Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Thyroid Hormone Sensitivity and Non-Alcoholic Fatty Liver Disease in Individuals with Normal Thyroid Function

Tingting Xu[1], Tianshu Han[2], Jingyu Zhai[3], Hong Qiao[1]

[1]Department of Endocrinology, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, 150000, People's Republic of China; [2]The National Key Discipline, Department of Nutrition and Food Hygiene, Public Health College, Harbin medical university, Harbin, Heilongjiang, 150000, People's Republic of China; [3]Department of Endocrinology, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, Heilongjiang, 161000, People's Republic of China

Correspondence: Hong Qiao, Department of Endocrinology, The Second Affiliated Hospital of Harbin Medical University, No. 246 Xuefu Road, Nangang District, Harbin, Heilongjiang, 150000, People's Republic of China, Email qiaohong@hrbmu.edu.cn

Introduction: Nonalcoholic fatty liver disease (NAFLD) is a globally prevalent metabolic disorder that has attracted increasing clinical and public health attention. Although several studies have suggested a potential link between thyroid hormone levels and the risk of NAFLD, existing epidemiological evidence remains limited and inconsistent. Therefore, this study aims to investigate the association between thyroid hormone sensitivity and NAFLD in individuals with normal thyroid function. Furthermore, we sought to explore whether this association differs according to the presence or absence of metabolic comorbidities, particularly type 2 diabetes mellitus (T2DM) and non-diabetic (non-DM) status.

Methods: We included 460 adults with normal thyroid function, comprising 229 patients with T2DM and 231 without diabetes. Steatosis was assessed using liver ultrasonography.

Results: Both the thyroid feedback quantile index based on free thyroxine (TFQI-FT4) and that based on free triiodothyronine (TFQI-FT3) were positively associated with the presence of NAFLD (Q4 vs Q1, Model 3: TFQI-FT4, OR = 3.290, 95% CI: 1.390–7.787, p = 0.007; TFQI-FT3, OR = 2.344, 95% CI: 1.010–5.439, p = 0.047). Among individuals with type 2 diabetes mellitus (T2DM), a higher FT3/FT4 ratio was associated with a lower risk of NAFLD (Q3 vs Q1, Model 2: OR = 0.221, 95% CI: 0.053–0.921, p = 0.038), although the comparison between Q4 and Q1 did not reach statistical significance (OR = 0.402, 95% CI: 0.100–1.614, p = 0.199). In contrast, among non-diabetic individuals, a higher FT3/FT4 ratio was positively associated with NAFLD (Q4 vs Q1, Model 2: OR = 3.390, 95% CI: 1.003–11.463, p = 0.049).

Conclusion: Thyroid hormone sensitivity is associated with the development of NAFLD development in individuals with normal thyroid function and may be influenced by the presence of T2DM.

Keywords: thyroid hormone sensitivity, thyroid hormone central sensitivity, thyroid hormone peripheral sensitivity, NAFLD, T2DM

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver condition characterized by hepatic steatosis affecting more than 5% of hepatocytes in the absence of significant alcohol consumption or other chronic liver diseases. It typically begins as simple steatosis but may progress in some individuals to nonalcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, or even hepatocellular carcinoma.[1,2] The global prevalence of NAFLD continues to rise, with recent epidemiological studies estimating a global prevalence of approximately 25%, and about 27% among Asian populations.[3] NAFLD is closely associated with type 2 diabetes mellitus (T2DM).[4] A recent meta-analysis indicated that the prevalence of NAFLD in patients with T2DM ranged from 47.3 to 63.7%, and these patients were more likely to develop advanced fibrosis, cirrhosis, and hepatocellular carcinoma than those without diabetes.[5] Furthermore, NAFLD also adversely affects the development of T2DM with increasing severity of liver fibrosis.[6] Therefore, early detection and prevention of NAFLD in patients with T2DM are essential.

Received: 23 June 2025
Accepted: 6 September 2025
Published: 20 September 2025

Liver plays a significant role in the activation, inactivation, transport, and metabolism of thyroid hormones, and therefor hepatic dysfunction may also result in thyroid dysfunction.[7] Thyroid hormones play a pivotal role in maintaining hepatic lipid homeostasis by regulating mitochondrial function, endoplasmic reticulum (ER) stress, and the synthesis, transport, and metabolism of fatty acids and cholesterol. Disruption of these regulatory processes may contribute to the onset and progression of nonalcoholic fatty liver disease (NAFLD).[8] A systematic review encompassing 43 studies further highlights that alterations in thyroid hormone levels or activity have a direct impact on hepatic metabolic function.[9] Meanwhile, existing research has also shown that, Abnormal thyroid hormone sensitivity has been associated with several metabolic diseases, such as diabetes, obesity, hyperuricemia, cardiovascular disease, metabolic syndrome, NAFLD, and hepatic fibrosis.[10–16] However, most studies focused on the impact of thyroid hormone sensitivity on patients with thyroid dysfunction.

Negative feedback regulation occurs between the hypothalamus, pituitary gland, and thyroid gland, mediating an inverse correlation between thyroid hormones and thyroid stimulating hormone (TSH). However, thyroid hormone and TSH levels are elevated in patients with thyroid hormone resistance syndrome, possibly due to genetic mutations.[17] Thyroid hormone resistance can develop central resistance to thyroid hormones, affecting the central nervous system feedback loops, inducing peripheral resistance, and reducing metabolic rates.[18,19] Laclaustra et al proposed that thyroid hormone resistance could also reduce sensitivity to central and peripheral thyroid hormones and could be evaluated by the thyroid feedback quartile-based index (TFQI). TFQI is an index of central thyroid hormone sensitivity that reflects thyroid homeostasis, which better describes the relationship between thyroid hormones, NAFLD, and diabetes. The index is also applicable to individuals with normal thyroid function.[15]

The Thyroid Feedback Quantile-based Index (TFQI), proposed by Martin Laclaustra et al in 2019, is a novel indicator designed to evaluate the sensitivity of the hypothalamic-pituitary-thyroid (HPT) axis feedback. One of the main advantages of TFQI is its robustness against extreme values. Its clinical relevance has been validated using data from the NHANES cohort, demonstrating significant associations with diabetes, obesity, and other components of metabolic syndrome.[15] In terms of clinical aspects, Two cross-sectional studies suggested that TFQI-FT3 and FT3/FT4 ratios could serve as novel predictors of NAFLD/MAFLD. However, evidence supporting the role of TFQI-FT4 in predicting NAFLD is insufficient.[14,20] Another study concluded that TFQI-FT4, TFQI-FT3, TSH index (TSHI), and thyrotropin-stimulating hormone-T4 resistance index (TT4RI) are potential predictors of MAFLD but did not include the thyroid hormone peripheral sensitivity index.[21] In a study involving patients with a primary diagnosis of T2DM, the prevalence of MAFLD increased with higher values of TFQI-FT3, thyrotropin triiodothyronine resistance index (TT3RI), TT4RI, and FT3/FT4. However, these correlations were insignificant after adjusting for body mass index (BMI) and the homeostatic model assessment for insulin resistance (HOMA-IR).[16] The results of these studies are controversial, and there are limited studies in both T2DM and non-diabetic populations. In addition, although previous studies have reported associations between body mass index (BMI), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum lipid profiles, and uric acid (UA) levels with the risk of nonalcoholic fatty liver disease (NAFLD),[22–26] the interplay between these metabolic indicators, thyroid hormone sensitivity, and NAFLD has not yet been fully elucidated.

Therefore, this study aimed to separately analyze patients with type 2 diabetes mellitus (T2DM) and non-diabetic (non-DM) individuals, using a more comprehensive set of thyroid hormone sensitivity indices along with metabolic biomarkers. We explored the associations between both central and peripheral thyroid hormone sensitivity and the presence of NAFLD, highlighting their commonalities and distinctions across metabolic backgrounds. This research provides novel clinical evidence on the relationship between thyroid hormone sensitivity and NAFLD and helps to fill the gap in current studies involving both T2DM and non-DM populations.

