

Relationship Between Thyroid Hormone and Liver Steatosis Analysis Parameter in Obese Participants: A Case-Control Study

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Objective: The thyroid hormone has been demonstrated to be associated with nonalcoholic fatty liver disease (NAFLD) in different populations. However, the relationship between thyroid hormone and the degree of liver steatosis in overweight/obese subjects is still unclear. Liver ultra-sound attenuation (LiSA) is a newly developed ultrasound attenuation parameter for the analysis of hepatic steatosis. The study aimed to characterize the relationship between thyroid hormone and LiSA in overweight/obese participants.

Methods: This case-control study was performed in Ningbo First Hospital, China. A total of 24 lean, 66 overweight and 49 obese participants were consecutively recruited from January 2021 to May 2021. Thyroid hormone and other clinical features were measured. LiSA was acquired by using a Hepatus ultrasound machine. Multiple linear regression analyses were performed to examine associations of LiSA and clinic indices.

Results: Obese subjects had higher LiSA, ft3 and TSH levels than lean participants of similar age and sex ($P < 0.05$). LiSA was positively associated with the ft3 level. The multiple linear regression analyses showed that ft3 ($\beta = 0.353$, $P < 0.001$) was independently associated with LiSA in overweight/obese participants.

Conclusion: The ft3 level was independently associated with the degree of liver steatosis among the overweight/obese participants.

Keywords: LiSA, obesity, NAFLD, thyroid hormone

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive lipid accumulation and liver injury in the absence of significant alcohol use, which subsumes a variety of entities ranging from simple fatty liver or hepatic steatosis, non-alcoholic steatohepatitis (NASH), to liver fibrosis and cirrhosis.¹⁻³ Currently, the prevalence of NAFLD is up to 20–30% and is projected to continue to increase because of the ongoing obesity epidemic beginning in childhood, the rise in the prevalence of diabetes, and other factors.^{4,5} The development of NAFLD has been ascribed to metabolic disease, such as obesity, insulin resistance, type-2 diabetes mellitus, and dyslipidemia.⁶ Early diagnosis and stratification of NAFLD are essential for early intervention and effective management. In 2020, experts from the European Liver Patient's Association (ELPA) proposed a change of nomenclature from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), defined as hepatic steatosis along with three metabolic conditions: obesity, diabetes and metabolic disorders.⁷ Although MAFLD was a more positive and clinical diagnosis compared to NAFLD, the concept

of MAFLD is new and the clinical research on MAFLD is relatively insufficient at present. Therefore, NAFLD instead of MAFLD was used in this study.

Among several noninvasive techniques (ultrasound, computed tomography, and magnetic resonance imaging) that can be used to diagnose liver steatosis, ultrasonography is the most widely used.⁸ The degree of fatty liver can be quantitatively evaluated by detecting the attenuation of ultrasound in the liver. Recently, controlled attenuation parameter (CAP) was widely used to quantitatively detect and evaluate fatty liver.^{9,10} However, the ultrasound signal used to calculate the CAP only comes from the one-dimensional ultrasound echo signal of a certain part of the liver. When the detected tissue position changes, the measurement result is unstable Liver Ultra-Sound Attenuation (LiSA), acquired by Hepatus (Mindray, China), is a newly developed ultrasound attenuation parameter for diagnosing liver steatosis analysis. The detection principle of LiSA is the same as that of CAP, and the results of both correspond to the sound attenuation parameters of 3.5Hz ultrasound. Compared with CAP, LiSA has obvious advantages: (1) Hepatus performs a quantitative assessment of liver fibrosis and fatty change under the visual guidance, ensuring that blood vessels and lesions are avoided, greatly reducing the difficulty of operating and improving the success rate; (2) The machine can obtain real-time two-dimensional ultrasound echo signals in a large range area and perform comprehensive calculations of ultrasound attenuation parameters. Therefore, the results are more stable and the detection efficiency is higher. A recent study has demonstrated that LiSA is an extremely efficient tool for assessing liver steatosis and can provide immediate results with high sensitivity; also, LiSA and CAP are highly correlated in diagnosing hepatic steatosis.¹¹ The cutoff value of CAP for diagnosing fatty liver (< 238dB/m, 238 ~ 258 dB/m, 259 ~ 291 dB/m, ≥ 292 dB/m) is also applicable to LiSA, because of the same detection principle and the high correlation confirmed by literature report.¹²

