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Correlation Between Thyroid Hormone and Controlled Attenuation Parameters: A Cross-Sectional Population-Based Study

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Objective: The aim of the present study was to investigate how thyroid hormone levels are related to controlled attenuation parameters (CAP), which may provide insights for understanding the role of these factors in hepatic steatosis.

Methods: A total of 3461 participants who underwent CAP diagnosis between 2018 and 2023 were included. The associations between thyroid hormone levels and CAP were evaluated through multiple linear regression, restricted cubic splines (RCS) and threshold effect analyses.

Results: Multiple linear regression analysis revealed an inverse relationship between free thyroxine (FT4) and CAP, with a coefficient of −0.855 and a confidence interval of −1.297 to −0.412. The negative connection in a subset examination persisted in males [−0.729 (−1.295, −0.162)] and females [−1.234 (−1.996, −0.473)]. A strong correlation was found between free 3,5,3′-triiodothyronine (FT3) and CAP, with values of 2.182 (1.154, 3.211). Further analysis was conducted on both male [1.626 (0.188, 3.065)] and female [2.835 (1.137, 4.533)] subgroups. In the severe liver steatosis group, there was a significant negative correlation between FT3 and CAP based on the subgroup analysis stratified by the level of liver steatosis [−3.804 (−6.711, −0.898)]. The RCS analysis showed a nonlinear association between FT4 and CAP, with a turning point at 11.14 pmol/L.

Conclusion: There was a significant linear and nonlinear relationship between FT4, FT3 and CAP. Thyroid hormones could have a significant impact on liver steatosis, offering fresh perspectives on how to prevent and treat this condition.

Keywords: thyroid hormone, nonalcoholic fatty liver disease, free thyroxine, free 3,5,3′-triiodothyronine, controlled attenuation parameters, transient elastography

Introduction

NAFLD is the buildup of fat in the liver without heavy alcohol intake This liver disease is widespread globally, affecting up to a quarter of the population according to epidemiological studies.[1] NAFLD can progress to nonalcoholic steatohepatitis, leading to liver fibrosis, cirrhosis, and liver cancer[2,3] and resulting in significant morbidity and mortality.[4] In different regions of China, the prevalence of NAFLD ranges from 12.9% to 43.3%.[5] The increasing occurrence of health crises such as obesity, diabetes, and metabolic syndrome suggests that NAFLD will become a more pressing public health concern in China in the future.[6] Thus, the prevention and treatment of NAFLD are crucial. Due to its accuracy and noninvasive nature, transient elastography is widely used clinically for NAFLD screening, with CAP used to assess liver steatosis.[7] In 2023, the term "metabolic dysfunction-associated steatotic liver disease" (MASLD)was proposed by three major multinational liver associations to replace NAFLD.[8] MASLD represents a novel terminology designed to highlight the link between fatty liver disease and metabolic disorders. It is characterized by the presence of fatty liver in conjunction with specific metabolic impairments, including obesity, type 2 diabetes, or hypertension. In our study, we

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evaluated liver steatosis by utilizing the CAP. Eligibility for the study was established when individuals exhibited a CAP value of ≥274 dB/m, in accordance with exclusion criteria that disqualified those who did not fulfill the necessary conditions. Consequently, we have maintained the use of the term NAFLD.

Thyroid hormones are essential for controlling energy metabolism, inflammation, and immune function. They participate in regulating liver steatosis by affecting pathways of fat metabolism in the liver, such as fatty acid synthesis, oxidation, and secretion.[9,10] Reduced thyroid hormone levels can result in high cholesterol levels, which is a crucial factor in the development of NAFLD[11] caused by hypothyroidism. Numerous studies have investigated the correlation between thyroid hormone levels and the incidence of NAFLD both domestically and internationally; however, the results are inconsistent, possibly due to differences in study population ethnicity, age range, study design, and diagnostic methods for fatty liver.[12] Using a substantial sample size, this research sought to investigate the correlation between thyroid hormone levels and controlled attenuation parameters, offering insights for the management and treatment of NAFLD.

Materials and Methods

Study Subjects

Data were collected from individuals who received noninvasive testing (FibroTouch) for fatty liver at the People's Hospital of Guangxi Zhuang Autonomous Region from November 2018 to October 2023. The exclusion criteria were as follows: 1) high alcohol intake (men >140 g/week, women >70 g/week); 2) prior diagnosis of hepatitis, cirrhosis, or other chronic liver conditions (such as autoimmune liver disease, primary sclerosing cholangitis, drug-induced liver disease); and 3) serious systemic illnesses (such as heart, lung, liver, kidney diseases, infectious diseases, mental illnesses, etc). The process of selecting participants is illustrated in Figure 1

