $\text{LDL-C} \geq 3.4 \text{ mmol/L}$. Hyperuricemia was defined as $\text{UA} \geq 420 \text{ } \mu\text{mol/L}$ in males and $\geq 360 \text{ } \mu\text{mol/L}$ in females.²¹ The normal range of thyroid function in this study was TSH ($0.55\text{--}4.78 \text{ } \mu\text{IU/mL}$), FT3 ($3.54\text{--}6.47 \text{ pmol/L}$), and FT4 ($11.45\text{--}22.65 \text{ pmol/L}$).

Seven different indices were calculated to evaluate sensitivity to thyroid hormones. Thyroid feedback quartile-based index for FT4 (TFQI_{FT4}) was calculated as $\text{cdf FT4} - (1 - \text{cdf TSH})$.¹¹ Thyroid feedback quartile-based index for FT3 (TFQI_{FT3}) was calculated as $\text{cdf FT3} - (1 - \text{cdf TSH})$. TSHI was calculated as $\ln \text{TSH (mIU/L)} + 0.1345 \times \text{FT4 (pmol/L)}$.²² TT4RI was defined as $\text{FT4 (pmol/L)} \times \text{TSH (mU/L)}$.²² Thyrotropin triiodothyronine resistance index (TT3RI) was defined as $\text{FT3 (pmol/L)} \times \text{TSH (mU/L)}$. The value of TFQI_{FT4} and TFQI_{FT3} ranged from -1 to 1 . Positive values indicate poor central sensitivity to thyroid hormones, while negative values suggest good thyroid hormone sensitivity. As for TSHI, TT4RI, and TT3RI, the higher the values, the lower the central thyroid hormone sensitivity. Peripheral sensitivity to thyroid hormone was assessed by FT3/FT4 .

The severity of liver fibrosis was evaluated using noninvasive fibrosis scores including the NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, and aminotransferase-to-platelet ratio index (APRI). NFS was calculated as $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting plasma glucose/diabetes (yes = 1, no = 0)} + 0.99 \times [\text{AST (IU/L)/ALT (IU/L)}] - 0.013 \times \text{PLT (10}^9/\text{L)} - 0.66 \times \text{ALB (g/dL)}$.²³ FIB-4 was calculated based on the formula: $\text{Age (years)} \times \text{AST (U/L)} / [\text{PLT (10}^9/\text{L)} \times \text{ALT (U/L)}]$. The upper limit of normal value (ULN) of AST level was 40 IU/L .²⁴ APRI was calculated as $(\text{AST/AST ULN}) \times 100 / \text{PLT (10}^9/\text{L)}$.²⁵ NFS, FIB-4, and APRI were divided into three tertile groups, and the first tertile group was considered the reference group.

Statistics

SPSS 22.0 (Chicago, IL, USA) and GraphPad Prism 8.3 (Inc, CA, USA) were used for the statistical analyses. The distribution of the continuous data was assessed using normal P-P plots. Normally distributed continuous data were expressed as mean $\pm$ standard deviation (SD) and non-normally distributed continuous variables were described as median and interquartile ranges and were analyzed after natural log transformed. For continuous variables, comparisons between the NAFLD group and the non-NAFLD group were performed using Student's *t*-tests. Categorical variables were defined as numbers (percentages) and were assessed by chi-square tests. P for trend was analyzed by linear regression analyses. Univariate and multivariate logistic regression analysis was used to evaluate the relationship between thyroid hormone sensitivity and NAFLD and metabolic disorders. Ordinal logistic regression was performed to analyze the association of thyroid hormone sensitivity with the severity of liver fibrosis. The two-sided P value < 0.05 was considered statistically significant.

Results

Characteristics of the Study Population

Of the 29386 participants finally included in this study, 8389 (28.5%) had NAFLD. As shown in Table 1, patients with NAFLD had significantly higher age, BMI, SBP, DBP, ALT, AST, TC, TG, LDL-C, glucose, Cr, and UA than those without NAFLD (all $P < 0.001$), while they had lower levels of HDL-C ($P < 0.001$). The prevalence of obesity, hypertension, hyperglycemia, hyperuricemia, and dyslipidemia was higher in NAFLD group (all $P < 0.001$). NAFLD was more common in males than females. For thyroid function and sensitivity to thyroid hormone indices, FT3, FT4, TFQI_{FT4} , TFQI_{FT3} , TSHI, TT3RI, and FT3/FT4 levels were significantly higher (all $P < 0.001$), but TSH was lower in subjects with NAFLD compared with those without NAFLD.