Materials and Methods

Participants and Study Design

Between October 2022 and October 2023, the study recruited a total of 460 individuals from The Second Affiliated Hospital of Harbin Medical University, among which229 were patients with T2DM. Inclusion criteria included T2DM diagnosis based on the 2020 edition of the Chinese T2DM Prevention and Treatment Guidelines[27] and normal thyroid hormone levels. Exclusion criteria included a history of alcohol over-consumption (defined as not less than 210 g of ethanol per week for men and 140 g per week for women within the past 12 months); other diseases causing fatty liver, such as autoimmune and viral liver diseases; a history of liver and gallbladder surgery; presence of endocrine system disorders, such as acute complications of diabetes, hypothalamic and pituitary disorders, thyroid disease history, or previous thyroid surgery; use of drugs that affect thyroid metabolism, such as amiodarone and corticosteroids; infectious diseases, immunological diseases, malignant tumors, and blood system diseases; pregnancy or breastfeeding; age < 18 years; incomplete medical records. For the remaining 231 non-DM patients, the inclusion criteria included normal thyroid function, normal blood glucose and glycated hemoglobin levels, and no history of diabetes, and the exclusion criteria were the same as those for patients with T2DM. The Ethics Committee of The Second Affiliated Hospital of Harbin Medical University approved the study (approval number: YJSKY2023-371). Informed consent was obtained from all participants, as required by the ethics committee.

Data Collection

In our hospital, patients' age, sex, T2DM duration, height, and weight obtained by specialized nurses. Fasting blood samples were collected from all patients for analysis of serum levels of FT3, FT4, TSH, thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (TPOAb) d using chemiluminescence. A fully automated biochemical analyzer was used to measure alanine aminotransferase (ALT), aspartate transaminase (AST), glutamyl transpeptidase (GGT), glycosylated hemoglobin (HbA1c), albumin, uric acid (UA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), and fasting C-peptide (FCP) levels. Liver ultrasonography was also performed by an experienced sonographer after patients fasted for at least 8 hours as part of the routine examination. All data were retrieved retrospectively from medical and laboratory records.

Data Definitions and Calculation Formulas

Thyroid Hormone Sensitivity

Indices used to evaluate central thyroid hormone sensitivity include the Thyroid Feedback Quantile-based Index (TFQI), with values ranging from –1 to +1. A TFQI value closer to –1 indicates higher sensitivity and a strong feedback response, whereas a value closer to +1 reflects reduced sensitivity and impaired feedback regulation, A value of 0 indicates normal sensitivity.[15] In euthyroid individuals, additional indices reflecting the FT4–TSH feedback relationship include the Thyroid-Stimulating Hormone Index (TSHI)[18] and the Thyrotroph T4 Resistance Index (TT4RI).[19] By substituting FT3 for FT4 in the TFQI-FT4 formula, the TFQI-FT3 can be calculated, and a similar approach is used to derive the Thyrotroph T3 Resistance Index (TT3RI).[14] Peripheral thyroid hormone sensitivity is assessed using the FT3/FT4 ratio. The specific calculation formulas are as follows:

$$\mathrm{TFQI} - \mathrm{FT4} = \mathrm{cdfFT4} - (1 - \mathrm{cdf\ TSH})$$

$$\mathrm{TFQI} - \mathrm{FT3} = \mathrm{cdfFT3} - (1 - \mathrm{cdfTSH})$$

$$\mathrm{TSHI} = \ln\mathrm{TSH}\ (\mathrm{mIU/L}) + 0.1345 * \mathrm{FT4}\ (\mathrm{pmol/L})$$

$$\mathrm{TT4RI} = \mathrm{FT4}\ (\mathrm{pmol/L}) * \mathrm{TSH}\ (\mathrm{mIU/L})$$

$$\mathrm{TT3RI} = \mathrm{FT3}\ (\mathrm{pmol/L}) * \mathrm{TSH}\ (\mathrm{mIU/L})$$

$$\mathrm{FT3/FT4} = \mathrm{FT3}\ (\mathrm{pmol/L}) / \mathrm{FT4}\ (\mathrm{pmol/L})$$

The term cdf refers to the empirical cumulative distribution function of hormone concentrations, representing the percentile rank of a given hormone level within the overall sample.

TSHI is defined as the maximum theoretical TSH level, assuming no pituitary feedback inhibition when the FT4 value is zero. Higher TSHI, TT4RI, and TT3RI values indicate decreased central sensitivity to thyroid hormones, whereas a higher FT3/FT4 ratio indicates increased peripheral sensitivity.

Non-Invasive Fibrosis Scores

NAFLD fibrosis score (NFS), fibrosis-4 index (FIB-4),[28] and aspartate aminotransferase-to-platelet ratiometric index (APRI)[29] were calculated using the following formulas:

NFS = $-1.675 + 0.037 \times$ age (year) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glucose/DM (yes = 1, no = 0) + $0.99 \times$ AST/ALT $- 0.013\times$ platelet count ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dL)

FIB-4 = [age (years) × AST (U/L)]/{platelet count ($\times 10^9$/L) × [ALT (U/L)1/2]}

APRI = [(AST/upper limit of normal)/platelet count ($\times 10^9$/L)] × 100

NFS > 0.676, FIB-4 > 2.67, and APRI > 1.5 indicate a risk of advanced liver fibrosis.

Otherwise

Reference ranges for thyroid parameters: FT3 (2.43–6.01 pmol/L), FT4 (9.01–19.5 pmol/L), TSH (0.35–4.94 μIU/mL), TgAb (0–4.11 IU/mL), and TPOAb (0–4.11 IU/mL). Normal thyroid function was defined as FT3, FT4, TSH, TPOAb, and TgAb levels above the lower limit of the assay and below its upper limit. The ultrasound manifestations of NAFLD included blurred intrahepatic bile duct structures, diffuse enhancement of hepatic near-field echoes, and gradual attenuation of far-field echoes.

BMI = weight (kg)/height (m^2).

HOMA-IR = FPG (mmol/L) × fasting insulin (FINS, μIU/mL)/22.5.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). The Kolmogorov–Smirnov test was used to assess the normality of the data. Continuous normally distributed variables are presented as mean ± standard deviation. Intergroup comparisons were made using a *t*-test. Medians (interquartile ranges) were calculated for continuous variables with skewed distributions, and the rank-sum test was applied to compare groups. Categorical variables are presented as percentages (%), and intergroup comparisons were made using the chi-squared test. Binary logistic regression was used to analyze the relationship between the thyroid hormone sensitivity index and NAFLD. Post hoc power analysis was performed using R software to assess the robustness of the logistic regression results obtained in this study. We controlled for patient sex, age, and duration of T2DM in Model 1, then adjusted for T2DM in Model 2, and adjusted for metabolic factors, including FPG, HbA1c, TC, TG, HDL-C, LDL-C, and UA levels in Model 3. Participants were then separated into the T2DM and non-DM groups, and binary logistic regression was used to analyze the relationship between the thyroid hormone sensitivity index and NAFLD in both groups. In the T2DM group, Model 1 was adjusted for sex, age, T2DM duration, and metabolic factors, including FPG, HbA1c, HOMA-IR, TC, TG, HDL-C, LDL-C, and UA levels, and further adjusted for BMI in Model 2. In the non-DM group, Model 1 was adjusted for sex, age, and FPG, TC, TG, HDL-C, LDL-C, and UA levels, and Model 2 was further adjusted for BMI. We examined the participants' receiver operating characteristic curves (ROCs), plotted the sensitivity against 1-specificity, and calculated the critical values based on the results. Finally, Spearman's rank correlation analysis was used to explore correlations between thyroid parameters and non-invasive fibrosis scores. Data are expressed as two-sided p-values. Statistical significance was set at $p < 0.05$. GraphPad Prism 8.0.2 software was used to create graphics.

Results

Clinical Characteristics of Participants

Among 460 participants, 251 (54.6%) were diagnosed with NAFLD, while 209 (45.4%) were not. The percentage of male participants and BMI, HbA1c, FPG, FINS, FCP, HOMA-IR, ALT, AST, GGT, FT3, FT4, TC, TG, LDL-C, UA, TSHI, TT4RI, TT3RI, and FT3/FT4 levels were higher in NAFLD group than non-NAFLD group, whereas HDL-C, TFQI-FT4 and TFQI-FT3 values were lower in the NAFLD group ($p < 0.05$) (Table 1).

