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ORIGINAL RESEARCH

Association Between Thyroid Hormone Sensitivity Indicators and Controlled Attenuation Parameter (CAP) Values in Euthyroid Adults with Overweight/Obesity

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Background: Obesity is an established contributor to hepatic steatosis. Despite weight control efforts, the incidence of steatosis and its associated hepatic complications continues to increase, highlighting the critical need to identify obesity-related pathogenic mechanisms for developing effective therapeutic strategies.

Aim: This study aims to explore the association between thyroid hormone sensitivity indicators and hepatic steatosis assessed by controlled attenuation parameter (CAP) values in euthyroid individuals with overweight/obesity.

Methods: Sensitivity to THs, was evaluated using $TFQI_{FT3}$, $TFQI_{FT4}$, TSHI, TT4RI, TT3RI, and FT3/FT4 ratio. Hepatic steatosis was diagnosed via Vibration-controlled Transient Elastography (VCTE). Linear regression, binary logistic regression, and restricted cubic spline regression (RCS) were used to analyze the associations between these composite indices and CAP levels. Bayesian mediation analysis was performed to assess the mediation effect of liver enzymes and lipids on the relationship between sensitivity parameters to THs and CAP.

Results: Compared to the non-severe hepatic steatosis group, the severe hepatic steatosis group exhibited significantly higher levels of $TFQI_{FT3}$, and FT3/FT4 ratio (all $P < 0.05$). After adjustment for multiple risk factors, $TFQI_{FT3}$ ($\beta = 25.38$, 95% CI 10.21–40.55) and the FT3/FT4 ratio ($\beta = 210.92$, 95% CI 116.37–305.47) increased with CAP ($P<0.001$), but not in TFQIFT4 ($p = 0.071$). These associations remained significant in binary logistic regression analysis and RCS. Further mediation analysis and subgroup analysis showed that the correlation was not mediated by blood lipid and liver enzyme impairment, and remained stable across all subgroups.

Conclusion: The correlation between TH sensitivity and hepatic steatosis was significantly stronger in $TFQI_{FT3}$ than in $TFQI_{FT4}$. $TFQI_{FT3}$ and the FT3/FT4 ratio can be used as new indicators for predicting hepatic steatosis in individuals with overweight/obesity.

Keywords: obesity, thyroid hormone sensitivity, hepatic steatosis, TFQI, FT3/FT4 ratio

Introduction

Obesity, a global epidemic, is inherently associated with metabolic dysregulation, encompassing conditions such as type 2 diabetes mellitus (T2DM), hepatic steatosis, cardiovascular disease, dyslipidemia, and hypertension. Among these, hepatic steatosis emerges as a prevalent and clinically meaningful comorbidity, characterized by the accumulation of lipids in over 5% of hepatic parenchymal cells.[1] Steatosis will be accompanied by steatohepatitis, which can result in progressive fibrosis ultimately leading to cirrhosis and the complications. Recent research conducted in China showed

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that the prevalence of hepatic steatosis in the general population was 44.39%, with a substantially higher rate observed in individuals with obesity (78.21%) compared to non-obese individuals (23.02%),[2] and this trend continues to rise. Obesity-induced lipotoxicity and insulin resistance are established contributors to hepatic lipid accumulation;[3–5]however, even with effective control of these established risk factors, the annual incidence of steatosis and its associated liver complications continues to rise. Therefore, identifying the causes of hepatic steatosis in populations with obesity is crucial for formulating effective therapeutic strategies.

Thyroid hormones (THs), particularly free thyroxine (FT4) and free triiodothyronine (FT3), are major endocrine regulators of energy and lipid metabolism. Thyroid dysfunction, including subclinical hypothyroidism[6] and low-normal thyroid function, has garnered considerable attention as a common metabolic disorder associated with hepatic steatosis and its serious complications.[7,8] Recent studies have shown that even individuals with normal thyroid function may exhibit impaired tissue sensitivity to THs—a condition in which THs fail to effectively exert their metabolic regulatory effects, referred to as "thyroid hormone resistance".[9] This state is quantified by indices such as the thyroid feedback quantile index, thyrotropin T4 resistance index (TT4RI), TSH index (TSHI), and FT3/FT4 ratio. Recent studies have indicated that reduced thyroid hormone (TH) sensitivity is closely associated with a cluster of intertwined metabolic abnormalities, including obesity, dyslipidemia, insulin resistance (IR), hyperuricemia, diabetes, metabolic syndrome, visceral adiposity, polycystic ovary syndrome (PCOS), metabolic dysfunction-associated steatotic liver disease (MASLD), and the severity of liver fibrosis.[9–25] However, the direct association between thyroid hormone resistance (THR) and the progression of hepatic steatosis in individuals with overweight or obesity, as well as the underlying mechanisms, remains to be elucidated.

Vibration-controlled transient elastography (VCTE), a non-invasive technique, has been validated for the standardizing assessment of hepatic steatosis via the controlled attenuation parameter (CAP). CAP demonstrates higher sensitivity and diagnostic accuracy than conventional ultrasound. However, to date, the relationship between TH sensitivity and hepatic steatosis risk, specifically in euthyroid individuals with overweight or obesity, remains unelucidated. We hypothesize that thyroid hormones may contribute jointly or interact to an increased risk of hepatic steatosis. The aim of the current research was to explore the association between thyroid hormone sensitivity indices, including the FT3/FT4 ratio, $TFQI_{FT4}$, and $TFQI_{FT3}$, with CAP and hepatic steatosis in euthyroid adults with overweight or obesity. Additionally, hyperlipidemia and hepatic function are interdependent, potentially modifying hepatic and systemic metabolic status. Therefore, a further objective was to examine whether liver enzymes and blood lipids mediate the association between thyroid hormone sensitivity and hepatic steatosis severity under euthyroid conditions.