Table 1 Comparisons of Clinical Parameters Between Subjects with NAFLD and Those without NAFLD

Parameters	Total Population	Non-NAFLD	NAFLD	P
N	29386	20,997	8389	N/A
Sex, male (%)	13,576(46.2%)	7615(36.3%)	5961(71.1%)	<0.001
Age (years)	40.9±12.3	39.3±12.1	45.0±12.0	<0.001
BMI (kg/m ²)	24.1±3.7	22.8±3.0	27.4±3.3	<0.001
SBP (mmHg)	121.4±16.7	118.3±15.7	129.4±16.5	<0.001
DBP (mmHg)	72.6±11.5	70.3±10.6	78.2±11.7	<0.001
PLT (*10 ⁹)	248.6±56.8	248.1±56.2	249.7±58.1	0.034
ALT* (U/L)	18.2(13.2–27.0)	16.0(12.0–22.0)	28.0(20.2–40.0)	<0.001
AST* (U/L)	20.0(17.0–24.0)	19.0(17.0–22.3)	23.0(19.3–28.0)	<0.001
ALB (g/L)	46.7±2.5	46.5±2.5	47.0±2.5	<0.001
TC (mmol/L)	4.85±0.90	4.75±0.87	5.09±0.94	<0.001
TG* (mmol/L)	1.18(0.84–1.73)	1.01(0.76–1.39)	1.81(1.32–2.53)	<0.001
HDL-C (mmol/L)	1.36±0.35	1.45±0.34	1.15±0.25	<0.001
LDL-C (mmol/L)	2.79±0.80	2.68±0.75	3.06±0.85	<0.001
Glucose* (mmol/L)	5.01(4.62–5.44)	4.92(4.55–5.31)	5.29(4.82–5.83)	<0.001
Cr (μmol/L)	64.8±13.7	63.0±13.2	69.4±13.9	<0.001
UA (μmol/L)	340.2±91.4	316.7±80.4	398.9±90.8	<0.001
Obesity, N(%)	4178(14.2%)	969(4.6%)	3209(38.3%)	<0.001
Hypertension, N(%)	4242(14.4%)	2042(9.7%)	2200(26.2%)	<0.001
Hyperglycemia, N(%)	5368(18.3%)	2592(12.3%)	2776(33.1%)	<0.001
Hyperuricemia, N(%)	7036(23.9%)	3254(15.5%)	3782(45.1%)	<0.001
Dyslipidemia, N(%)	14,956(50.9%)	8379(39.9%)	6577(78.4%)	<0.001
FT3 (pmol/L)	4.95±0.52	4.88±0.51	5.12±0.52	<0.001
FT4 (pmol/L)	16.02±1.98	15.94±1.95	16.23±2.02	<0.001
TSH* (mIU/L)	1.84(1.33–2.50)	1.84(1.33–2.51)	1.80(1.31–2.46)	0.015
TFQI _{FT4}	−0.004±0.385	−0.013±0.385	0.019±0.382	<0.001
TFQI _{FT3}	−0.001±0.393	−0.036±0.394	0.086±0.377	<0.001
TSHI	2.75±0.49	2.74±0.49	2.77±0.49	<0.001
TT4RI	31.73±14.13	31.71±14.14	31.76±14.10	0.815
TT3RI	9.83±4.39	9.75±4.37	10.04±4.44	<0.001
FT3/FT4	0.312±0.041	0.310±0.039	0.319±0.042	<0.001

Notes: Continuous data are expressed as mean ± SD or median with interquartile range and categorical variable is expressed as N (%). *Non-normally distributed continuous variables were compared after natural log-transformed. Data were analyzed by Student's *t*-test.

Abbreviation: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TFQI_{FT4}, thyroid feedback quartile-based index for FT4; TFQI_{FT3}, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; and TT3RI, thyrotropin triiodothyronine resistance index.

Associations of Thyroid Hormone Sensitivity with NAFLD and Associated Metabolic Disorders

We found that subjects with higher TFQI_{FT4}, TFQI_{FT3}, TSHI, TT4RI, TT3RI, and FT3/FT4 quartiles were associated with progressively increased risks of obesity, hypertension, hyperuricemia, and dyslipidemia (Table 2). Interestingly, the prevalence of NAFLD was progressively increased with the elevating quartiles of TFQI_{FT4}, TFQI_{FT3}, TSHI, TT3RI, and FT3/FT4 (Figure 1, all *P* for trend < 0.001). Logistics regression analysis showed that higher quartiles of TFQI_{FT4}, TFQI_{FT3}, TSHI, TT3RI, and FT3/FT4 were significantly associated with increased NAFLD risk, even after adjusting age, sex, and BMI. This association was consistent across subgroups, including males, females, non-obese, and obese individuals (Table S1 and Table S2). After further adjusting DBP, glucose, UA, TC, and TG, TFQI_{FT3} (OR 1.25, 95% CI 1.13–1.39, *P* < 0.001) and FT3/FT4 (OR 1.45, 95% CI 1.32–1.60, *P* < 0.001) still had strong correlations with the risk of NAFLD (Table 3 and Figure 2).