Correlation Between Thyroid Hormone Sensitivity and NAFLD

Thyroid hormone sensitivity indices were divided into quartiles (Q1–Q4), and logistic regression analyses were performed. In Model 1, adjusted for age, sex, and duration of T2DM, higher quartiles of TFQI-FT4 (Q4 vs Q1: OR = 2.345, 95% CI: 1.358–4.051, p = 0.002), TFQI-FT3 (OR = 3.271, 95% CI: 1.841–5.812, $p < 0.001$), TSHI (OR = 2.266, 95% CI: 1.248–4.114, p = 0.007), TT4RI (OR = 1.863, 95% CI: 1.056–3.287, p = 0.032), and TT3RI (OR = 2.130, 95% CI: 1.222–3.715, p = 0.008) were all significantly associated with an increased risk of NAFLD. In contrast, the FT3/FT4

Table 1 Characteristics of the Study Population According to NAFLD Status

	All	**Non-NAFLD**	**NAFLD**	**P**
Number (%)	460	209 (45.4)	251 (54.6)	
Clinical Info				
T2DM (%)	229	97 (42.4)	132 (57.6)	0.187
Sex				**< 0.001**
Male	247 (53.7)	90 (36.4)	157 (63.6)	
Female	213 (46.3)	119 (55.9)	94 (44.1)	
Age (years)	52.00 (40.00, 59.00)	55.00 (47.25, 61.00)	48.00 (38.00, 57.00)	0.645
Duration of T2DM (years)	5.00 (2.00, 10.00)	8.00 (3.00, 13.00)	4.00 (1.00, 9.00)	0.864
BMI (kg/m^2)	25.05 (22.13, 29.00)	22.10 (20.59, 23.67)	27.85 (25.27, 30.79)	**< 0.001**
Laboratory parameters				
HbA1c (%)	8.10 (7.00, 9.35)	7.40 (6.73, 9.00)	8.5 (7.33, 9.50)	**0.016**
FPG (mmol/L)	7.14 (6.03, 8.28)	6.81 (5.85, 8.30)	7.36 (6.17, 8.30)	**< 0.001**
FINS	16.30 (11.50, 22.23)	13.65 (9.65, 19.10)	17.55 (12.30, 25.10)	**< 0.001**
FCP	1.30 (0.99, 2.21)	1.10 (0.79, 1.41)	1.81 (1.10, 2.61)	**< 0.001**
HOMA-IR	5.25 (3.34, 7.36)	4.63 (2.49, 6.81)	6.05 (4.08, 8.35)	**< 0.001**
ALB (g/L)	46.58±3.14	46.48±3.05	46.66±3.22	0.522
ALT (U/L)	20.00 (14.00, 33.75)	17.00 (12.25, 20.75)	27.00 (17.00, 54.75)	**< 0.001**
AST (U/L)	19.00 (15.00, 24.00)	16.00 (14.25, 19.00)	22.00 (16.00, 35.5)	**< 0.001**
GGT (U/L)	27.00 (17.00, 46.75)	17.00 (13.00, 23.75)	40.00 (26.25, 64.00)	**<0.001**
TC (mmol/L)	4.86±0.98	4.64±0.88	5.04±1.03	**<0.001**
TG (mmol/L)	1.64 (1.10, 2.85)	1.24 (0.94, 1.63)	2.40 (1.42, 3.91)	**<0.001**
HDL-C (mmol/L)	1.09 (0.92, 1.29)	1.21 (1.03, 1.35)	1.02 (0.87, 1.19)	**<0.001**
LDL-C (mmol/L)	3.04±0.89	2.92±0.82	3.13±0.93	**0.012**
UA (μmol/L)	322.00 (270.00, 374.75)	297.00 (268.00, 331.75)	348.00 (270.33, 416.60)	**<0.001**
Thyroid parameters				
FT3 (pmol/L)	4.72±0.68	4.49±0.58	4.90±0.70	**<0.001**
FT4 (pmol/L)	16.80 (15.09, 18.91)	15.78 (14.51, 17.28)	17.66 (15.93, 19.59)	**0.005**
TSH (μIU/mL)	1.99 (1.43, 2.75)	1.93 (1.36, 2.69)	2.03 (1.45, 2.81)	0.205
TFQI-FT4	–0.029±0.39	–0.088±0.38	0.020±0.39	**0.003**
TFQI-FT3	–0.004±0.41	–0.107±0.38	0.082±0.41	**<0.001**
TSHI	3.01 (2.53, 3.30)	2.80 (2.41, 3.13)	3.08 (2.69, 3.45)	**0.007**
TT4RI	33.54(24.27, 44.91)	30.00 (22.00, 42.08)	37.27 (25.91, 47.80)	**0.031**
TT3RI	10.21 (6.83, 13.81)	9.17 (6.51, 12.85)	11.00 (7.70, 14.39)	**0.003**
FT3/FT4	0.32±0.05	0.31±0.05	0.32±0.05	**0.022**

Notes: The bold values indicate statistically significant differences when compared with the non-NAFLD group ($p < 0.05$). Data are presented as means ± standard deviations or medians (interquartile ranges) for continuous variables, and numbers (proportions) for categorical variables. P values are calculated by *t*-test and Mann–Whitney tests for continuous variables, Chi-square tests for categorical variables.

Abbreviations: T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; FINS, fasting insulin; FCP, fasting C-Peptide; HOMA-IR, homeostasis model assessment of insulin resistance; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; UA, uric acid; PLT, platelet count; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TFQI-FT4, the thyroid feedback quantile-based index calculated by FT4; TFQI-FT3, the thyroid feedback quantile-based index calculated by FT3; TSHI, TSH index; TT4RI, thyrotropin T4 resistance index; TT3RI, thyrotropin T3 resistance index; FT3/FT4, FT3 to FT4 ratio.

ratio showed no significant association (OR = 1.481, 95% CI: 0.849–2.583, $p > 0.05$). In Model 2, which further adjusted for T2DM status, TFQI-FT4 (OR = 2.286, 95% CI: 1.319–3.963, $p = 0.003$) and TFQI-FT3 (OR = 3.148, 95% CI: 1.763–5.619, $p < 0.001$) remained significantly associated with NAFLD. However, the associations for TSHI and TT4RI were no longer statistically significant (TSHI: OR = 1.896, 95% CI: 0.984–3.652, $p > 0.05$; TT4RI: OR = 1.528, 95% CI: 0.837–2.791, $p > 0.05$). Interestingly, the FT3/FT4 ratio became positively associated with NAFLD (Q4 vs Q1: OR = 1.823, 95% CI: 1.021–3.257, $p = 0.042$). In Model 3, with additional adjustments for FPG, HbA1c, TC, TG, HDL-C, LDL-C, and UA, only TFQI-FT4 (OR = 3.290, 95% CI: 1.390–7.787, $p = 0.007$) and TFQI-FT3 (OR = 2.344, 95% CI: 1.010–5.439, $p = 0.047$) remained significantly associated with NAFLD. The associations for TSHI, TT4RI, TT3RI, and

FT3/FT4 ratio were no longer statistically significant (see Table 2). To further visualize the relationship between thyroid hormone sensitivity indices and NAFLD, scatter plots with fitted trend lines were generated (Figure 1). TFQI-FT3 and TFQI-FT4 showed a clear positive correlation with NAFLD, providing additional support for the findings from the regression analysis.

In the T2DM group, thyroid hormone sensitivity indices were categorized into quartiles. In Model 1, which was adjusted for age, sex, duration of T2DM, FPG, HbA1c, HOMA-IR, TC, TG, HDL-C, LDL-C, and UA, the highest quartile (Q4) compared to the lowest (Q1) showed significant positive associations with NAFLD for TFQI-FT4 (OR = 5.495, 95% CI: 1.986–15.206, p = 0.001), TFQI-FT3 (OR = 4.001, 95% CI: 1.496–10.697, p = 0.006), TSHI (OR = 2.623, 95% CI: 1.028–6.697, p = 0.044), TT4RI (OR = 5.466, 95% CI: 1.992–14.999, p < 0.001), and TT3RI (OR = 4.088, 95% CI: 1.547–10.802, p = 0.005). However, the FT3/FT4 ratio was not significantly associated with NAFLD in Model 1 (OR = 0.945, 95% CI: 0.364–2.457, p > 0.05). After further adjusting for BMI in Model 2, the associations for all five indices were no longer statistically significant (p > 0.05), suggesting that BMI may act as a mediator or confounder in these relationships. Notably, although the comparison of Q4 vs Q1 for the FT3/FT4 ratio did not reach statistical significance (OR = 0.402, 95% CI: 0.100–1.614, p = 0.199), the comparison of Q3 vs Q1 revealed a significant protective association (OR = 0.221, 95% CI: 0.053–0.921, p = 0.038), indicating a potential risk-reducing effect at moderate FT3/FT4 levels (see Table 3).