The study used a formula $n=Z^2_{1-\alpha/2}P(1-P)/d^2$ to estimate the sample size,[13] assuming a NAFLD prevalence of 12.9% in China from literature.[5] The allowable error was set at 10% of the prevalence, or d = 0.1p = 0.013, with a significance level of $\alpha = 0.05$. The calculation resulted in a required sample size of n = 2677. To ensure statistical significance and

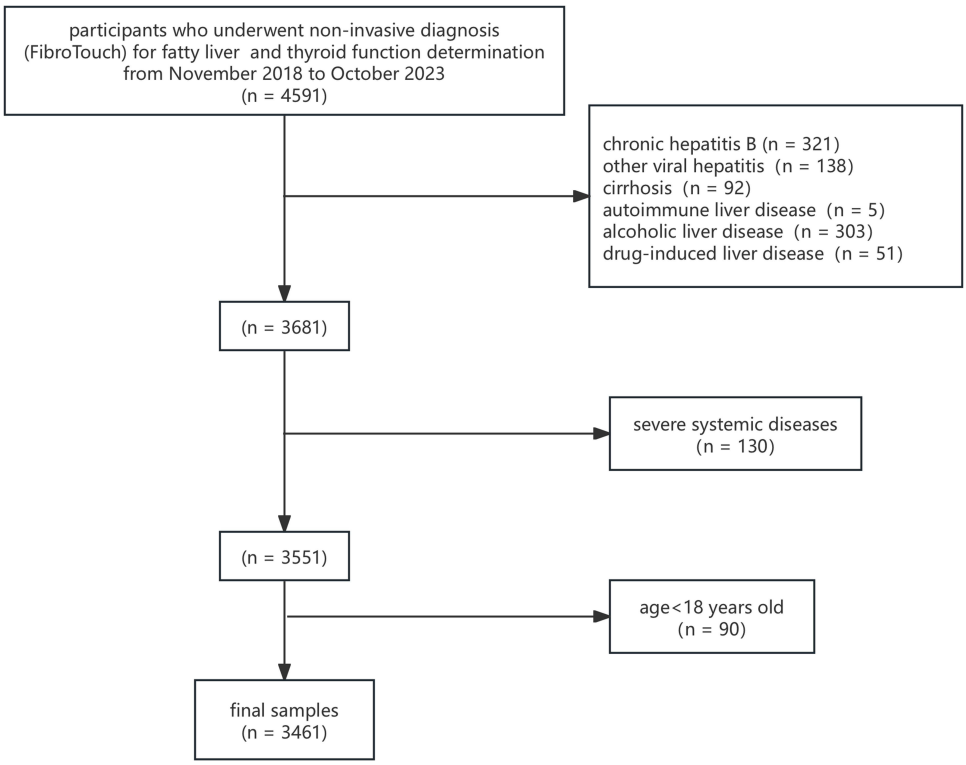

Figure 1 Flowchart of participant selection.

reliability, we aimed for at least 2677 participants. Over an extended time period and following strict criteria, we included 3461 patients in the study.

Data Collection

The sex, age, diabetes status, hypertension status, and coronary heart disease history of the study subjects were obtained from outpatient records or admission records. Nursing records provided the measurements of the patients' height and weight. The laboratory conducted tests on various biochemical markers, including FT3, FT4, Thyroid-Stimulating Hormone(TSH), alanine aminotransferase(ALT), aspartate aminotransferase(AST), total bilirubin(TBIL), direct bilirubin-(DBIL), indirect bilirubin(IBIL), alkaline phosphatase(ALP), creatinine(CR), uric acid(UA), urea nitrogen(UREA), total cholesterol(TC), triglycerides(TG), high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose(FBG). BMI was determined by dividing weight by height squared in kilograms per square meter. Every samples were collected after an overnight fast. A Fibrotouch transient elastography diagnostic instrument (pro5000, Wuxi Hisky Medical Technology Co. Ltd.) was used for testing strictly in accordance with the instructions manual. All the above data information were obtained from the database of the People's Hospital of Guangxi Zhuang Autonomous Region. We ensure that the confidentiality and informed consent of participants are strictly observed.

Related Definitions

Eddowes PJet al investigated the diagnostic precision of FibroScan's vibration-controlled transient elastography Controlled Attenuation Parameter (CAP) and liver stiffness measurement (LSM) for the evaluation of steatosis and fibrosis in individuals suspected of having nonalcoholic liver disease (NAFLD). The research findings suggest that a CAP score of ≥274 dB/m serves as an indicator for NAFLD. Furthermore, a CAP value of ≥302 dB/m is considered a sign of severe steatosis, with the diagnostic assessment boasting a sensitivity rate of 90%.[7] Consequently, our study defines the following grades of steatosis: S0: CAP < 274 dB/m; S1: 274 dB/m ≤ CAP < 302 dB/m; S2: CAP ≥ 302 dB/m.