Materials and Methods

Study Design and Participants

This is a cross-sectional study. The participants were adult patients who visited the Obesity Clinic of the Health Management Center at Tianjin People's Hospital, People's Hospital Affiliated to Nankai University in Tianjin, from January 2022 to April 2024.The inclusion criteria were as follows: (1) Age: 18 years or older. (2) Obesity diagnosis: body mass index (BMI) of ≥ 24 kg/m^2 indicated overweight, and a BMI of ≥ 28 kg/m^2 was defined as obesity. (3) Examination history: Patients had undergone thyroid function tests and transient elastography ultrasound of the liver. Among the 586 patients who met the inclusion criteria, the following individuals were further excluded from the study: (1) Patients with excessive alcohol consumption, viral hepatitis, secondary causes of fatty liver disease (such as total parenteral nutrition, inflammatory bowel disease, Cushing's syndrome), or other forms of secondary liver injury. (2) Those with thyroid tumors, and patients who had undergone thyroid surgery, received relevant treatment, taken oral antithyroid drugs (such as methimazole and propylthiouracil), taken THs, or taken medications affecting serum TH levels. (3) Patients with concurrent tumors, infections, or severe dysfunction of the heart, liver, kidneys, or lungs. (4) Pregnant or lactating women. (5) Patients with psychiatric disorders or cognitive impairments, or those unable to provide informed consent. Eventually, 434 study participants were incorporated into our research. The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Tianjin Union Medical Center (No.2021C06). All subjects provided informed consent forms prior to their participation in the study.

Data Collection and Measures

All medical information data in this study, including age, sex, weight, height, and medical history, were collected and recorded by researchers who underwent standardized training. Weight and height were measured by the DST600 fully automatic height and weight meter. BMI was calculated by dividing the weight (in kilograms) by the square of the height (in meters) (kg/m^2). Given ethnic differences, the study applied the obesity diagnostic criteria recommended by the World Health Organization (WHO) for the Chinese population. Specifically, a BMI of ≥ 24 kg/m^2 indicated overweight, and a BMI of ≥ 28 kg/m^2 was defined as obesity.[26]

Venous blood samples were collected from all participants in the morning after at least 8 hours of overnight fasting. Serum biochemical parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), fasting insulin, glycated hemoglobin (HbA1c), creatinine (Cr), uric acid (UA), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), were measured according to standard procedures in the clinical laboratories of Tianjin Union Medical Center. The insulin resistance index (HOMA-IR) was calculated by multiplying FPG (mmol/L) by fasting insulin levels (μ IU/mL), and then dividing the result by 22.5.

Calculations of Thyroid Hormone Sensitivity

The central thyroid hormone sensitivity indices (THSIs), including the thyroid feedback quantile-based indices ($TFQI_{FT4}$ and $TFQI_{FT3}$), thyroid hormone sensitivity index (TSHI), thyrotropin T4 resistance index (TT4RI), and thyrotropin T3 resistance index (TT3RI), were calculated based on FT3,FT4 and TSH levels. Elevated values of these indices are indicative of diminished central TH sensitivity. These indices were calculated as follows:

$TFQI_{FT4}$ = cdf FT4 – (1 –cdf TSH);[9]

$TFQI_{FT3}$ = cdf FT3 – (1 – cdf TSH).[27] $TFQI_{FT3}$ and $TFQI_{FT4}$ ranged from −1 to 1, a range that reflects the central sensitivity to THs. Specifically, negative values of $TFQI_{FT3}$ and $TFQI_{FT4}$ indicated a higher degree of central sensitivity to THs, whereas positive values were indicative of reduced central sensitivity.[15]

TSHI = Ln (TSH, μIU/mL) + 0.1345 × FT4 (pmol/L);[28]

TT4RI = FT4 (pmol/L) × TSH (μIU/mL);[29]

TT3RI =FT3 (pmol/L) × TSH (mIU/L).[27] The lower levels of TSHI, TT4RI and TT3RI indicated higher central TH sensitivity.

FT3/FT4=FT3 (pmol/L) FT4 (pmol/L). Peripheral TH sensitivity is represented by the FT3/FT4 ratio, and the lower FT3/FT4 values suggest reduced sensitivity to THs in the periphery.[30]

Measurement and Definition of Hepatic Steatosis

The vibration - controlled transient elastography (VCTE) provides liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) values, which allow for a relatively reliable estimation of the degree of fibrosis and steatosis, respectively.[31,32] Trained technicians used the FibroScan 502 Touch (Echosens, Shenzhen, China) with an XL probe to perform 10 or more CAP and LSM measurements on the subjects and to calculate the average values. It was ensured that each participant fasted for 8 hours before the examination. In this study, we adopted the non-invasive assessment criteria for hepatic steatosis and liver fibrosis recommended by the Liver Disease Branch of the Chinese Medical Association.[33] Hepatic steatosis was defined as a CAP ≥ 248 dB/m, severe hepatic steatosis was defined as a CAP ≥ 294 dB/m, and liver fibrosis was defined as a LSM ≥ 8 kPa. Insulin resistance was defined as a homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.5.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 27, GraphPad Prism 10, and R 4.3.0, with statistical significance set at $P < 0.05$ (two-tailed). Normally distributed continuous variables were presented as mean ± standard deviation, whereas skewed continuous variables are expressed as median (interquartile range). To assess statistical differences in means and proportions between the two groups, the Mann–Whitney *U*-test and chi-square test were employed. Using CAP thresholds for hepatic steatosis diagnosis, participants were classified into severe (≥294 dB/m) and