Table 2 Correlation of Thyroid Hormone Sensitivity Quartiles and NAFLD in Binary Logistic Regression Analysis

Index	**Model 1**		**Model 2**		**Model 3**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
TFQI-FT4						
Q2 vs Q1	1.802(1.053–3.085)	**0.032**	1.780(1.037–3.055)	**0.036**	2.260(0.991–5.155)	0.053
Q3 vs Q1	1.436 (0.883–2.461)	0.188	1.433(0.834–2.463)	0.193	1.243(0.531–2.906)	0.616
Q4 vs Q1	2.345(1.358–4.051)	**0.002**	2.286(1.319–3.963)	**0.003**	3.290(1.390–7.787)	**0.007**
TFQI-FT3						
Q2 vs Q1	0.940(0.551–1.604)	0.822	0.906(0.529–1.554)	0.721	0.861(0.380–1.954)	0.720
Q3 vs Q1	1.435 (0.837–2.459)	0.189	1.386(0.806–2.386)	0.238	0.976(0.445–2.138)	0.951
Q4 vs Q1	3.271(1.841–5.812)	**<0.001**	3.148(1.763–5.619)	**<0.001**	2.344(1.010–5.439)	**0.047**
TSHI						
Q2 vs Q1	0.731(0.426–1.253)	0.254	0.707(0.411–1.215)	0.209	0.719(0.269–1.923)	0.511
Q3 vs Q1	1.038(0.603–1.789)	0.892	0.919(0.517–1.633)	0.773	0.697(0.266–1.825)	0.463
Q4 vs Q1	2.266(1.248–4.114)	**0.007**	1.896(0.984–3.652)	0.056	1.255(0.465–3.385)	0.654
TT4RI						
Q2 vs Q1	0.802(0.470–1.369)	0.419	0.770(0.450–1.318)	0.341	0.530(0.211–1.330)	0.176
Q3 vs Q1	0.934(0.544–1.603)	0.804	0.796(0.452–1.399)	0.428	0.558(0.226–1.374)	0.204
Q4 vs Q1	1.863(1.056–3.287)	**0.032**	1.528(0.837–2.791)	0.168	0.916(0.366–2.293)	0.851
TT3RI						
Q2 vs Q1	0.810 (0.475–1.383)	0.441	0.800 (0.468–1.367)	0.414	0.904(0.379–2.158)	0.820
Q3 vs Q1	1.524(0.888–2.617)	0.126	1.415(0.817–2.452)	0.215	0.920(0.383–2.207)	0.851
Q4 vs Q1	2.130(1.222–3.715)	**0.008**	1.870(1.047–3.342)	**0.035**	1.323(0.571–3.065)	0.514
FT3/FT4						
Q2 vs Q1	0.867 (0.510–1.474)	0.598	0.952 (0.553–1.637)	0.858	0.957(0.442–2.074)	0.912
Q3 vs Q1	1.035 (0.605–1.770)	0.901	1.220(0.701–2.124)	0.482	0.653(0.283–1.507)	0.318
Q4 vs Q1	1.481(0.849–2.583)	0.167	1.823(1.021–3.257)	**0.042**	1.329(0.537–3.288)	0.538

Notes: Bold values indicate statistically significant differences ($p < 0.05$). Model 1 adjusted for age, sex, and T2DM duration; Model 2 adjusted for Model 1 covariates and T2DM; Model 3 adjusted for Model 2 covariates and fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA).

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TFQI-FT4, the thyroid feedback quantile-based index calculated by FT4; TFQI-FT3, the thyroid feedback quantile-based index calculated by FT3; TSHI, TSH index; TT4RI, thyrotropin T4 resistance index; TT3RI, thyrotropin T3 resistance index; FT3/FT4, FT3 to FT4 ratio.

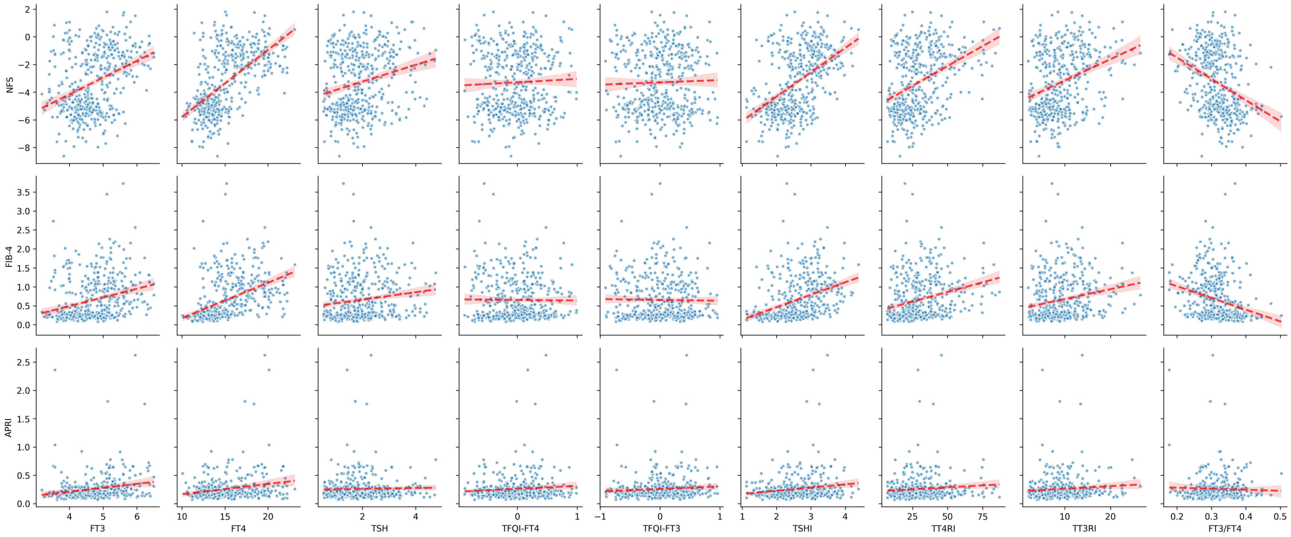

Figure 1 Associations between thyroid hormone sensitivity indices and liver fibrosis scores. Scatter plots show the relationships between various thyroid function parameters (x-axes: FT3, FT4, TSH, TFQI-FT4, TFQI-FT3, TSHI, TT4RI, TT3RI, and FT3/FT4 ratio) and three liver fibrosis surrogate scores (y-axes: NFS, FIB-4, and APRI). Each subplot displays individual participant data points (blue dots) with overlaid linear regression lines (red dashed lines) and 95% confidence intervals (red shaded areas).

In the non-diabetic group, Model 1 (adjusted for age, sex, FPG, TC, TG, HDL-C, LDL-C, and UA) showed a significant positive association between TFQI–FT3 and NAFLD (Q4 vs Q1: OR = 3.138, 95% CI: 1.246–7.900, p = 0.015). However, after further adjustment for BMI in Model 2, this association was attenuated and no longer statistically significant (Q4 vs Q1: OR = 2.560, 95% CI: 0.799–8.207, p = 0.114).

Table 3 Correlation of Thyroid Hormone Sensitivity Quartiles and NAFLD in Binary Logistic Regression Analysis in Patients with T2DM

Index	**Model 1**		**Model 2**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
TFQI-FT4				
Q2 vs Q1	2.077 (0.814–5.300)	0.126	1.708 (0.506–5.764)	0.389
Q3 vs Q1	1.212 (0.440–3.335)	0.710	1.277 (0.335–4.868)	0.721
Q4 vs Q1	5.495 (1.986–15.206)	**0.001**	3.072 (0.808–11.675)	0.099
TFQI-FT3				
Q2 vs Q1	1.426 (0.562–3.621)	0.455	0.958 (0.280–3.283)	0.946
Q3 vs Q1	1.147 (0.444–2.962)	0.777	0.642 (0.190–2.170)	0.475
Q4 vs Q1	4.001 (1.496–10.697)	**0.006**	1.247 (0.392–4.726)	0.745
TSHI				
Q2 vs Q1	0.914 (0.365–2.286)	0.847	0.639 (0.185–2.201)	0.477
Q3 vs Q1	1.081 (0.407–2.873)	0.876	1.047 (0.284–3.856)	0.945
Q4 vs Q1	2.623 (1.028–6.697)	**0.044**	1.353 (0.381–4.806)	0.640
TT4RI				
Q2 vs Q1	2.092 (0.828–5.288)	0.119	0.717 (0.207–2.481)	0.600
Q3 vs Q1	1.294 (0.477–3.505)	0.613	0.680 (0.196–2.360)	0.544
Q4 vs Q1	5.466 (1.992–14.999)	**<0.001**	0.712 (0.207–2.448)	0.589
TT3RI				
Q2 vs Q1	1.483 (0.588–3.741)	0.403	0.464 (0.132–1.627)	0.230
Q3 vs Q1	1.174 (0.457–3.017)	0.739	0.374 (0.099–1.410)	0.146
Q4 vs Q1	4.088 (1.547–10.802)	**0.005**	0.294 (0.076–1.140)	0.077

(*Continued*)

Table 3 (Continued).