Statistical Analysis

SPSS 26 and R, version 4.1.3, were used for the statistical analysis. CAP subgroups were used to statistically describe the baseline characteristics of the study population. Continuous variables are presented as the mean and standard deviation (SD) and were analyzed for differences between groups using one-way ANOVA. Categorical variables are represented as percentages and were analyzed using the chi-square test in a cross-tabulation. Beta values and 95% confidence intervals for the correlation between thyroid function (FT4, FT3, TSH) and CAP were calculated using multiple linear regression analysis. Three different models were developed for conducting multivariable analysis: Model 1 without any covariate adjustments; Model 2 with adjustments for sex, age, diabetes status, hypertension status, and history of CHD; and Model 3 with adjustments for all covariates. RCS regression was employed to investigate the nonlinear correlation between the levels of thyroid hormones and CAP, and inflection points were detected through threshold effect analysis utilizing two-piece linear regression. A p value less than 0.05 indicated statistical significance.

Results

Baseline Characteristics of the Participants

A total of 3461 participants were involved in the study, with an average age of 45.07 years (SD = 11.83). Among these participants, 68.4% were male, and 31.6% were female. The mean (SD) concentrations of CAP and thyroid function tests (FT3, FT4, and TSH) were 251.19 dB/m, 5.297 pmol/L, 11.404 pmol/L, and 2.274 μlU/mL, respectively. The clinical features of every participant are displayed in Table 1, categorized by CAP. Statistically significant differences (all $p < 0.05$) were found in sex, age, diabetes and hypertension rates, BMI, liver and kidney function tests, cholesterol levels, thyroid hormones, and blood glucose levels among the three groups.

Table 1 Characteristics of the Study Population Based on Controlled Attenuated Parameter (CAP)

	Reference Range	S0: (CAP < 274 dB/m, n = 2410)	S1: (274 ≤CAP < 302 dB/m, n = 717)	S2: (CAP≥302 dB/m, n = 334)	X^2/F	P
DM, n(%)						
NO		2125 (88.2)	590 (82.3)	272 (81.4)	23.612	<0.001
YES		285 (11.8)	127 (17.7)	62 (18.6)		
CHD, n(%)						
NO		2262 (93.9)	659 (91.9)	306 (91.6)	4.87	0.08
YES		148 (6.1)	58 (8.1)	28 (8.4)		
Hypertension, n(%)						
NO		2026 (84.1)	555 (77.4)	263 (78.7)	19.704	<0.001
YES		384 (15.9)	162 (22.6)	71 (21.3)		
Sex, n(%)						
Male		61.60%	82.00%	84.70%	153.42	<0.001
Female		38.40%	18.00%	15.30%		
Age, years		44.52±11.992	47.04±11.524	44.76±10.831	12.706	<0.001
CAP, dB/m		231.45±28.04	285.7±7.808	319.6±17.845	2839.867	<0.001
BMI, kg/m^2		23.335±2.746	26.952±2.125	29.608±3.593	1088.15	<0.001
ALT, U/L	9–50	23.088±23.980	31.388±18.969	41.455±26.473	110.466	<0.001
AST, U/L	15–40	24.613±17.187	26.258±9.134	30.168±14.273	19.751	<0.001
TBIL, μmol/L	0–26	14.193±6.013	14.375±5.690	13.790±4.868	1.14	0.32
DBIL, μmol/L	0–6.8	2.570±1.618	2.485±0.964	2.429±0.855	2.027	0.132
IBIL, μmol/L	5.1–18.3	11.613±4.737	11.870±4.756	11.441±4.106	1.199	0.302
ALP, U/L	45–125	69.900±19.907	76.060±20.607	74.87±18.495	31.194	<0.001
Cr, μmol/L	59–104	79.051±22.452	83.428±17.230	80.686±16.754	12.178	<0.001
UA, μmol/L	208–428	372.107±91.402	430.315±93.411	458.440±101.664	201.8	<0.001
UREA, mmol/L	3.1–8.0	4.929±1.264	5.017±1.317	5.085±1.087	3.073	0.046
TC, mmol/L	0–5.18	5.283±1.037	5.437±1.096	5.595±1.078	16.335	<0.001
TG, mmol/L	0–1.7	1.472±1.1349	2.125±1.611	2.547±2.292	127.294	<0.001
HDL-C, mmol/L	1.04–1.55	1.402±0.300	1.252±0.245	1.209±0.220	124.922	<0.001
LDL-C, mmol/L	0–3.37	3.412±0.780	3.562±0.777	3.673±0.772	22.952	<0.001
FT3, pmol/L	3.53–7.37	5.246±1.182	5.371±0.865	5.500±0.682	10.254	<0.001
FT4, pmol/L	7.98–16	11.488±2.742	11.228±2.093	11.175±1.686	4.408	0.012
TSH, ulU/mL	0.56–5.8	2.288±2.267	2.235±1.487	2.254±1.506	0.199	0.819
FBG, mmol/L	3.9–6.1	5.196±1.088	5.586±1.344	5.816±1.558	59.049	<0.001

Notes: Mean values (±SD) for continuous variables, percentages (%) for categorical variables.