Table 2 The Associations of Sensitivity to Thyroid Hormones and NAFLD-Related Metabolic Disorders

Parameters	Obesity		Hypertension		Hyperglycemia		Hyperuricemia		Dyslipidemia	
	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
TFQI _{FT4}										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.02(0.93–1.12)	0.695	1.03(0.93–1.13)	0.593	1.00(0.92–1.09)	0.963	1.17(1.08–1.27)	<0.001	1.05(0.98–1.12)	0.158
Q3	1.17(1.07–1.29)	0.001	1.09(1.00–1.20)	0.060	0.98(0.90–1.06)	0.548	1.37(1.27–1.48)	<0.001	1.17(1.10–1.25)	<0.001
Q4	1.19(1.09–1.31)	<0.001	1.26(1.15–1.38)	<0.001	1.02(0.94–1.11)	0.637	1.65(1.53–1.78)	<0.001	1.35(1.26–1.44)	<0.001
TFQI _{FT3}										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.49(1.35–1.66)	<0.001	1.16(1.05–1.27)	0.003	1.09(1.00–1.18)	0.057	1.42(1.31–1.54)	<0.001	1.20(1.13–1.28)	<0.001
Q3	1.86(1.68–2.06)	<0.001	1.34(1.22–1.48)	<0.001	1.19(1.09–1.29)	<0.001	1.65(1.52–1.79)	<0.001	1.33(1.25–1.42)	<0.001
Q4	2.27(2.05–2.50)	<0.001	1.47(1.34–1.61)	<0.001	1.15(1.05–1.25)	0.002	2.11(1.95–2.28)	<0.001	1.62(1.51–1.72)	<0.001
TSHI										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.07(0.97–1.17)	0.185	1.09(0.99–1.19)	0.089	0.94(0.87–1.03)	0.171	1.14(1.05–1.23)	0.001	1.05(0.99–1.12)	0.123
Q3	1.15(1.05–1.26)	0.004	1.05(0.96–1.15)	0.313	0.92(0.85–1.00)	0.054	1.27(1.17–1.38)	<0.001	1.13(1.06–1.20)	<0.001
Q4	1.13(1.03–1.24)	0.013	1.26(1.15–1.38)	<0.001	0.90(0.83–0.98)	0.014	1.37(1.27–1.48)	<0.001	1.26(1.19–1.35)	<0.001
TT4RI										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.09(1.00–1.20)	0.063	0.99(0.90–1.09)	0.834	0.90(0.83–0.97)	0.009	1.00(1.01–1.18)	0.021	1.06(1.00–1.13)	0.068
Q3	1.13(1.03–1.24)	0.011	0.94(0.85–1.03)	0.174	0.83(0.77–0.90)	<0.001	1.11(1.03–1.20)	0.007	1.06(1.00–1.13)	0.072
Q4	1.07(0.97–1.17)	0.172	1.13(1.03–1.24)	0.007	0.81(0.75–0.88)	<0.001	1.13(1.05–1.22)	0.002	1.17(1.09–1.24)	<0.001
TT3RI										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.14(1.04–1.26)	0.008	1.00(0.91–1.10)	0.978	0.90(0.83–0.97)	0.009	1.09(1.01–1.18)	0.024	1.06(0.99–1.12)	0.131
Q3	1.26(1.15–1.39)	<0.001	1.07(0.97–1.17)	0.171	0.90(0.83–0.98)	0.012	1.14(1.06–1.20)	<0.001	1.09(1.03–1.17)	0.007
Q4	1.28(1.17–1.41)	<0.001	1.14(1.04–1.25)	0.004	0.83(0.76–0.90)	<0.001	1.15(1.06–1.24)	<0.001	1.21(1.13–1.29)	<0.001
FT3/FT4										
Q1	1.00		1.00		1.00		1.00		1.00	
Q2	1.12(1.01–1.23)	0.032	0.94(0.86–1.03)	0.184	0.94(0.86–1.02)	0.118	0.97(0.90–1.05)	0.417	0.97(0.91–1.04)	0.369
Q3	1.30(1.18–1.43)	<0.001	0.98(0.90–1.00)	0.71	1.00(0.92–1.09)	0.992	1.01(0.93–1.09)	0.899	0.98(0.92–1.05)	0.536
Q4	1.81(1.65–1.98)	<0.001	1.14(1.04–1.25)	0.005	1.11(1.02–1.21)	0.013	1.12(1.04–1.21)	0.003	1.15(1.08–1.23)	<0.001

Notes: Data was analyzed by logistic regression.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TFQI_{FT4}, thyroid feedback quartile-based index for FT4; TFQI_{FT3}, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; and TT3RI, thyrotropin triiodothyronine resistance index.