Index	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
FT3/FT4				
Q2 vs Q1	1.083 (0.423–2.773)	0.868	0.646 (0.185–2.259)	0.494
Q3 vs Q1	0.652 (0.257–1.654)	0.368	0.221 (0.053–0.921)	**0.038**
Q4 vs Q1	0.945 (0.364–2.457)	0.908	0.402 (0.100–1.614)	0.199

Notes: Bold values indicate statistically significant associations ($p < 0.05$). Model 1 controlled for age, sex, type 2 diabetes mellitus (T2DM) disease course, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), uric acid (UA), and lipids including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C); Model 2 further controlled for body mass index (BMI).
Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TFQI-FT4, the thyroid feedback quantile-based index calculated by FT4; TFQI-FT3, the thyroid feedback quantile-based index calculated by FT3; TSHI, TSH index; TT4RI, thyrotropin T4 resistance index; TT3RI, thyrotropin T3 resistance index; FT3/FT4, FT3 to FT4 ratio.

Table 4 Correlation of Thyroid Hormone Sensitivity Quartiles with NAFLD in Binary Logistic Regression Analysis in Non-Diabetics

Index	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
TFQI–FT3				
Q2 vs Q1	1.052 (0.439–2.524)	0.909	0.852 (0.281–2.588)	0.778
Q3 vs Q1	1.032 (0.420–2.536)	0.945	0.544 (0.173–1.711)	0.298
Q4 vs Q1	3.138 (1.246–7.900)	**0.015**	2.560 (0.799–8.207)	0.114
FT3/FT4				
Q2 vs Q1	1.919 (0.805–4.574)	0.142	1.661 (0.477–5.785)	0.426
Q3 vs Q1	2.911 (1.208–7.407)	**0.018**	3.854 (1.119–13.277)	**0.033**
Q4 vs Q1	2.850 (1.147–7.077)	**0.024**	3.390 (1.003–11.463)	**0.049**

Notes: Bold values indicate statistically significant associations ($p < 0.05$). Model 1 controlled for age, sex, fasting plasma glucose (FPG), uric acid (UA), and lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C); Model 2 was further adjusted for body mass index (BMI). Bold: $p<0.05$.

In contrast, the FT3/FT4 ratio was significantly and positively associated with NAFLD in Model 1 (Q4 vs Q1: OR = 2.850, 95% CI: 1.147–7.077, $p = 0.024$), and this association remained significant after additional adjustment for BMI in Model 2 (Q4 vs Q1: OR = 3.390, 95% CI: 1.003–11.463, $p = 0.049$), suggesting that a higher FT3/FT4 ratio may be an independent risk factor for NAFLD (see Table 4).

Relationship Between Thyroid Hormone Sensitivity Indices and NAFLD Prevalence

The prevalence of NAFLD in the T2DM group increased with higher quartile subgroups of TFQI-FT4, TFQI-FT3, and TSHI ($p < 0.05$). In the non-DM group, the prevalence of NAFLD increased with the quartile subgroups of TFQI-FT3 and FT3/FT4 ratio ($p < 0.05$) (Figure 2).

Prediction of NAFLD Using the Thyroid Hormone Sensitivity Index

As illustrated in Figure 3A, the receiver operating characteristics (ROC) analysis for the T2DM group indicated that TFQI-FT4, TFQI-FT3, and TSHI values could serve as predictors of NAFLD (all $p < 0.001$), with areas under the curves (AUCs) of 0.669, 0.665, and 0.635, respectively. The optimal thresholds for these predictors were 0.069, 0.129, and 3.122, respectively. As shown in Figure 3B, the ROC analysis for the non-DM group indicated that the AUC of FT3/FT4 for predicting NAFLD was 0.663 ($p<0.001$), with an optimal threshold of 0.318 (Supplementary Table 1).

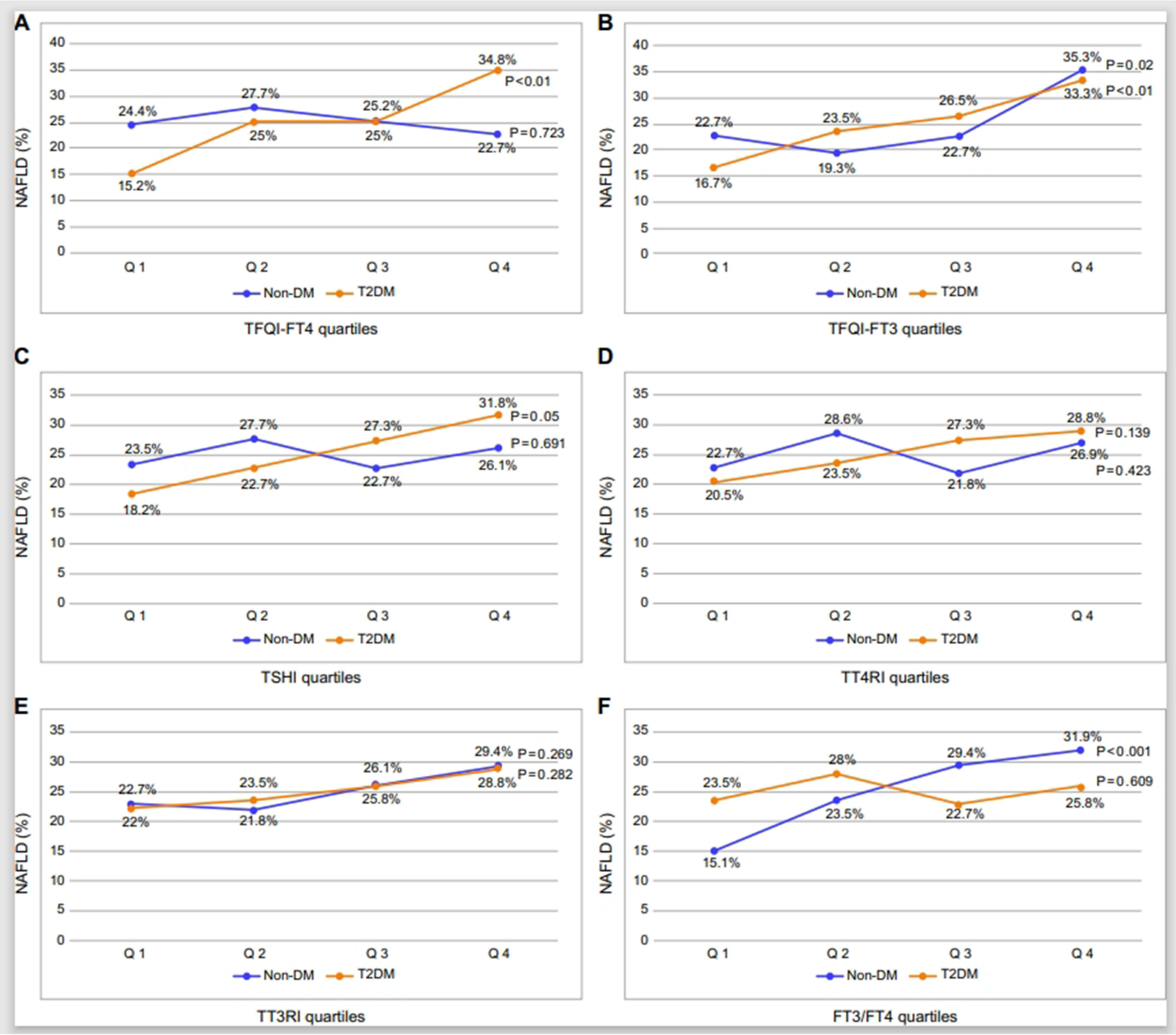

Figure 2 (**A**) the thyroid feedback quantile-based index calculated by free thyroxine (TFQI-FT4), (**B**) the thyroid feedback quantile-based index calculated by free triiodothyronine (TFQI-FT3), (**C**) thyroid-stimulating hormone index (TSHI), (**D**) thyrotropin T4 resistance index (TT4RI), (**E**) thyrotropin T3 resistance index (TT3RI), (**F**) FT3 to FT4 ratio (FT3/FT4).