Abbreviations: DM, Diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALP, alkaline phosphatase; CR, creatinine; UA, uric acid; UREA, urea nitrogen; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

Correlation Between Thyroid Hormone Levels and CAP

The findings from the multiple regression analysis are displayed in Table 2. According to the unadjusted model, FT3 was strongly correlated with CAP [6.891 (5.396, 8.386)]. This significant correlation remained after adjusting for covariates such as sex, age, hypertension status, diabetes status, and coronary heart disease status [5.981 (4.56, 7.403)]. After adjusting for all covariates, Model 3 also showed a positive correlation between FT3 and CAP [2.182 (1.154, 3.211)]. The regression analysis of FT4 and CAP indicated a negative correlation in all three models (−2.776 (−3.422, −2.13), −2.46 (−3.07, −1.851), and −0.855 (−1.297, −0.412)]. Our findings in the subgroup analysis by sex showed a strong positive relationship between FT3 and CAP, as well as a notable negative relationship between FT4 and CAP across all three models. According to the subgroup analysis based on the level of liver fat accumulation, FT3 was positively associated with CAP in both the non-NAFLD and NAFLD groups. However, in the severe steatosis group, FT3 showed a negative correlation with CAP even after accounting for all potential influencing factors [−3.804 (−6.711, −0.898)]. In the non-NAFLD group, there was an inverse relationship between FT4 and CAP, although this relationship did not reach

Table 2 The Association Between Thyroid Hormone Levels and CAP

	Model 1 β (95% CI) P value		Model 2β (95% CI) P value		Model 3 β (95% CI) P value	
FT3	6.891 (5.396,8.386)	<0.001	5.981 (4.56,7.403)	<0.001	2.182 (1.154, 3.211)	<0.001
FT4	−2.776 (−3.422, −2.13)	<0.001	−2.46 (−3.07, −1.851)	<0.001	−0.855 (−1.297, −0.412)	<0.001
TSH	−0.046 (−0.685,0.592)	0.887	0.179 (−0.428,0.787)	0.562	0.042 (−0.391, 0.474)	0.850
Male						
FT3	5.916 (3.918,7.915)	<0.001	6.534 (4.523,8.546)	<0.001	1.626 (0.188, 3.065)	0.027
FT4	−2.17 (−2.963, −1.376)	<0.001	−2.23 (−3.02, −1.44)	<0.001	−0.729 (−1.295, −0.162)	0.012
TSH	0.503 (−0.298,1.305)	0.218	0.407 (−0.392,1.207)	0.318	0.166 (−0.397, 0.729)	0.563
Female						
FT3	5.249 (2.906,7.593)	<0.001	5.479 (3.234,7.725)	<0.001	2.835 (1.137, 4.533)	0.001
FT4	−2.519 (−3.583, −1.455)	<0.001	−2.575 (−3.596, −1.554)	<0.001	−1.234 (−1.996, −0.473)	0.002
TSH	0.338 (−0.624,1.3)	0.491	−0.264 (−1.195,0.666)	0.577	−0.207 (−0.893, 0.478)	0.553
S0						
FT3	3.016 (1.758,4.274)	<0.001	2.389 (1.194,3.584)	0.001	1.259 (0.218, 2.301)	0.018
FT4	−1.291 (−1.838, −0.743)	<0.001	−1.047 (−1.565, −0.53)	<0.001	−0.497 (−0.948, −0.045)	0.031
TSH	0.216 (−0.282,0.715)	0.395	0.234 (−0.241,0.708)	0.334	0.155 (−0.254, 0.563)	0.458
S1						
FT3	1.168 (0.434,1.902)	0.002	1.107 (0.36,1.853)	0.004	0.759 (0.071, 1.447)	0.031
FT4	−0.348 (−0.652, −0.043)	0.025	−0.338 (−0.643, −0.033)	0.03	−0.149 (−0.434, 0.136)	0.304
TSH	0.123 (−0.268,0.513)	0.537	0.16 (−0.238,0.559)	0.431	0.185 (−0.178, 0.548)	0.318
S2						
FT3	−2.473 (−5.297,0.35)	0.086	−3.341 (−6.236, −0.445)	0.024	−3.804 (−6.711, −0.898)	0.01
FT4	0.202 (−0.954,1.358)	0.731	−0.194 (−1.36,0.972)	0.744	−0.11 (−1.346, 1.126)	0.861
TSH	0.323 (−0.971,1.618)	0.623	0.393 (−0.884,1.67)	0.545	0.023 (−1.264, 1.309)	0.972