non-severe groups. All THSIs underwent standardization via Z-score transformation to eliminate scale heterogeneity. First, Pearson's and partial correlation analyses assessed associations between standardized indices and continuous CAP values. Second, multivariable linear regression models examined relationships between standardized thyroid indices and CAP. Third, binary logistic regression analyses with identical adjustment models evaluated associations with severe steatosis risk. Finally, restricted cubic splines (RCS) were applied to explore potential nonlinear dose–response relationships. Mediation analyses evaluated whether liver enzymes and lipids mediated thyroid indices-CAP associations. Subgroup analyses by sex, age, BMI, and IR status assessed effect stability.

Results

Description of Basic Information About Participants

Between January 2022 and April 2024, we evaluated 586 potentially eligible participants. After exclusion, 434 individuals (136 males and 298 females) were included in the final retrospective cross-sectional analysis (Figure S1). The study participants had a mean age of 34.00 ± 9.80 years and a mean BMI of 34.60 ± 5.45 kg/m^2, indicating a predominantly overweight middle-aged and young adult population. Based on the clinical CAP cutoff value (≥294 dB/m), the study participants were categorized into a severe and a non-severe hepatic steatosis group. Compared to the non-severe hepatic steatosis group, the significant hepatic steatosis group had a significantly lower proportion of females ($P < 0.001$). The severe hepatic steatosis group exhibited significantly higher values for body weight, BMI, FT3, $TFQI_{FT3}$, FT3/FT4, CAP, LSM, FINS, HOMA-IR, HbA1c, Cr, UA, TG, LDL-C, GGT, ALT, and AST (all $P < 0.05$). Furthermore, HDL-C levels were significantly lower in the severe hepatic steatosis group ($P < 0.001$). Notably, the severe hepatic steatosis group demonstrated elevated $TFQI_{FT3}$ values and increased FT3/FT4 ratios, suggesting that patients with higher hepatic fat content exhibit relative reductions in central sensitivity and relative increases in peripheral sensitivity to THs. No statistically significant differences were observed between the groups for age, TSH, FT4, $TFQI_{FT4}$, TSHI, TT3RI, TT 4 RI, FPG and TC (all $P > 0.05$). Detailed information is provided in Table 1.

Association Between TH Sensitivity Indices and CAP

All TH sensitivity indices were standardized by Z-score transformation for subsequent correlation and regression analyses. As shown in Table S1, $TFQI_{FT3}$ (Pearson's $r = 0.333$, $P < 0.001$) and FT3/FT4 ($r = 0.254$, $P < 0.001$) were both significantly positively correlated with CAP values, whereas $TFQI_{FT4}$ showed no significant association with CAP ($r = 0.040$, $P = 0.407$). After adjusting for confounding factors including sex, age, BMI, FPG, FIN, HbA1c, Cr, and UA, the correlations between $TFQI_{FT3}$ ($r = 0.340$, $P < 0.001$) and FT3/FT4 ($r = 0.255$, $P < 0.001$) with CAP values remained statistically significant (see Table S1).

Multivariable linear regression analysis further confirmed the aforementioned associations (Table 2). For each 1-standard deviation (SD) increase in standardized $TFQI_{FT3}$ and FT3/FT4, CAP values increased by 15.58 dB/m (95% CI: 11.31–19.86; $P < 0.001$) and 12.18 dB/m (95% CI: 7.81–16.55; $P < 0.001$), respectively. These associations persisted after full adjustment for sex, age, BMI, FPG, FIN, HbA1c, Cr, and UA (Model 2, Table 2). Specifically, each 1-SD increase in standardized $TFQI_{FT3}$ was associated with a 7.26 dB/m increase in CAP (95% CI: 2.92–11.60; $P < 0.001$), while the FT3/FT4 ratio exhibited a stronger effect (β = 8.70 dB/m per 1-SD increase; 95% CI: 4.80–12.59; $P < 0.001$). In contrast, $TFQI_{FT4}$ showed no significant association with CAP after full adjustment ($P = 0.071$).

To investigate associations between severe hepatic steatosis and thyroid hormone sensitivity indices (THSIs), binary logistic regression analysis was performed. According to the clinical cutoff value of CAP (≥294 dB/m), patients were categorized into severe hepatic steatosis (n = 269) and non-severe hepatic steatosis (n = 165) groups. Both before and after covariate adjustment, elevated $TFQI_{FT3}$ and FT3/FT4 were associated with an increased risk of severe hepatic steatosis, while $TFQI_{FT4}$ showed no significant association (P = 0.486). After adjusting for metabolic confounders, each 1-SD increase in standardized $TFQI_{FT3}$ was associated with a 41% higher risk of severe steatosis (OR = 1.41, 95% CI: 1.08–1.82; P = 0.010; Model 2). The FT3/FT4 ratio was similarly associated with increased risk (OR = 1.56, 95% CI: 1.22–1.99; P < 0.001), whereas $TFQI_{FT4}$ showed no significant association (P > 0.05).