Relationship Between Thyroid Parameters and the Risk of Advanced Liver Fibrosis

Patients with NAFLD and T2DM (NFS, 6.8%; FIB-4, 2.3%; and APRI, 3.0%) had significantly higher odds of developing advanced liver fibrosis than the non-DM patients (0) (Supplementary Figure 1). In the T2DM group, elevated FT3 levels (r = 0.182, p = 0.006) were positively correlated with increased APRI staging, while elevated FT4 levels (r = –0.147, p = 0.027) were negatively correlated with increased FIB-4 staging (Supplementary Table 2).

A post hoc power analysis was conducted to evaluate whether the current sample size was sufficient to detect statistically significant associations observed in the logistic regression models. For instance, in the Q4 vs Q1 comparison, Model 3 demonstrated a significant positive association between TFQI-FT4 and NAFLD (OR = 3.290, 95% CI: 1.390–7.787, p = 0.007), as well as between TFQI-FT3 and NAFLD (OR = 2.344, 95% CI: 1.010–5.439, p = 0.047), both with a statistical power of 1.000. Additionally, among individuals with T2DM, a higher FT3/FT4 ratio (Q3 vs Q1) was significantly associated with a lower risk of NAFLD (Model 2: OR = 0.221, 95% CI: 0.053–0.921, p = 0.038), with a corresponding power of 0.999. In the non-diabetic population, a higher FT3/FT4 ratio (Q4 vs Q1) was positively associated with NAFLD (Model 2: OR = 3.390, 95% CI: 1.003–11.463, p = 0.049), with a power of 1.000. Taken

https://doi.org/10.2147/DMSO.S538911

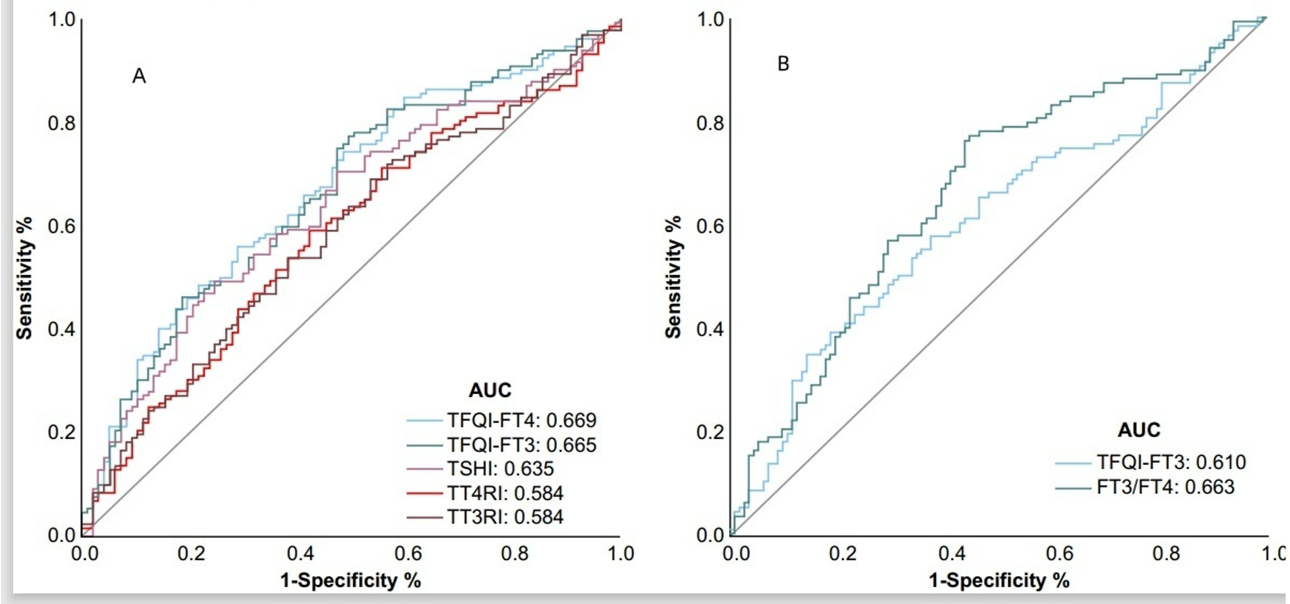

Figure 3 (**A**) Receiver operating characteristic curve (ROC) of the thyroid feedback quantile-based index calculated by free thyroxine (TFQI-FT4), the thyroid feedback quantile-based index calculated by free triiodothyronine (TFQI-FT3), thyroid-stimulating hormone index (TSHI), thyrotropin T4 resistance index (TT4RI), thyrotropin T3 resistance index (TT3RI) and non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM). (**B**) ROC of TFQI-FT3, FT3/FT4 and NAFLD in patients without diabetes mellitus.

together, these findings indicate that the study has sufficient statistical power to detect the key associations examined, supporting the robustness and reliability of the results.

Discussion

Our study demonstrated that reduced central sensitivity to thyroid hormones promotes the development of NAFLD in adults with normal thyroid function. In contrast, the relationship between peripheral thyroid hormone sensitivity and NAFLD appears to be influenced by the presence of T2DM. In our logistic regression analysis, the FT3/FT4 ratio was not associated with NAFLD in Model 1. However, a positive association was observed after adjusting for T2DM as a confounder in Model 2. After participants were categorized into T2DM and non-DM groups, further analysis indicated that decreased central thyroid hormone sensitivity is a contributing factor to NAFLD in the T2DM population, while elevated peripheral thyroid hormone sensitivity serves as a protective factor against NAFLD development. After correcting for BMI, the correlation between all central thyroid hormone sensitivity indices and NAFLD disappeared. In contrast, higher peripheral thyroid hormone sensitivity indices (FT3/FT4) were independently associated with NAFLD. In the non-DM group, the central thyroid hormone sensitivity index related to NAFLD was TFQI-FT3; however, this relationship was lost after adjusting for BMI. In contrast, higher FT3/FT4 ratio was associated with an increased risk of developing NAFLD, even after correcting for BMI.

Several studies indicated that fluctuations in thyroid hormone levels within the normal range may be associated with T2DM, NAFLD, and liver fibrosis.[30,31] The mechanisms underlying the association between thyroid hormones and NAFLD are likely related to factors such as systemic chronic inflammation, oxidative stress, and insulin resistance (IR).[32,33] Thyroid hormone levels in the body can induce insulin resistance by regulating the expression of glucose transporter 2 (GLUT2) and affecting hepatic gluconeogenesis and glycogenolysis.[34] Regarding chronic inflammation and oxidative stress, an animal study demonstrated that levels of carbonyls (a marker of protein oxidation) and TBARS (thiobarbituric acid reactive substances, indicating lipid peroxidation) were significantly elevated in MASLD model mice, suggesting a pronounced state of oxidative stress. The study further indicated that thyroid hormones, particularly T3, are closely involved in regulating genes related to mitochondrial function and endoplasmic reticulum (ER) stress. Dysregulation in this context is not only associated with impaired hepatic mitochondrial function and increased ER stress, but may also play a key role in the progression of hepatic fibrosis in MASLD, thereby contributing to the disease's onset and development.[35]

Notably, in studies on insulin resistance, there is growing evidence of a bidirectional interaction between oxidative stress and insulin resistance. The accumulation of reactive oxygen species (ROS) can trigger inflammatory responses by inducing mitochondrial stress, thereby exacerbating insulin resistance[36] Conversely, insulin resistance can activate NADPH oxidase, leading to excessive ROS production and further amplifying oxidative stress.[37,38] Furthermore, these metabolic disruptions may form a vicious cycle through a series of interrelated pathways: insulin resistance promotes ROS production and ER stress via NADPH oxidase; ROS and ER stress in turn disrupt thyroid hormone receptor expression and deiodinase activity, resulting in thyroid hormone (TH) resistance; TH resistance then impairs lipid metabolism, further aggravating insulin resistance. This complex interplay highlights the potential pathophysiological mechanisms underlying MASLD and provides biological support for the utility of thyroid hormone sensitivity indices (such as FTQI or the FT3/FT4 ratio) in predicting MASLD risk.