Notes: Model 1: no covariate adjustment. Model 2: adjusted for age, gender, diabetes, hypertension, and history of coronary heart disease. Model 3: adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, Cr, UA, UREA,and BMI. TC was not adjusted due to multicollinearity with LDL-C, and correlation analysis indicated no significant relationship between TC and CAP. Gender was not adjusted in the gender-stratified subgroup analysis.

statistical significance in the remaining groups. According to any model or any subgroup analysis, TSH was not significantly correlated with CAP.

An RCS regression analysis was conducted to illustrate the nonlinear correlation between FT4 and CAP, as shown in Figure 2 An L-shaped relationship was found between FT4 and CAP (P-nonlinear<0.05), with an inflection point at 11.14 pmol/L. The inflection point for the male group was 12.12 pmol/L, and for the female group, it was 11.05 pmol/L. Two-piece linear regression was used to analyze the threshold effect, as shown in Table 3. When FT4 was < 11.14 pmol/L, FT4 was negatively correlated with CAP [−2.235 (−3.355 – −1.115), P<0.001], and when FT4 was >11.14 pmol/L, the correlation between FT4 and CAP was not statistically significant. According to the female group threshold effect analysis, FT4 was negatively correlated with CAP when FT4 was <11.05 pmol/L, while when FT4 was >11.05 pmol/L, the correlation between FT4 and CAP was not statistically significant. The likelihood ratio (LR) P value was <0.05 pmol/L.

Figure 3 shows the nonlinear relationship between FT3 and CAP after controlling for all confounding factors, P-nonlinear>0.05. We also attempted two-piece linear regression (Table 4). When FT3 was greater than the inflection point, there was a positive correlation between FT3 and CAP in all participants and subgroups grouped by sex, but the likelihood ratio P value was not statistically significant.

Figure 4 shows the nonlinear relationship between TSH and CAP after controlling for all confounding factors (P-nonlinear>0.05). Consequently, we opted not to pursue piecewise regression analysis.

Discussion

The development of nonalcoholic fatty liver disease (NAFLD) is complex. The liver plays a crucial role in cholesterol and triglyceride metabolism, while thyroid hormones are essential for maintaining liver lipid balance by controlling fatty acid and cholesterol synthesis and breakdown.[14] Thyroid hormones also promote the movement of free fatty acids to the

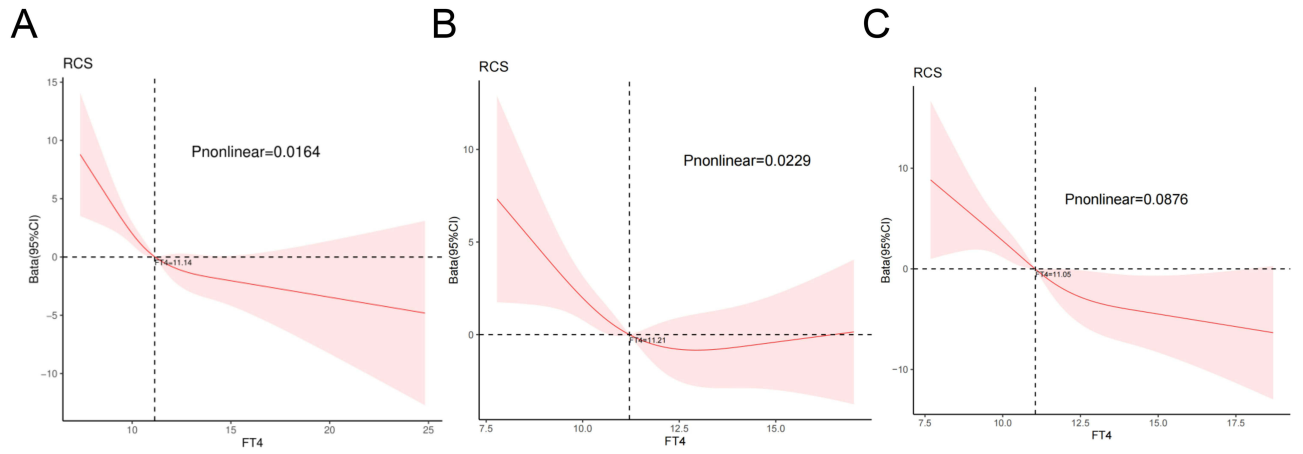

Figure 2 Nonlinear relationship between FT4 and CAP with RCS. (**A**) All participants. (**B**) Male participants. (**C**)Female participants. We selected four nodes (located at the 5th, 35th, 65th, and 95th percentiles of CAP), with regression coefficients Beta represented by solid lines and 95% CI by shaded areas. The reference line is Beta=0 in the prediction table. Adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, UA, Cr, UREA, and BMI.

liver for conversion into triglycerides and enhance fatty acid oxidation, impacting liver fat storage.[15] Furthermore, thyroid hormones have anti-inflammatory effects and can regulate immune responses by influencing the function of immune cells, such as macrophages and T cells.[16] FT4, for example, has been shown to block the synthesis of proinflammatory cytokines such as TNF-α and IL-6,[17] which play crucial roles in the inflammatory process that causes liver steatosis and the progression of fatty liver inflammation.