Table 1 Clinical Characteristics of the Study Population Stratified by Severe Hepatic Steatosis Status

Variables	Total (n=434)	Non-Severe Hepatic Steatosis Group (n=165)	Severe Hepatic Steatosis Group (n=269)	P
Sex, n (%)				<0.001***
Male	136 (31.34)	24 (14.55)	112 (41.64)	
Female	298 (68.66)	141 (85.45)	157 (58.36)	
Age, (years)	34.00 ± 9.80	33.93 ± 10.43	34.04 ± 9.41	0.912
Weight, (kg)	96.92 ± 19.17	86.90 ± 13.44	103.06 ± 19.59	<0.001***
BMI, (kg/m2)	34.60 ± 5.45	32.24 ± 4.53	36.04 ± 5.48	<0.001***
Thyroid Hormones				
TSH, (μIU/mL)	2.31 (1.63, 3.25)	2.48 (1.72, 3.27)	2.21 (1.60, 3.22)	0.193
FT3, (pmol/L)	4.64 (4.25, 5.02)	4.42 (4.12, 4.83)	4.77 (4.38, 5.16)	<0.001***
FT4, (pmol/L)	15.94 (14.41, 17.44)	15.90 (14.24, 17.23)	16.04 (14.53, 17.56)	0.472
Thyroid hormone sensitivity indices				
TFQI-FT3	−0.03 ± 0.29	−0.13 ± 0.27	0.04 ± 0.28	<0.001***
TFQI-FT4	−0.02 ± 0.30	−0.04 ± 0.29	−0.02 ± 0.30	0.487
TSHI	3.01 (2.63, 3.41)	3.04 (2.67, 3.37)	2.99 (2.59, 3.42)	0.640
TT3RI	10.92 (7.53, 15.53)	10.94 (7.66, 14.33)	10.85 (7.51, 15.91)	0.787
TT4RI	37.71 (26.42, 51.86)	39.79 (26.94, 51.49)	36.54 (26.13, 52.31)	0.379
FT3/FT4 ratio	0.30 (0.27, 0.32)	0.29 (0.25, 0.31)	0.30 (0.28, 0.33)	<0.001***
Liver				
CAP, (dB/m)	306.40 ± 47.93	256.86 ± 29.09	336.78 ± 27.48	<0.001***
LSM, (kPa)	6.30 (5.10, 8.70)	5.60 (4.70, 6.90)	7.30 (5.50, 10.10)	<0.001***
Metabolic factors				
FPG, (mmol/L)	4.96 (4.56, 5.50)	4.92 (4.57, 5.28)	4.99 (4.56, 5.72)	0.065
FINS, (mU/L)	18.29 (14.77, 27.40)	16.03 (12.60, 20.84)	20.29 (16.31, 31.79)	<0.001***
HOMA-IR	4.17 (3.21, 6.77)	3.46 (2.74, 4.73)	4.86 (3.72, 8.58)	<0.001***
HbA1c, (%)	5.70 (5.40, 6.10)	5.60 (5.40, 5.90)	5.71 (5.50, 6.20)	<0.001***
Cr, (mmol/L)	61.02 ± 20.41	57.16 ± 11.38	63.38 ± 24.06	<0.001***
UA, (mmol/L)	390.02 ± 106.07	359.83 ± 84.72	408.54 ± 113.49	<0.001***
TC, (mmol/L)	5.47 ± 9.57	4.98 ± 1.02	5.77 ± 12.13	0.400
TG, (mmol/L)	1.60 (1.15, 2.46)	1.31 (1.01, 1.86)	1.73 (1.30, 2.67)	<0.001***
HDL-C, (mmol/L)	1.18 (1.04, 1.36)	1.24 (1.11, 1.42)	1.14 (0.98, 1.28)	<0.001***
LDL-C, (mmol/L)	3.16 (2.72, 3.60)	3.08 (2.63, 3.49)	3.21 (2.79, 3.65)	0.004**
Hepatic enzymes				
GGT (U/L)	60.21 ± 15.54	58.06 ± 16.09	61.52 ± 15.07	<0.001***
ALP (U/L)	60.21 ± 15.54	58.06 ± 16.09	61.52 ± 15.07	0.024*
ALT (U/L)	30.95 (19.00, 59.22)	21.00 (14.20, 33.00)	40.00 (25.40, 68.80)	<0.001***
AST (U/L)	23.45 (18.10, 34.85)	19.50 (15.50, 25.20)	26.40 (20.30, 38.00)	<0.001***

Notes: Continuous variables are expressed as mean ± standard deviation or median with interquartile range. *P*values were calculated using paired *t*-test or Wilcoxon signed-rank test according to variable type.*P<0.05;**P<0.01; ***P<0.001.

Abbreviations: BMI, body mass index; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TFQIFT3, thyroid feedback quantile-based index calculated by FT3; TFQIFT4, thyroid feedback quantile-based index calculated by FT4; TSHI, TSH index; TT3RI, thyrotrophic T3 resistance index;TT4RI,thyrotrophic T4 resistance index; FT3/FT4 ratio, FT3 to FT4 ratio; CAP, controlled attenuation parameter;LSM, liver stiffness measurement;FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Table 2 Association Between Thyroid Hormone Sensitivity Indices and CAP in the Euthyroid Population