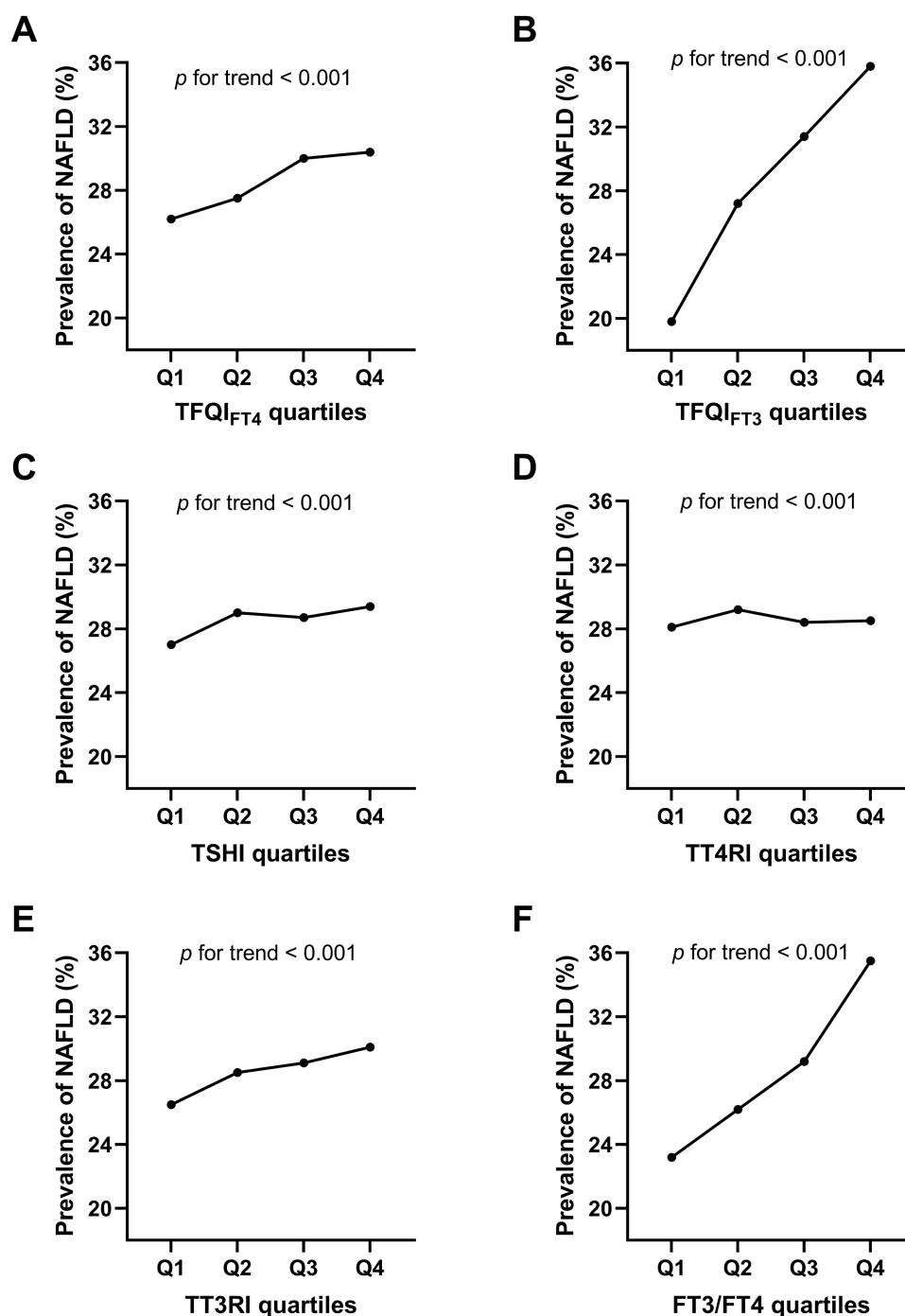


Figure 1 The prevalence of NAFLD in subjects with different thyroid hormone sensitivity. (A) TFQI_{FT4}; (B) TFQI_{FT3}; (C) TSHI; (D) TT4RI; (E) TT3RI; and (F) FT3/FT4. P for trend was analyzed by linear regression analyses. NAFLD, non-alcoholic fatty liver disease; FT3, free triiodothyronine; FT4, free thyroxine; TFQI_{FT4}, thyroid feedback quartile-based index for FT4; TFQI_{FT3}, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; and TT3RI, thyrotropin triiodothyronine resistance index.

The Association Between Sensitivity to Thyroid Hormones and the Severity of Liver Fibrosis Evaluated by the Noninvasive Fibrosis Markers in NAFLD Participants

To examine the relationship between sensitivity to thyroid hormones and the severity of liver fibrosis, ordinal logistic regression analyses were performed (Table 4). The severity of liver fibrosis was stratified by tertiles of the noninvasive fibrosis markers: NFS, FIB-4, and APRI, with the lowest tertiles as the reference. After adjustment for age, sex, BMI, glucose, the level of FT3/FT4 was positively correlated to the tertiles of all liver fibrosis markers, including NFS, FIB-4,

Table 3 The Associations of Sensitivity to Thyroid Hormones with the Risk of NAFLD