Some other studies revealed that the AMP-activated protein kinase (AMPK) pathway plays a role in IR and thyroid metabolism, and its activation leads to enhanced insulin sensitivity and a reduction in the expression of genes associated with steatosis and fibrosis in NAFLD.[39] Thyroid hormones also accelerate energy metabolism in the liver against ischemia-reperfusion injury by upregulating AMPK.[40] Huang et al suggested that IR and thyroid hormone resistance-like manifestations in the presence of normal thyroid function may be associated with the pathogenesis of NAFLD in patients with T2DM.[41] Thyroid hormone resistance may lead to an energy imbalance that promotes the development of both T2DM and NAFLD,[15] which may explain why reduced thyroid hormone sensitivity increases the risk of developing NAFLD.

The FT3/FT4 ratio may serve as an indicator of peripheral deiodinase activity, reflecting the peripheral sensitivity of thyroid hormones.[42] Panicker et al suggested that reduced activity of iodothyronine deiodinase type 1 could affect the conversion of circulating FT4 to FT3, which may contribute to oxidative stress and hepatocyte injury, even in participants with normal thyroid function.[43] Thyroid hormones are known to protect against diabetes by increasing energy expenditure, glucose metabolism, fatty acid oxidation, and lipolysis.[10,44,45] Evidence indicates a negative association between FT3/FT4 ratio and T2DM in individuals with normal thyroid function, potentially due to deiodinase-mediated regulation of the basal metabolic rate through thyroid hormone signaling.[46] The protective effects of thyroid hormones against T2DM may further contribute to the negative association between FT3/FT4 and the development of NAFLD in individuals with T2DM. Zhang et al observed no association between FT3/FT4 ratio and NAFLD in patients with new-onset T2DM and normal thyroid function,[16] which contrasts with our findings. This discrepancy may be attributed to the differences in the T2DM stages among the study populations, with varying degrees of glycemic abnormalities and metabolic disorders. The mechanism by which elevated peripheral thyroid hormone sensitivity increases the risk of developing NAFLD is unclear. However, some study results are consistent with the current study,[14,20,47] possibly because they did not include or included fewer patients with diabetes, making the results more comparable to the current study results with non-DM patients. While the current study provides initial findings on the protective effect of a higher FT3/FT4 ratio against NAFLD in patients with T2DM, further research is required to explore the underlying mechanisms involved.

Our findings suggest that individuals with T2DM and NAFLD have significantly higher odds of developing advanced hepatic fibrosis than the non-DM patients. In contrast, NAFLD is mostly asymptomatic, and accurately assessing fibrosis risk staging is critical for treatment. The NAFLD practice guidelines recommend prioritizing identification of individuals with advanced fibrosis in the structured pathway for recognizing patients at risk of NAFLD.[48] Thyroid hormones might initiate hepatic stellate cell activation and fibrosis, thereby accelerating the progression of liver fibrosis.[49] The results of current study indicated a positive correlation between elevated FT3 levels and the risk of advanced liver fibrosis, which is consistent with the findings of Chen et al[50] and contrary to those of Du et al.[51] Consistent with the findings of Bano et al[52] and Kim et al,[53] our results indicated a positive association between reduced FT4 levels and the risk of advanced liver fibrosis, and further indicated that higher TSH levels increased the risk of hepatic fibrosis in patients, although we did not observe this correlation in our study. These discrepancies are likely due to differences in population inclusion, study methodologies, or diagnostic criteria. Further prospective study is required to obtain more accurate and comprehensive results.

There are some limitations in our study. First, the sonographic diagnosis of hepatic steatosis without liver biopsy confirmation may pose challenges in differentiating between NASH and fibrosis, although we attempted to control for known confounders such as the use of metformin. Second, it is well known that microvascular and macrovascular complications, as well as the use of antidiabetic medications, may influence the prevalence of NAFLD. However, due to the retrospective design of this study, such data were not collected for further analysis. Third, this study was conducted among Chinese individuals recruited from a single medical center, which may limit the generalizability of our findings to other populations. Fourth, although we attempted to adjust for major metabolic confounders, the retrospective nature of the study and limited data availability prevented us from collecting detailed information on medication use (eg, hypoglycemic agents, lipid-lowering drugs, thyroid hormone replacement therapy). Therefore, potential residual confounding related to medication use cannot be ruled out and may have influenced our results. Fifth, the sample size of this study was not determined a priori. Although post hoc power analyses confirmed adequate statistical power for key findings, future multicenter prospective studies involving multi-ethnic populations are needed to further validate and generalize the association between thyroid hormone sensitivity and NAFLD.

Conclusion

In summary, thyroid hormone sensitivity is associated with NAFLD development in individuals with normal thyroid function. Associations between peripheral thyroid hormone sensitivity and NAFLD differed between individuals with T2DM and the non-DM patients, suggesting that the presence of T2DM may impact the relationship between peripheral thyroid hormone sensitivity and NAFLD.

Data Sharing Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Harbin Medical University (YJSKY2023-371).

Consent to Participate

Informed consent was obtained from all participants, as required by the ethics committee.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The work was not funded by any funding.

Disclosure

The authors declared that they have no conflicts of interest regarding this work.

References

1. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64(6):1388–1402. doi:10.1016/j.jhep.2015.11.004