Variables	Model	Linear Regression		Binary Logistic Regression	
		β (95% CI)	P	OR (95% CI)	P
TFQIFT3	Unadjusted	15.58 (11.31 ~ 19.86)	<0.001***	1.83 (1.48 ~ 2.26)	<0.001***
	Model 1	12.34 (7.68 ~ 17.00)	<0.001***	1.64 (1.30 ~ 2.07)	<0.001***
	Model 2	7.26 (2.92 ~ 11.60)	0.001**	1.41 (1.08 ~ 1.82)	0.010
TFQIFT4	Unadjusted	1.91 (−2.61 ~ 6.43)	0.407	1.07 (0.88 ~ 1.30)	0.486
	Model 1	−1.43 (−5.88 ~ 3.02)	0.528	0.93 (0.76 ~ 1.15)	0.516
	Model 2	−3.66 (−7.63 ~ 0.30)	0.071	0.82 (0.64 ~ 1.04)	0.098
FT3/FT4	Unadjusted	12.18 (7.81 ~ 16.55)	<0.001***	1.62 (1.31 ~ 2.00)	<0.001***
	Model 1	10.56 (6.30 ~ 14.83)	<0.001***	1.56 (1.25 ~ 1.94)	<0.001***
	Model 2	8.70 (4.80 ~ 12.59)	<0.001***	1.56 (1.22 ~ 1.99)	<0.001***

Notes: All thyroid hormone sensitivity indices were standardized using Z-score transformation to eliminate the dimensional differences among different indicators. Model1: Adjusted for Sex, Age;Model2: Adjusted for Sex, Age, BMI,FPG,FIN,HbA1c, Cr, UA. p<0.05 was considered statistically significant.**P<0.01; ***P<0.001.

Abbreviations: TFQIFT3, thyroid feedback quantile-based index calculated by FT3; TFQIFT4, thyroid feedback quantile-based index calculated by FT4; TSHI, TSH index; TT3RI, thyrotrophic T3 resistance index; TT4RI, thyrotrophic T4 resistance index; FT3/FT4 ratio, FT3 to FT4 ratio.

In Figure 1, we nonlinearly modeled and visualized relationships between CAP and $TFQI_{FT3}$, $TFQI_{FT4}$, and the FT3/FT4 ratio using RCS. Analysis revealed linear dose-response relationships of $TFQI_{FT3}$ and FT3/FT4 ratio with CAP values (overall $P < 0.001$; nonlinear $P > 0.05$; Figures 1A–C). Conversely, TFQI-FT4 showed no significant association with CAP (overall $P > 0.05$; nonlinear $P > 0.05$; Figure 1B). All models were adjusted for sex, age, BMI, FPG, FIN, HbA1c, Cr, and UA.

Liver Enzymes and Serum Lipids Do Not Mediate the Association Between Thyroid Hormone Sensitivity Indices

Mediation analyses (Figure 2 and Table S2) were conducted to explore whether liver enzymes (GGT, ALP, ALT, AST) and/or serum lipids (TC, TG, HDL-C, LDL-C) mediate the association between THSIs ($TFQI_{FT3}$ and FT3/FT4 ratio) and CAP. For $TFQI_{FT3}$, the estimated proportions of the association mediated by GGT, ALP, ALT, AST, TC, TG, HDL-C, and LDL-C were 5.23%, 0.52%, 6.60%, 0.80%, 0.38%, 1.53%, −3.29%, and 0.39%, respectively. For the FT3/FT4 ratio, the mediation proportions by GGT, ALP, ALT, AST, TC, TG, HDL-C, and LDL-C were 5.47%, 0.34%, 5.08%, 0.40%, 0.85%, −1.06%, −3.02%, and 0.37%, respectively. After adjusting for confounders including sex, age, BMI, FPG, FIN, HbA1c, Cr, and UA, the mediation analysis demonstrated non-significant indirect effects through hepatic enzymes or lipid pathways (all $P > 0.05$), indicating the absence of significant mediation by these biomarkers. Notably, the direct effects of $TFQI_{FT3}$ and the FT3/FT4 ratio on CAP values remained statistically significant after full adjustment for liver enzymes, lipids, and all covariates.

Subgroup Analysis

As shown in Table S3, we performed a subgroup analysis by sex (male or female), age (<35, 35–50, or ≥50 years), BMI (<28 or ≥28 kg/m^2), and insulin resistance (no or yes) to investigate whether the results varied across different populations. The relationship between $TFQI_{FT3}$, the FT3/FT4 ratio, and CAP values remained stable across all subgroups, including sex (P for interaction = 0.264), age (P for interaction = 0.375), BMI (P for interaction = 0.821), and insulin resistance (P for interaction = 0.078). The relationship between CAP values and the FT3/FT4 ratio also remained stable across all subgroups, including sex (P for interaction = 0.958), age (P for interaction = 0.149), BMI (P for interaction = 0.577), and insulin resistance (P for interaction = 0.306).