Current research consistently indicates that hypothyroidism is a significant risk factor for NAFLD.[18,19] This cross-sectional retrospective study revealed a marked negative correlation between FT4 levels and liver CAP, which remained significant even after adjusting for demographic characteristics such as gender and age, as well as common risk factors for fatty liver disease like cholesterol levels, hyperglycemia, heart disease, and liver and kidney function. This finding suggests that lower FT4 levels may be associated with higher liver fat content, aligning with previous studies that proposed a link between low FT4 levels and a higher incidence of NAFLD.[20,21] Upon further analysis of the non-linear relationship, we found that the regression coefficient between FT4 and CAP exhibited an L-shaped distribution after controlling for all confounding factors. Based on this finding, we conducted threshold effect analysis using segmented linear regression. The results showed that when FT4 concentrations were below 11.14 pmol/L, the negative correlation between FT4 and CAP was highly significant (P<0.001). However, when FT4 concentrations were at or above 11.14 pmol/L, a negative correlation between FT4 and CAP was still observed, but it did not reach statistical significance.

Table 3 Threshold Effect Analysis Between FT4 and CAP

Two - Piecewise Linear Regression Model	β (95% CI)	P
FT4<11.14	−2.235 (−3.355 – −1.115)	<0.001
FT4≥11.14	−0.392 (−0.952–0.169)	0.171
Log - likelihood ratio test		0.008
Male		
FT4<12.12	−1.960 (−3.320 – −0.601)	0.005
FT4≥12.12	−0.198 (−0.975–0.579)	0.617
Log - likelihood ratio test		0.057
Female		
FT4<11.05	−3.158 (−5.152 – −1.165)	0.002
FT4≥11.05	−0.712 (−1.662–0.198)	0.125
Log - likelihood ratio test		0.041

Notes: Adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, UA, Cr, UREA, and BMI.

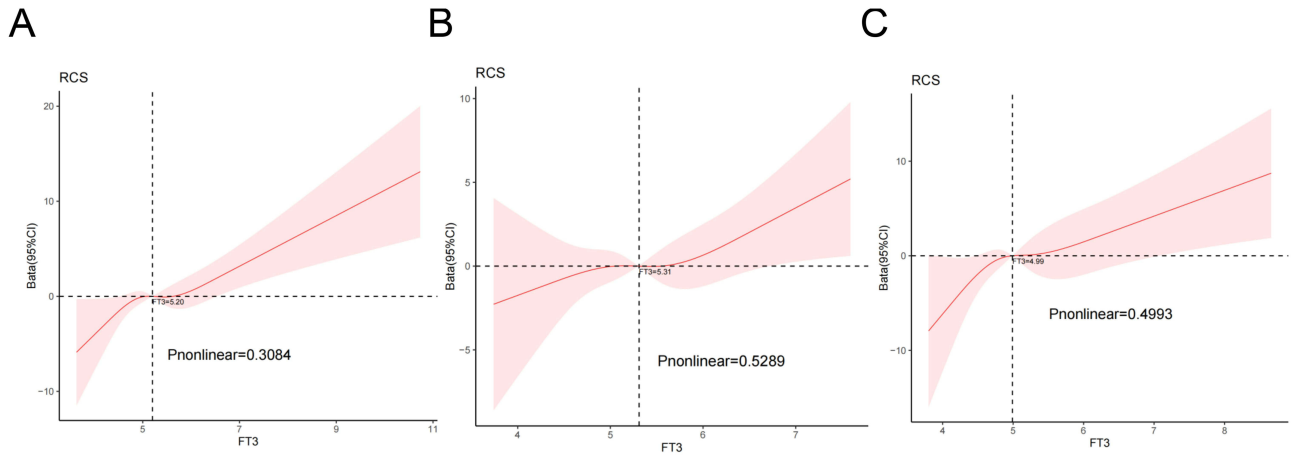

Figure 3 Nonlinear relationship between FT3 and CAP with RCS. (**A**) All participants. (**B**) Male participants. (**C**) Female participants. We selected four nodes (located at the 5th, 35th, 65th, and 95th percentiles of CAP), with regression coefficients Beta represented by solid lines and 95% CI by shaded areas. The reference line is Beta=0 in the prediction table. Adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, UA, Cr, UREA, and BMI.