Parameters	Model 1		Model 2		Model 3	
	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
TFQI _{FT4}						
Q1	1.00		1.00		1.00	
Q2	1.07(0.99–1.15)	0.086	1.05(0.96–1.15)	0.284	1.02(0.93–1.13)	0.673
Q3	1.21(1.12–1.30)	<0.001	1.13(1.03–1.23)	0.011	1.03(0.94–1.14)	0.532
Q4	1.35(1.14–1.32)	<0.001	1.11(1.01–1.21)	0.032	0.93(0.84–1.03)	0.146
TFQI _{FT3}						
Q1	1.00		1.00		1.00	
Q2	1.51(1.40–1.63)	<0.001	1.19(1.08–1.31)	<0.001	1.15(1.04–1.28)	<0.001
Q3	1.86(1.72–2.00)	<0.001	1.29(1.17–1.42)	<0.001	1.24(1.12–1.37)	<0.001
Q4	2.25(2.09–2.43)	<0.001	1.36(1.24–1.50)	<0.001	1.25(1.13–1.39)	<0.001
TSHI						
Q1	1.00		1.00		1.00	
Q2	1.10(1.03–1.18)	0.008	1.11(1.02–1.22)	0.020	1.09(0.99–1.20)	0.078
Q3	1.09(1.01–1.17)	0.025	1.03(0.94–1.13)	0.494	0.95(0.87–1.05)	0.325
Q4	1.13(1.05–1.21)	0.001	1.09(1.00–1.20)	0.054	0.94(0.85–1.03)	0.193
TT4RI						
Q1	1.00		1.00		1.00	
Q2	1.05(0.98–1.13)	0.153	1.03(0.94–1.13)	0.486	1.01(0.92–1.11)	0.804
Q3	1.01(0.94–1.09)	0.728	0.99(0.90–1.08)	0.783	0.93(0.84–1.02)	0.126
Q4	1.02(0.95–1.09)	0.657	1.04(0.95–1.14)	0.359	0.93(0.85–1.03)	0.158
TT3RI						
Q1	1.00		1.00		1.00	
Q2	1.11(1.03–1.19)	0.005	1.09(0.99–1.19)	0.069	1.06(0.96–1.17)	0.225
Q3	1.14(1.06–1.23)	<0.001	1.02(0.93–1.11)	0.746	0.97(0.88–1.06)	0.470
Q4	1.20(1.11–1.29)	<0.001	1.12(1.03–1.23)	0.014	1.03(0.94–1.14)	0.520
FT3/FT4						
Q1	1.00		1.00		1.00	
Q2	1.18(1.10–1.27)	<0.001	1.12(1.02–1.23)	0.019	1.21(1.09–1.34)	<0.001
Q3	1.37(1.27–1.48)	<0.001	1.17(1.07–1.28)	0.001	1.30(1.18–1.44)	<0.001
Q4	1.83(1.70–1.97)	<0.001	1.26(1.15–1.38)	<0.001	1.45(1.32–1.60)	<0.001

Notes: Data was analyzed by univariate or multivariate logistic regression model. Model 1, unadjusted; model 2, adjusted for age, sex, and BMI; model 3, adjusted for age, sex, BMI, DBP, glucose, UA, TC, and TG.

Abbreviation: NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TFQI_{FT4}, thyroid feedback quartile-based index for FT4; TFQI_{FT3}, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; and TT3RI, thyrotropin triiodothyronine resistance index.

and APRI ($P < 0.05$). The contribution between FT3/FT4 and APRI was the highest (β 2.38, OR per SD 10.80, 95% CI 4.12–28.53, $P < 0.001$), followed by NFS (β 1.555, OR per SD 4.74, 95% CI 1.56–14.38, $P = 0.006$) and FIB-4 (β 1.165, OR per SD 3.21, 95% CI 1.02–10.08, $P = 0.046$).