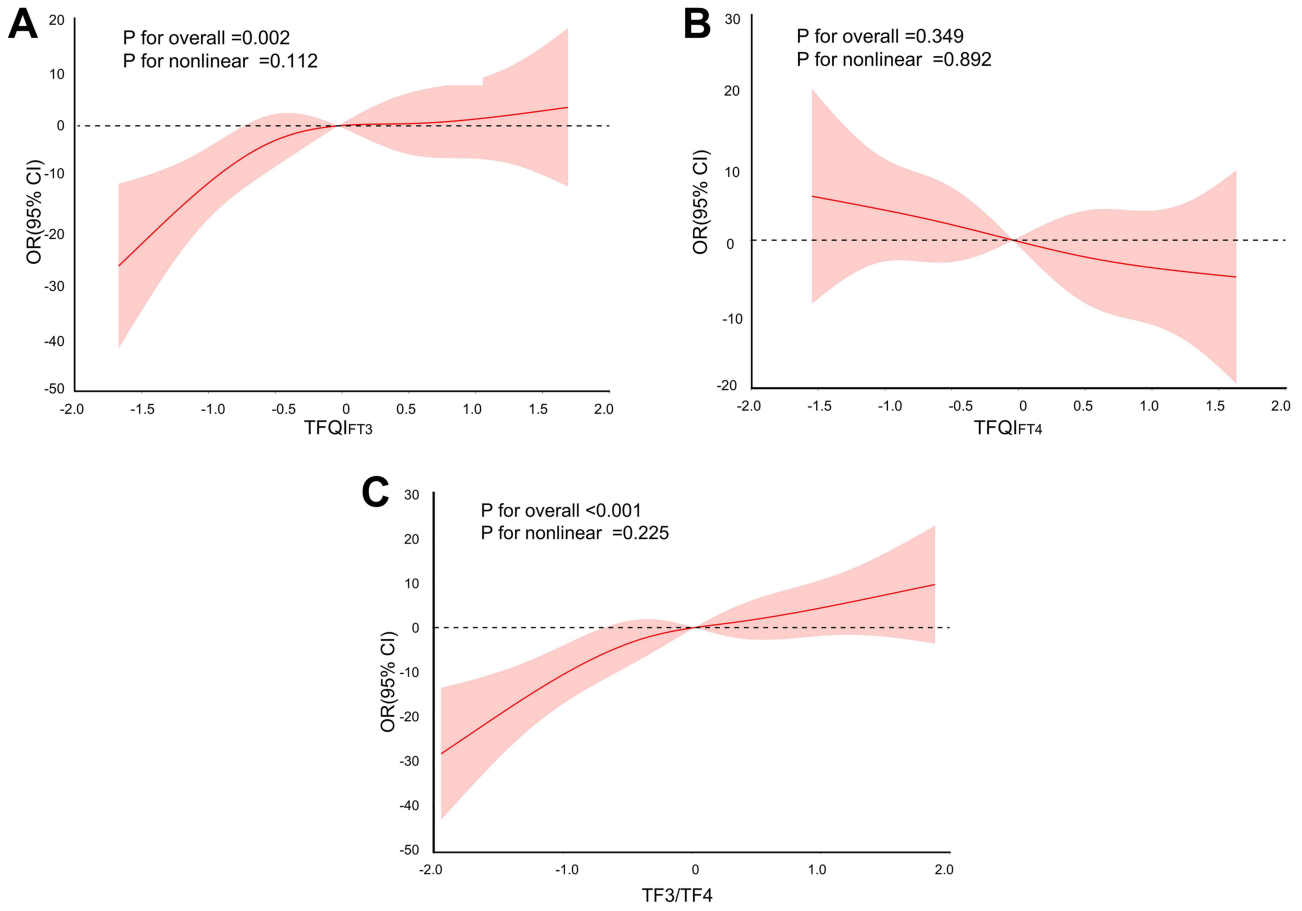

Figure 1 Nonlinear relationships of Thyroid Hormone Sensitivity Indices with CAP. Restricted cubic spline (RCS) analysis was conducted. (**A**) Nonlinear relationships of TFQIFT3 and CAP (**B**) Nonlinear relationships of TFQIFT4 and CAP (**C**) Nonlinear relationships of FT3/FT4 ratio and CAP. The model was adjusted for Sex, Age, BMI, FPG, FIN, HbA1c, Cr and UA. P for overall <0.05 was considered statistically significant. P for nonlinear >0.05 indicates evidence of linearity in the relationship.

Discussion

This study found that in euthyroid Chinese individuals with overweight/obesity, elevated FT3/FT4 ratio and $TFQI_{FT3}$, but not $TFQI_{FT4}$, were associated with CAP values measured by FibroScan. Furthermore, higher $TFQI_{FT3}$ and FT3/FT4 ratio were associated with increased risk of severe hepatic steatosis, whereas $TFQI_{FT4}$ showed no significant correlation with it. Notably, mediation analysis revealed no significant mediating role of liver enzymes or blood lipids, and subgroup analyses confirmed the robustness of these associations across different strata. These findings highlight the potential of $TFQI_{FT3}$ and the FT3/FT4 ratio as novel markers for evaluating hepatic steatosis in populations with overweight/obesity.

THs are critical regulators of hepatic lipid metabolism, primarily through THRβ-mediated genomic programs influencing lipogenesis, fatty acid oxidation, and cholesterol handling.[34] Dysregulation of thyroid function, such as in hypothyroidism, is linked to metabolic disorders including MASLD. However, studies on the relationship between circulating TH levels and hepatic steatosis in euthyroid individuals have yielded conflicting results,[25,35–41] likely due to variations in study characteristics and the inherent limitations of single hormone measurements in reflecting complex tissue-level thyroid status. In this study, we found that high-normal FT3 levels, but not TSH or FT4, were associated with higher CAP values even after adjustment for metabolic risk factors. Circulating FT3, FT4, and TSH are maintained in dynamic equilibrium via negative feedback regulation within the hypothalamic–pituitary–thyroid (HPT) axis. Given this complex physiological interplay, using composite indices such as $TFQI_{FT3}$, $TFQI_{FT4}$, and the FT_3/FT_4 ratio is essential to comprehensively assess thyroid hormone homeostasis and overcome the limitations of individual hormone measurements.