2. Paul S, Davis AM. Diagnosis and management of nonalcoholic fatty liver disease. *JAMA*. 2018;320(23):2474–2475. doi:10.1001/jama.2018.17365
3. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol*. 2020;73(1):202–209. doi:10.1016/j.jhep.2020.03.039
4. Muzica CM, Sfarti C, Trifan A, et al. Nonalcoholic fatty liver disease and type 2 diabetes mellitus: a bidirectional relationship. *Can J Gastroenterol Hepatol*. 2020;2020:6638306. doi:10.1155/2020/6638306
5. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793–801. doi:10.1016/j.jhep.2019.06.021
6. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut*. 2021;70(5):962–969. doi:10.1136/gutjnl-2020-322572
7. Piantanida E, Ippolito S, Gallo D, et al. The interplay between thyroid and liver: implications for clinical practice. *J Endocrinol Invest*. 2020;43(7):885–899. doi:10.1007/s40618-020-01208-6
8. Marschner RA, Roginski AC, Ribeiro RT, Longo L, Álvares-da-Silva MR, Wajner SM. Uncovering actions of type 3 deiodinase in the metabolic dysfunction-associated fatty liver disease (MAFLD). *Cells*. 2023;12(7):1022. doi:10.3390/cells12071022
9. Marschner RA, Arenhardt F, Ribeiro RT, Wajner SM. Influence of altered thyroid hormone mechanisms in the progression of metabolic dysfunction associated with fatty liver disease (MAFLD): a systematic review. *Metabolites*. 2022;12(8):675. doi:10.3390/metabo12080675
10. Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. *Nat Rev Endocrinol*. 2018;14(5):259–269. doi:10.1038/nrendo.2018.10
11. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev*. 2019;40(3):789–824. doi:10.1210/er.2018-00163
12. Wu Z, Jiang Y, Li P, et al. Association of impaired sensitivity to thyroid hormones with hyperuricemia through obesity in the euthyroid population. *J Transl Med*. 2023;21(1):436. doi:10.1186/s12967-023-04276-3
13. Sun Y, Teng D, Zhao L, et al. Impaired sensitivity to thyroid hormones is associated with hyperuricemia, obesity, and cardiovascular disease risk in subjects with subclinical hypothyroidism. *Thyroid*. 2022;32(4):376–384. doi:10.1089/thy.2021.0500
14. Lai S, Li J, Wang Z, Wang W, Guan H. Sensitivity to thyroid hormone indices are closely associated with NAFLD. *Front Endocrinol*. 2021;12:766419. doi:10.3389/fendo.2021.766419
15. Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, et al. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. *Diabetes Care*. 2019;42(2):303–310. doi:10.2337/dc18-1410
16. Zhang X, Chen Y, Ye H, et al. Correlation between thyroid function, sensitivity to thyroid hormones and metabolic dysfunction-associated fatty liver disease in euthyroid subjects with newly diagnosed type 2 diabetes. *Endocrine*. 2023;80(2):366–379. doi:10.1007/s12020-022-03279-2
17. Ortiga-Carvalho TM, Sidhaye AR, Wondisford FE. Thyroid hormone receptors and resistance to thyroid hormone disorders. *Nat Rev Endocrinol*. 2014;10(10):582–591. doi:10.1038/nrendo.2014.143
18. Yagi H, Pohlenz J, Hayashi Y, Sakurai A, Refetoff S. Resistance to thyroid hormone caused by two mutant thyroid hormone receptors beta, R243Q and R243W, with marked impairment of function that cannot be explained by altered in vitro 3,5,3'-triiodothyroinine binding affinity. *J Clin Endocrinol Metab*. 1997;82(5):1608–1614. doi:10.1210/jcem.82.5.3945
19. Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH index. *Clin Endocrinol*. 2009;71(4):529–534. doi:10.1111/j.1365-2265.2009.03534.x
20. Liu H, Xing Y, Nie Q, Li Z, Meng C, Ma H. Association between sensitivity to thyroid hormones and metabolic dysfunction-associated fatty liver disease in euthyroid subjects: a cross-sectional study. *Diabetes Metab Syndr Obes*. 2023;16:2153–2163. doi:10.2147/DMSO.S420872
21. Zeng H, Liu H, Zhang Y. Relationship between impaired sensitivity to thyroid hormones and MAFLD with elevated liver enzymes in the euthyroid population. *Int J Diabetes Dev Ctries*. 2024;44(4):746–753. doi:10.1007/s13410-023-01308-y
22. Yu C, He S, Peng N, et al. The fasting plasma glucose to high-density lipoprotein cholesterol ratio: a novel index for identifying NAFLD. *BMC Gastroenterol*. 2025;25(1):236. doi:10.1186/s12876-025-03831-0
23. Xu J, Deng M, Weng Y, Feng H, He X. Cross-sectional study on the association between serum uric acid levels and non-alcoholic fatty liver disease in an elderly population. *Sci Rep*. 2025;15(1):5678. doi:10.1038/s41598-025-90590-3
24. Wu QY, Mo LR, Nan J, Huang WZ, Wu Q, Su Q. The association between the hemoglobin glycation index and cardiometabolic diseases: a mini-review. *J Clin Hypertens*. 2025;27(7):e70092. doi:10.1111/jch.70092
25. Cui Y, Li F, Li T, Sun W, Shi H, Cheng Y. A nomogram for predicting metabolic-associated fatty liver disease in non-obese newly diagnosed type 2 diabetes patients. *Front Endocrinol*. 2025;16:1521168. doi:10.3389/fendo.2025.1521168
26. Lan J, Que T, Lan H, Zhang M, Ban L. Development and validation of a nomogram-based risk prediction model for non-alcoholic fatty liver disease (NAFLD): a logistic regression analysis in a physical examination population. *BMC Gastroenterol*. 2025;25(1):532. doi:10.1186/s12876-025-04115-3
27. Zhu D. Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus. *Chin Med J*. 2021;37:668–695.
28. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. *Hepatology*. 2018;67(1):328–357. doi:10.1002/hep.29367
29. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518–526. doi:10.1053/jhep.2003.50346
30. Jun JE, Jee JH, Bae JC, et al. Association between changes in thyroid hormones and incident type 2 diabetes: a seven-year longitudinal study. *Thyroid*. 2017;27(1):29–38. doi:10.1089/thy.2016.0171
31. Zhang Y, Li J, Liu H. Correlation between the thyroid hormone levels and nonalcoholic fatty liver disease in type 2 diabetic patients with normal thyroid function. *BMC Endocr Disord*. 2022;22(1):144. doi:10.1186/s12902-022-01050-2
32. Lim S, Kim JW, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. *Trends Endocrinol Metab*. 2021;32(7):500–514. doi:10.1016/j.tem.2021.04.008
33. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep*. 2019;1(4):329–341. doi:10.1016/j.jhepr.2019.08.002
34. Brenta G. Why can insulin resistance be a natural consequence of thyroid dysfunction? *J Thyroid Res*. 2011;2011:152850. doi:10.4061/2011/152850

35. Longo L, Marschner RA, de Freitas LBR, et al. Redefining the role of ornithine aspartate and vitamin E in metabolic-dysfunction-associated steatotic liver disease through its biochemical properties. *Int J Mol Sci*. 2024;25(13):6839. doi:10.3390/ijms25136839
36. Al-Lahham R, Deford JH, Papaconstantinou J. Mitochondrial-generated ROS down regulates insulin signaling via activation of the p38MAPK stress response pathway. *Mol Cell Endocrinol*. 2016;419:1–11. doi:10.1016/j.mce.2015.09.013
37. Ziolkowska S, Binienda A, Jabłkowski M, Szemraj J, Czarny P. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. *Int J Mol Sci*. 2021;22(20):11128. doi:10.3390/ijms222011128
38. Vesković M, Šutulović N, Hrnčić D, Stanojlović O, Macut D, Mladenović D. The Interconnection between hepatic insulin resistance and metabolic dysfunction-associated steatotic liver disease-the transition from an adipocentric to liver-centric approach. *Curr Issues Mol Biol*. 2023;45 (11):9084–9102. doi:10.3390/cimb45110570
39. Garcia D, Hellberg K, Chaix A, et al. Genetic liver-specific AMPK activation protects against diet-induced obesity and NAFLD. *Cell Rep*. 2019;26 (1):192–208.e6. doi:10.1016/j.celrep.2018.12.036
40. Vargas R, Videla LA. Thyroid hormone suppresses ischemia-reperfusion-induced liver NLRP3 inflammasome activation: role of AMP-activated protein kinase. *Immunol Lett*. 2017;184:92–97. doi:10.1016/j.imlet.2017.01.007
41. Huang B, Yang S, Ye S. Association between thyroid function and nonalcoholic fatty liver disease in euthyroid type 2 diabetes patients. *J Diabetes Res*. 2020;2020:6538208. doi:10.1155/2020/6538208
42. Bilgin H, Pirgon Ö. Thyroid function in obese children with non-alcoholic fatty liver disease. *J Clin Res Pediatr Endocrinol*. 2014;6(3):152–157. doi:10.4274/jcrpe.1488
43. Panicker V, Cluett C, Shields B, et al. A common variation in deiodinase 1 gene DIO1 is associated with the relative levels of free thyroxine and triiodothyronine. *J Clin Endocrinol Metab*. 2008;93(8):3075–3081. doi:10.1210/jc.2008-0397
44. Salvatore D, Simonides WS, Dentice M, Zavacki AM, Larsen PR. Thyroid hormones and skeletal muscle--new insights and potential implications. *Nat Rev Endocrinol*. 2014;10(4):206–214. doi:10.1038/nrendo.2013.238
45. Carmean CM, Cohen RN, Brady MJ. Systemic regulation of adipose metabolism. *Biochim Biophys Acta*. 2014;1842(3):424–430. doi:10.1016/j.bbadis.2013.06.004
46. Gu Y, Li H, Bao X, et al. The relationship between thyroid function and the prevalence of type 2 diabetes mellitus in euthyroid subjects. *J Clin Endocrinol Metab*. 2017;102(2):434–442. doi:10.1210/jc.2016-2965
47. Zhou L, Jiang L, An Y, et al. Association of sensitivity to thyroid hormones and non-alcoholic fatty liver disease and the severity of liver fibrosis in euthyroid adults: a retrospective study. *Diabetes Metab Syndr Obes*. 2025;18:479–490. doi:10.2147/DMSO.S499517
48. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2021;161(5):1657–1669. doi:10.1053/j.gastro.2021.07.049
49. Zvibel I, Atias D, Phillips A, Halpern Z, Oren R. Thyroid hormones induce activation of rat hepatic stellate cells through increased expression of p75 neurotrophin receptor and direct activation of Rho. *Lab Invest*. 2010;90(5):674–684. doi:10.1038/labinvest.2010.48
50. Chen P, Hou X, Wei L, et al. Free triiodothyronine is associated with the occurrence and remission of nonalcoholic fatty liver disease in euthyroid women. *Eur J Clin Invest*. 2019;49(4):e13070. doi:10.1111/eci.13070
51. Du J, Chai S, Zhao X, Sun J, Zhang X, Huo L. Association between thyroid hormone levels and advanced liver fibrosis in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease. *Diabetes Metab Syndr Obes*. 2021;14:2399–2406. doi:10.2147/DMSO.S313503
52. Bano A, Chaker L, Plompen EP, et al. Thyroid function and the risk of nonalcoholic fatty liver disease: the rotterdam study. *J Clin Endocrinol Metab*. 2016;101(8):3204–3211. doi:10.1210/jc.2016-1300
53. Kim D, Yoo ER, Li AA, et al. Low-normal thyroid function is associated with advanced fibrosis among adults in the United States. *Clin Gastroenterol Hepatol*. 2019;17(11):2379–2381. doi:10.1016/j.cgh.2018.11.024