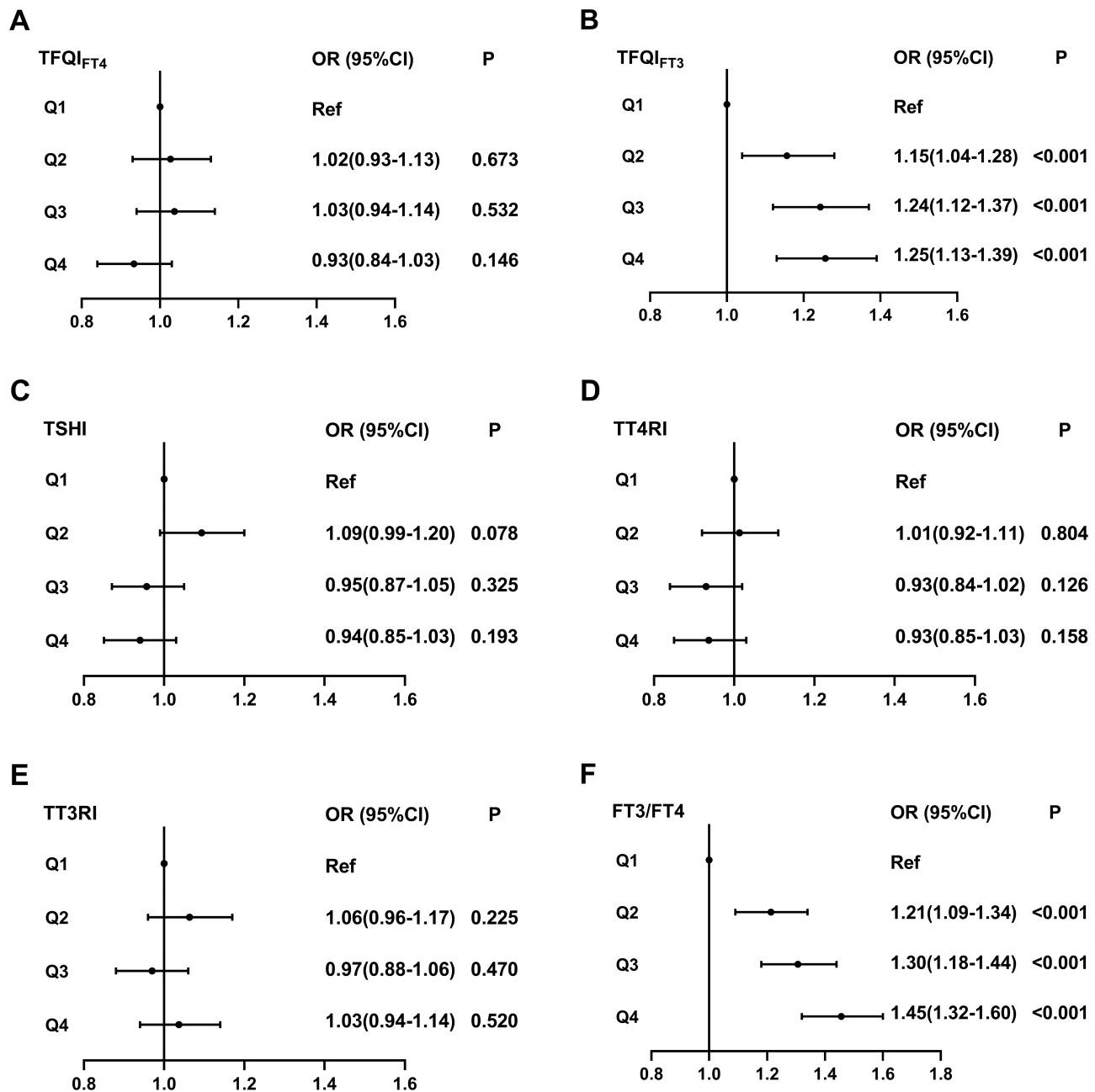


Figure 2 Logistic analysis of the association between NAFLD and sensitivity to thyroid hormones. (A) $TFQI_{FT4}$; (B) $TFQI_{FT3}$; (C) TSHI; (D) TT4RI; (E) TT3RI; and (F) FT3/FT4. The odds ratios were adjusted for age, sex, BMI, DBP, glucose, UA, TC, and TG. NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; $TFQI_{FT4}$, thyroid feedback quartile-based index for FT4; $TFQI_{FT3}$, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; and TT3RI, thyrotropin triiodothyronine resistance index.

Discussion

In this large-scale cohort, we showed that impaired central sensitivity to FT3 and higher FT3/FT4 were related to higher risks of NAFLD and associated metabolic disorders even after adjusting multiple confounders. Among patients with NAFLD, higher FT3/FT4 positively correlated with the severity of liver fibrosis evaluated by noninvasive liver fibrosis markers.

The etiology and pathogenesis of NAFLD are not completely uncovered. Recently, the association of the thyroid function with NAFLD gained more and more attention. Growing evidence demonstrated that subjects with hypothyroidism had higher risks of developing NAFLD.^{26,27} Serum FT3 and FT4 showed a negative correlation with NAFLD and TSH levels presented a positive relationship in patients with thyroid dysfunction.⁴ However, other studies did not show

Table 4 Associations Between Sensitivity to Thyroid Hormone Indices and the Severity of Liver Fibrosis Evaluated by the Noninvasive Fibrosis Markers in Participants With NAFLD After Adjusting Age, Sex, BMI, Glucose, TC, and TG