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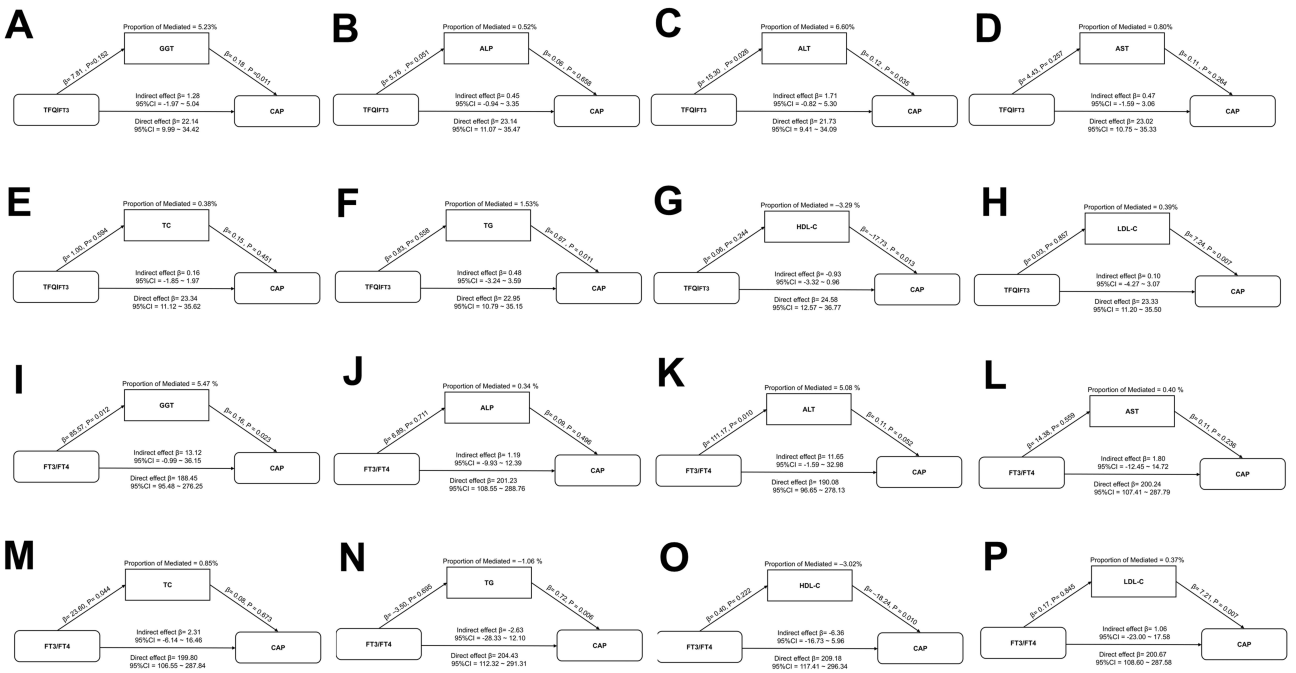

Figure 2 The mediation effects of liver enzymes (GGT, ALP, ALT, AST) and serum lipids (TG, TC, LDL-C, HDL-C) in the relationships of TH sensitivity indices with CAP. Exposure: TFQIFT3, FT3/FT4 ratio; mediator: liver enzymes (GGT, ALP, ALT, AST) and serum lipids (TG, TC, LDL-C, HDL-C); outcome: CAP. Subplots (**A-H**) illustrate the path analyses examining the association between the thyroid hormone sensitivity index TFQI-FT3 (independent variable, (X) and hepatic steatosis (CAP, outcome variable, Y), with eight different metabolic indicators tested as potential mediating variables (M). Subplots (**I-P**) illustrate the corresponding path analyses when the free triiodothyronine to free thyroxine ratio (FT3/FT4) is used as the exposure (X), with the same eight metabolic indicators tested as potential mediators (M) for the association with the CAP value (Y). Proportion Mediated represents the proportion of the indirect effect of the total effect (sum of indirect and direct effects). The model was adjusted for Sex, Age, BMI, FPG, FIN, HbA1c, Cr and UA. $p<0.05$ was considered statistically significant. 95% confidence intervals in brackets.

Previous studies conducted in euthyroid subjects showed that impaired thyroid hormone sensitivity was an independent predictor of metabolic diseases, including dyslipidemia, gestational diabetes, prediabetes, diabetes mellitus, metabolic syndrome, fatty liver disease, liver fibrosis, and all-cause mortality.[9,11,14,22,24] Consistent with Lai et al,[15] we found that higher values of most central TH sensitivity indices were associated with MASLD. Specifically, our study demonstrated that TFQI $_{FT3}$, an index reflecting central FT3 sensitivity derived from the TFQI $_{FT4}$ formula, was positively associated with increased CAP values and greater prevalence of severe hepatic steatosis, even after rigorous adjustment for metabolic confounders (including BMI, fasting glucose, insulin, uric acid, and renal function) and across various stratified analyses. This aligns with other cross-sectional studies[11,15,24] linking TFQI $_{FT3}$, but not TFQI$_{FT4}$, to obesity, MASLD prevalence, and liver fibrosis progression. Lai et al[15] proposed several explanations including compensatory conversion from FT4 to FT3 and racial variations. Wan et al[24] suggested that the possible cause might be the decrease in thyroid hormone levels and signal transduction in the liver, which leads to a compensatory adaptive increase in serum FT3 levels to enhance energy expenditure. Our study's unique focus on euthyroid overweight/obese individuals and comprehensive adjustment for metabolic confounders may explain some divergences from previous studies that involved different populations or covariate sets. This approach further underscores the validity of TFQI $_{FT3}$ as an indicator in this specific context, although continued investigation is warranted.