Previous studies have identified a negative non-linear relationship between FT4 levels and the incidence of non-alcoholic fatty liver disease,[22,23] but did not delve into threshold effect analysis. The exact mechanism behind this phenomenon remains unclear, but studies have confirmed the importance of thyroid hormones in maintaining immune balance and reducing inflammation within a certain range.[24] Our data suggest that exceeding this threshold might diminish the immunomodulatory effects of FT4, thereby reducing its protective influence on hepatic steatosis. Thyroid hormone treatment for NAFLD may potentially reduce liver fat content to some extent,[25,26] but the related research primarily uses TSH as the main observation point, with the optimal treatment threshold still undefined, and changes in FT4 levels during treatment not being statistically significant. Based on the L-shaped relationship between FT4 and CAP and the results of the threshold effect analysis, we propose for the first time that in the clinical context of substitution therapy for hypothyroidism, efforts should be made to increase FT4 levels if they are below 11.14 pmol/L to reduce the risk of hepatic steatosis. However, if FT4 levels are at 11.14 pmol/L or above, increasing the dose may not further reduce liver fat levels and could potentially exacerbate the side effects of thyroid hormones, such as osteoporosis and palpitations. To validate these observations, future longitudinal studies should be conducted to explore causal relationships and confirm the persistence of these findings. Additionally, the general applicability of these findings to other populations should be considered, as factors such as race, lifestyle, and dietary habits may influence the relationship between thyroid hormones and liver health.[12] Further research in diverse populations is recommended. In summary, the relationship between FT4

Table 4 Threshold Effect Analysis Between FT3 and CAP

Two - Piecewise Linear Regression Model	β (95% CI)	P
FT3<5.2	1.884 (−0.893–4.662)	0.184
FT3≥5.2	2.264 (1.015–3.512)	<0.001
Log - likelihood ratio test		0.821
Male		
FT3<5.31	0.160 (−3.080–3.400)	0.923
FT3≥5.31	2.388 (0.304–4.471)	0.025
Log - likelihood ratio test		0.322
Female		
FT3<4.99	4.985 (−0.544–10.514)	0.077
FT3≥4.99	2.498 (0.611–4.386)	0.010
Log - likelihood ratio test		0.423

Notes: Adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, UA, Cr, UREA, and BMI.

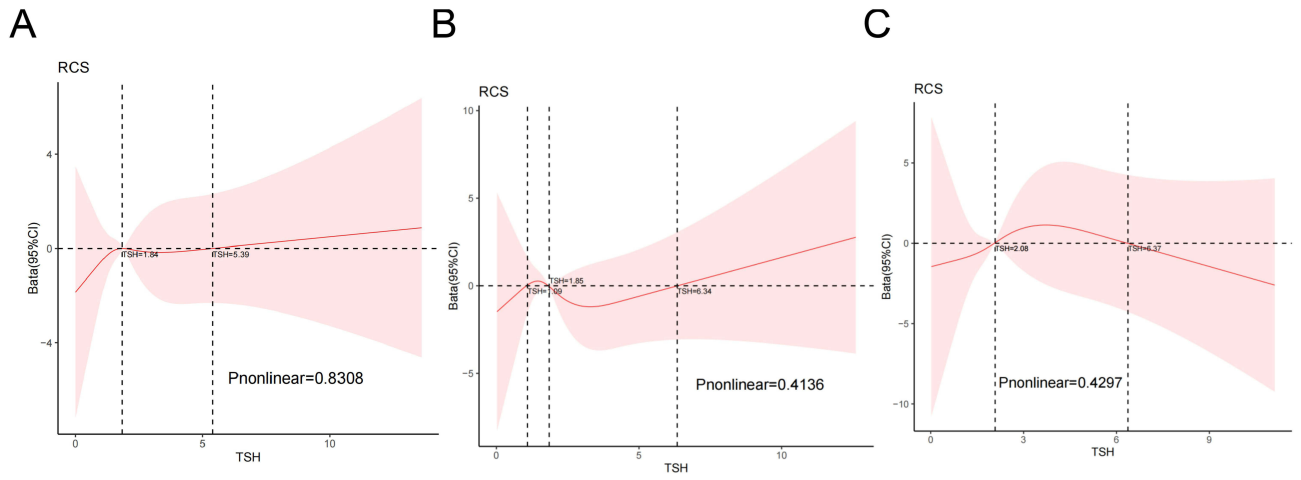

Figure 4 Nonlinear relationship between FT3 and CAP with RCS. (**A**) All participants. (**B**) Male participants. (**C**) Female participants. We selected four nodes (located at the 5th, 35th, 65th, and 95th percentiles of CAP), with regression coefficients Beta represented by solid lines and 95% CI by shaded areas. The reference line is Beta=0 in the prediction table. Adjusted for age, gender, diabetes, hypertension, coronary heart disease, ALT, AST, TBIL, DBIL, IBIL, ALP, TG, LDL-C, HDL-C, FBG, UA, Cr, UREA, and BMI.

and CAP suggests that healthcare providers should consider this FT4 level threshold when developing treatment plans, incorporating it into diagnostic procedures, treatment strategies, and patient education to optimize the management of patients with hypothyroidism.