Parameters	T1	T2	T3	P for trend	β	OR (95% CI)	P
NFS							
TFQI _{FT4}	0.057±0.379	0.013±0.381	-0.014±0.382	<0.001	-0.209	0.81 (0.72–0.92)	<0.001
TFQI _{FT3}	0.132±0.374	0.089±0.373	0.037±0.378	<0.001	-0.082	0.92 (0.81–1.05)	0.210
TSHI	2.81±0.48	2.75±0.48	2.74±0.49	<0.001	-0.116	0.89 (0.81–0.98)	0.018
TT4RI	32.47±14.09	31.38±13.92	31.41±14.26	0.005	-0.002	1.00 (0.99–1.00)	0.190
TT3RI	10.27±4.45	9.95±4.40	9.89±4.47	0.001	-0.002	1.00 (0.99–1.01)	0.750
FT3/FT4	0.319±0.041	0.320±0.042	0.318±0.044	0.278	1.555	4.74 (1.56–14.38)	0.006
FIB-4							
TFQI _{FT4}	0.059±0.373	0.005±0.388	-0.009±0.381	<0.001	0.012	1.01 (0.89–1.15)	0.850
TFQI _{FT3}	0.139±0.366	0.082±0.377	0.036±0.380	<0.001	0.126	1.13 (0.99–1.29)	0.063
TSHI	2.80±0.47	2.75±0.49	2.74±0.49	<0.001	0.052	1.05 (0.95–1.16)	0.302
TT4RI	32.14±13.69	31.38±14.16	31.74±14.42	0.294	0.003	1.00 (1.00–1.01)	0.074
TT3RI	10.19±4.33	9.94±4.44	9.98±4.56	0.084	0.014	1.01 (1.00–1.03)	0.011
FT3/FT4	0.320±0.040	0.320±0.043	0.317±0.043	0.029	1.165	3.21 (1.02–10.08)	0.046
APRI							
TFQI _{FT4}	0.009±0.375	0.013±0.386	0.034±0.384	0.013	0.072	1.07 (0.97–1.19)	0.184
TFQI _{FT3}	0.037±0.373	0.089±0.380	0.131±0.373	<0.001	0.338	1.40 (1.25–1.57)	<0.001
TSHI	2.76±0.48	2.76±0.49	2.78±0.49	0.073	0.082	1.09 (1.00–1.18)	0.052
TT4RI	31.73±14.16	31.46±14.03	32.08±14.10	0.353	0.004	1.01 (1.00–1.01)	0.011
TT3RI	9.90±4.39	9.97±4.44	10.24±4.49	0.004	0.019	1.02 (1.01–1.03)	<0.001
FT3/FT4	0.315±0.041	0.320±0.043	0.322±0.042	<0.001	2.380	10.80 (4.12–28.53)	<0.001

Notes: Data was analyzed by ordinal logistic regression.

Abbreviation: NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; NFS, NAFLD fibrosis score; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TFQI_{FT4}, thyroid feedback quartile-based index for FT4; TFQI_{FT3}, thyroid feedback quartile-based index for FT3; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index; TT3RI, thyrotropin triiodothyronine resistance index; FIB-4, fibrosis-4 index; and APRI, aminotransferase to platelet ratio index.

the association between NAFLD and hypothyroid.^{8,28} The relationship between NAFLD and serum thyroid hormone levels was also different in euthyroid populations. Gu et al did a prospective study in middle-aged and older euthyroid subjects and showed that high-normal FT3 and low-normal TSH in baseline were related to a higher incidence of NAFLD after approximately 6-year follow-up.⁹ In accordance with this study, our study also found that in euthyroid adults with NAFLD, the serum FT3 and FT4 levels were significantly higher, while TSH levels were significantly lower. Although differences in populations, sample size, and thyroid functions may partially explain the inconsistent results, an acquired resistance to thyroid hormones-like manifestation might exist in subjects with NAFLD.

Resistance to thyroid hormone (RTH) is characterized by elevating circulating thyroid hormones and non-suppressed TSH due to receptor mutations.^{29,30} In 2019, Laclaustra et al linked acquired thyroid hormone resistance represented by higher TFQI levels to increased risks of obesity, diabetes, and metabolic syndrome in US populations.¹¹ Subsequent studies showed that reduced thyroid hormone sensitivity was associated with higher adipocyte fatty acid-binding protein levels,³¹ as well as diabetes and hypertension in euthyroid populations.³² Consistently, our study also found that impaired central sensitivity to thyroid hormones and higher FT3/FT4 were associated with higher risks of obesity, hypertension, hyperuricemia, and dyslipidemia.

Given the close relationship between NAFLD and metabolic disorders, we hypothesized that reduced sensitivity to thyroid hormones was related to higher risks of NAFLD. Only one study preliminarily investigated this relationship in a general population and showed that TFQI_{FT3} could be used as an indicator for predicting NAFLD. In this study, to the best of our knowledge, we first detected the relationship between thyroid hormone sensitivity and NAFLD in a large

euthyroid population and found that the thyroid hormone sensitivity indices $TFQI_{FT4}$, $TFQI_{FT3}$, TSHI, TT3RI, and FT3/FT4 were all significantly higher in subjects with NAFLD compared with those without NAFLD. Impaired sensitivity to FT3 and higher FT3/FT4 correlated with higher risks of NAFLD. Interestingly, these relationships were independent of other metabolic factors, including blood pressure, serum glucose, UA, and lipid profiles, which indicates that there might be other underlying mechanisms linking NAFLD and thyroid hormone resistance.