The FT3/FT4 ratio—as a quantitative indicator of peripheral thyroid hormone sensitivity—primarily reflects deiodinase activity in peripheral tissues (such as liver, muscle, adipose tissue, the central nervous system, and the thyroid). This enzyme regulates local tissue concentrations of bioactive T3 by converting inactive T4 into highly bioactive T3. Previous studies have indicated a positive relationship between high FT3/FT4 ratios and metabolic diseases, such as obesity, diabetes, MASLD, and metabolic syndrome.[42–46] In particular, the study by Sommer-Ballarini et al[46] suggested that in euthyroid individuals, a higher ratio may represent a compensatory mechanism for mild intrahepatic lipid accumulation and early MASLD. Our findings are consistent with this and further indicate that in severe fatty liver disease, this elevation may reflect a compensatory upregulation of deiodinase activity to enhance hepatic T3 supply. This view is

supported by clinical and preclinical evidence that hepatic deiodinase expression is upregulated in obesity-related fatty liver disease.[47,48] Moreover, in euthyroid obese patients, TSH and FT3 levels are elevated, while the expression of thyroid-related genes in subcutaneous and visceral adipose tissues is decreased, particularly the genes for thyrotropin receptor (TSHR) and thyroid hormone receptor α1 (TRα1).[36,49–51] This indicates an overall alteration in thyroid hormone regulation, which may help understand thyroid hormone function in the context of MASLD.

Liver enzymes are markers of injury and oxidative stress, and dyslipidemia promotes lipotoxicity and insulin resistance. Together, they drive hepatic fat accumulation through a synergistic axis involving lipid buildup, oxidative stress, and inflammation. Given the interplay of thyroid dysfunction, liver injury, and dyslipidemia in MASLD pathogenesis, we investigated whether liver enzymes or blood lipids mediated the observed associations between TH sensitivity indices and hepatic steatosis. Our mediation analysis revealed no significant mediating role for these factors, suggesting a more direct link between altered TH sensitivity and hepatic lipid accumulation. The exact mechanisms remain to be fully elucidated but may involve reduced thyroid hormone sensitivity at the hepatocyte level, triggering a compensatory increase in DIO1 expression and activity, as previously discussed. This would elevate intrahepatic FT3 levels to bind THRβ, highly expressed in the liver, thereby promoting T3-target gene expression that enhances fatty acid oxidation, lipophagy, and reduces triglyceride deposition.[52,53] However, Sinha et al[33] caution that serum FT3/FT4 levels may not accurately reflect intrahepatic thyroid hormone status in NAFLD, possibly due to reduced intrahepatic TH concentrations and impaired hepatic FT3 sensitivity, which could paradoxically dampen thyroid hormone signaling and promote steatosis progression.

In conclusion, our study moved beyond single thyroid hormone measurements by investigating the relationship between comprehensive indices of central and peripheral thyroid hormone sensitivity and hepatic steatosis in euthyroid individuals with overweight/obesity. We identified TFQI $_{FT3}$ and the FT3/FT4 ratio as promising novel markers associated with hepatic fat content, independent of traditional metabolic confounders. These findings underscore the potential value of assessing thyroid hormone sensitivity in understanding and evaluating MASLD. However, several limitations must be acknowledged. First, its cross-sectional design precludes inference of causal relationships between thyroid hormone sensitivity and hepatic steatosis, necessitating validation by future prospective cohort studies. Second, the lack of gold-standard imaging techniques (such as computed tomography, MRI-PDFF) to assess hepatic fat accumulation limits the findings; validation with more sensitive techniques is needed in future studies. Third, the absence of data on lifestyle factors, diet, physical activity, pharmacotherapy, and thyroid autoantibodies may have influenced our findings, and inclusion of these parameters in future analyses is essential for a more comprehensive understanding. Finally, the single-center design and exclusive enrollment of a Chinese population may limit the generalizability of our conclusions; future multicenter, multi-ethnic studies are warranted to validate and extend our findings.

Conclusions

The findings of our research indicate a positive correlation between central and peripheral sensitivity to thyroid hormone indices with CAP and the increased risk of hepatic steatosis. Subgroup and sensitivity analyses further confirmed the robustness of these findings, showing consistent results across different demographic groups and under various analytical conditions. This highlights the importance of FT3 in their interactions with hepatic steatosis. $TFQI_{FT3}$ and the FT3/FT4 ratio can be used as new indicators for predicting hepatic steatosis in individuals with overweight/obesity. Further investigations are needed to validate these results and understand the underlying mechanisms.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author, L.C.J (Email: li_chunjun@126.com), upon request.

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Author Contributions

Yifang Zhang (Co-first author): Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. Cuiping Bao (Co-first author): Methodology, Investigation, Formal analysis, Writing – review & editing, Supervision. Lingling Liu: Data curation, Investigation, Writing – review & editing, Supervision. Renjiao Liu: Data curation, Visualization, Writing – review & editing. Xincheng Wang: Methodology, Project administration, Writing – review & editing. Xiaoxuan Guo: Conceptualization, Investigation, Visualization, Writing – review & editing. Chunjun Li (Corresponding author): Conceptualization, Supervision, Funding acquisition, Writing – review & editing, Project administration. All authors 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.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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