FT3 is biologically more active than FT4 as a regulator of metabolic processes.[27] In our research, we found a strong connection between FT3 and CAP through multivariate linear regression analysis, with consistent findings in the subgroup analysis based on sex. Previous studies have reached similar conclusions,[28] potentially because T3 stimulates the breakdown of adipose tissue to produce more free fatty acids, which then serve as substrates to produce more triglycerides.[29] In severe cases of fatty liver degeneration, a negative relationship was observed between FT3 and CAP even after accounting for demographic and metabolic factors. These findings suggest that FT3 plays a complex role in hepatic fat metabolism, potentially involving different mechanisms at various levels of hepatic fat accumulation. Previous research has indicated that T3 attaches to TRβ in hepatocytes, resulting in decreased triglyceride and cholesterol levels,[30] alleviation of inflammation and oxidative stress, recovery of liver cell mitochondrial function, and inhibition of TGF-β-induced reactions,[31,32] ultimately halting the development and progression of liver fibrosis. Regarding the switch from a positive to a negative correlation in patients with severe steatosis, we identified a turning point in the nonlinear regression fit curve, but the P value of the nonlinear relationship was greater than 0.05 after controlling for all confounding factors, showing no statistical significance. After examining the threshold effect, it was found that the p value from the likelihood ratio test was greater than 0.05, indicating that there was no statistically significant difference between the models. The dual nature of the relationship between FT3 and CAP highlights the need for further research to elucidate the underlying pathways and determine whether modulating FT3 levels could be a feasible strategy for managing hepatic steatosis.

TSH is primarily responsible for regulating the production and release of thyroid hormones, including FT4 and FT3. Studies on the correlation between TSH and NAFLD have shown conflicting results, with Xu et al[19] reporting a positive correlation between higher TSH levels and NAFLD incidence, while Liu et al[12] did not support this. Our research revealed no significant association between TSH levels and CAP, indicating that TSH may not have a direct impact on hepatic fat accumulation. Because of the intricate feedback systems that control thyroid function, TSH levels may not provide an accurate indication of the availability and effectiveness of thyroid hormones within tissues. Additionally, the effect of TSH on hepatic fat content may be masked by the direct effects of FT4 and FT3 on CAP. Further research is needed to explore the potential indirect effects of TSH on hepatic metabolism and clarify its role in the context of hepatic steatosis.

CAP represents a relatively novel approach for assessing liver steatosis in comparison to more invasive methods such as liver biopsies. The identification of a potential threshold for FT4 below which there is a negative correlation with CAP adds a new dimension to our understanding of how thyroid hormones might

impact liver fat content. The gender-specific correlations offer novel insights that could pave the way for more personalized treatment strategies in the future. However our study is conducted with a specific population, and the results may not be generalizable to other demographic groups or settings. Future studies could address this by including more diverse populations. The research can only establish associations, not causality, as a cross-sectional study. The temporality of the relationship between thyroid hormones and liver steatosis cannot be confirmed. While the study controls for several variables, other confounding factors not accounted for in the analysis may influence the results. A longitudinal study design could be considered in future research to better understand progression and causality. While CAP is a non-invasive method for assessing liver steatosis, its accuracy and reliability should be considered compared to more established diagnostic methods like liver biopsy.

Conclusion

Our research has uncovered significant linear and nonlinear relationships between thyroid hormone levels (FT4 and FT3) and liver fat content (CAP), suggesting that thyroid function may be a key factor in the progression of liver steatosis. These findings offer new perspectives and potential therapeutic approaches for the prevention and treatment of liver steatosis. Future studies should focus on overcoming the identified limitations, including conducting longitudinal studies and clinical validation research, to further validate our findings.

Data Sharing Statement

The data are available upon request to the corresponding author.

Ethical Approval

Our study complies with the Declaration of Helsinki, and the study was approved by the Medical Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (Ethics-KY-IIT-2023-91).

Ethics

Our study complies with the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

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Author Contributions

Sumei Li and Xingye Wu are first authors, 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.

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Disclosure

The authors report no competing or financial interests regarding the submitted work.

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