Though previous studies have demonstrated the effectiveness of thyroid hormones in reducing hepatic steatosis by promoting β -oxidation and reducing oxidative stress and fibrosis in animal models,^{33,34} the effect of thyroid functions and thyroid hormone sensitivity on fibrosis in NAFLD is unclear. The prevalence of advanced fibrosis was significantly higher in subjects with subclinical hypothyroidism than in those with normal thyroid function. Even within the normal range, higher TSH levels are closely associated with NASH and NASH-related advanced fibrosis, independent of known metabolic risk factors.^{35,36} More recently, investigators speculated that thyroid hormone receptor may activate hepatic stellate cells, implying the role of thyroid hormone signaling in liver fibrogenesis.³⁶ However, Mazo et al found no association between overt hypothyroidism and NASH and related fibrosis.⁷ As for evidence regarding the relationship between thyroid hormone sensitivity and liver fibrosis, Liu et al found that peripheral thyroid sensitivity index FT3/FT4, which also reflects a proxy of deiodinase activity, was not a significant influencing factor for NFS in NAFLD subjects with normal thyroid function but a valid and valuable predictor for NAFLD.³⁷ Whereas, another single-center study of liver biopsy-proven NAFLD suggested that FT3/FT4 ratio was equally influential in assessing the severity of cirrhosis.³⁸ Our study confirms a significant positive association between FT3/FT4 and liver fibrosis severity, as evaluated by NFS, FIB-4, and APRI in a large euthyroid population.

The specific biological mechanisms linking sensitivity to thyroid hormones to NAFLD, related metabolic disorders, and the severity of liver fibrosis are still mysterious. Central resistance, reflected by TFQI, TSHI, and TT4RI, and peripheral resistance, affecting metabolic processes, may coexist and contribute to these associations.^{11,39,40} Thyroid hormones play important roles in increasing energy expenditure, activating adipose tissue lipolysis, increasing fatty acid oxidation, and inhibiting lipid accumulation in the liver.¹¹ Increasing serum FT3/FT4 levels can stimulate the release of free fatty acids by lipolysis in adipose tissue, which can induce the activation of intrahepatic macrophages and up-regulate autophagy through transport into the liver. The progress will increase triglyceride synthesis in the liver and aggravate hepatocyte damage, leading to progressive fibrosis and nodule formation in the liver. The elevated serum FT3 levels, converted from serum FT4, can be viewed as a compensatory and adaptive mechanism to increase energy expenditure under the disordered metabolic situations such as NAFLD.⁴¹ Furthermore, FT3 can increase fatty acid β -oxidation and promote lipid production, which is associated with the occurrence of NAFLD.⁴² Additionally, impaired sensitivity to FT3 in the liver may result in a range of clinical processes of liver steatosis, including decreased hepatic lipases, lipophagy, mitochondrial oxidation of fatty acids, and hepatic triglyceride deposition, which can further develop into liver fibrosis, cirrhosis, and even liver failure, since FT3 was demonstrated to block TGF- β -mediated responses and prevent the occurrence and progression of liver fibrosis.⁴³ However, serum FT3 and FT4 levels may not accurately reflect intrahepatic thyroid hormone levels since the impaired intrahepatic FT3 signaling in NAFLD population.⁴⁴ More clinical studies and animal models are required to clarify the specific molecular mechanisms.

This study still has some limitations. First, as a retrospective study, it cannot establish causality between thyroid hormone sensitivity and NAFLD. Longitudinal studies are needed to explore the temporal association between thyroid sensitivity indices and NAFLD progression. Second, the lack of quantitative fibrosis assessments, such as biopsy or advanced imaging, limits the precision of fibrosis severity evaluation, though noninvasive markers provide useful insights. Additionally, the single-center Chinese cohort restricts generalizability, highlighting the need for broader multi-center studies in diverse populations. Moreover, the absence of anti-thyroid antibody data also limits understanding autoimmune mechanisms linking thyroid hormone sensitivity to NAFLD. Finally, while mechanisms are discussed, the lack of experimental data and intrahepatic thyroid signaling analysis restricts its depth. Future research should evaluate therapeutic approaches, such as selective thyroid hormone receptor β agonists to enhance fatty acid oxidation and reduce inflammation, lifestyle modifications to optimize thyroid hormone sensitivity, and integration of sensitivity indices into risk assessment tools to identify high-risk patients and personalize treatment strategies.

Conclusions

In conclusion, reduced central sensitivity to FT3 and higher FT3/FT4 were associated with higher risks of NAFLD and related metabolic disorders. Additionally, higher FT3/FT4 was also correlated with the severity of liver fibrosis in NAFLD populations. These thyroid hormone sensitivity indices might help to facilitate the monitoring and evaluation of the risk of NAFLD and the severity of liver fibrosis.

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Disclosure

The authors report no conflicts of interest in this work.

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