Thyroid hormone plays an important role in maintaining metabolic homeostasis at the systemic and hepatic levels by its influence on de novo lipogenesis, beta-oxidation, cholesterol metabolism, and carbohydrate metabolism.^{13,14} It is increasingly recognized that the thyroid hormone levels may be associated with the risk of NAFLD.¹⁵ Our previous study found that visceral fat and thyroid hormone interacted with each other.¹⁶ However, no studies examined the relationship between thyroid hormone and LiSA in overweight/obesity participants. In this context, a case-control study was performed to evaluate the relationship between thyroid hormone and LiSA in overweight/obese participants and to explore further the new understanding and direction of the pathophysiological mechanism of NAFLD.

Materials and Methods

Study Participants

The present study consecutively enrolled 24 lean healthy, 66 overweight, and 49 obese participants aged 18–60 years from the Ningbo First Hospital (Zhejiang province, China), between January 2021 and May 2021. Considering ethnic differences, our study adopted the obesity diagnostic criteria recommended by WHO for the Chinese people:¹⁷ BMI ≥ 24 kg/m² is overweight, and BMI ≥ 28 kg/m² is diagnosed as obesity. The exclusion criteria were as follows: (1) patients with a history of taking medications that can affect thyroid function; (2) hyperthyroidism or hypothyroidism; (3) History of thyroid cancer or thyroid surgery; (4) history of hypothalamus or pituitary disease; (5) long-term alcohol consumption; (6) history of viral hepatitis, autoimmune hepatitis, and Wilson's disease; (7) total parenteral nutrition, inflammatory bowel disease, or Cushing's syndrome; (8) Taking tamoxifen, amiodarone, sodium valproate, methotrexate, or glucocorticoids. Written informed consent was obtained from all the individuals, and the study was approved by the ethics committee of the Ningbo First Hospital. The purposes and procedures of the study were explained to the participants prior to the questionnaire and blood data collection.

Clinical and Laboratory Examination

The demographic data including age, sex and medical history were obtained from the clinical documents of outpatient department of Ningbo First Hospital and the National Standardized Metabolic Disease Management Center. According to the routine protocol, the information of complete physical examination including height, weight, waist circumference (WC) and blood pressure was recorded after overnight fasting for 8 to 10 hours, and BMI was calculated by body weight (kg)/ height squared (m²). The general laboratory tests included the levels of fasting blood glucose (FBG), fasting plasma

insulin (FINS), glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4). Insulin resistance index (HOMA-IR) was calculated by the formula $\text{FBG} \times \text{FINS}/22.5$. All biochemical parameters were detected by standard automated laboratory methods using commercially available kits following the manufacturers' protocols.

Measurement of Liver Steatosis

Measurement of LiSA was performed by Hepatus (Mindray, China), a newly developed ultrasound machine with a 3.5-MHz phased-array probe (LFP5-1U, Mindray, Re 6S, China). The attenuation of ultrasound propagation in the liver tissue was increased by fat accumulation. Therefore, the detection of ultrasonic attenuation coefficient is a quantitative method for grading liver steatosis.¹⁸ Experienced technicians performed examinations following the manufacturer's instructions. The operator obtained real-time two-dimensional ultrasound images through the probe to locate the interested detection site (avoiding gallbladder, liver capsule, fat layer, kidney, and thick blood vessels) before the measurement. All patients were placed in the dorsal decubitus position, with their right arms extended and lifted. The examinee breathes calmly for 6–7 s, and the right hepatic lobe is assessed through an intercostal approach using ultrasound imaging. During the measurement process, the real-time synchronous two-dimensional ultrasound image helped the operator to observe whether the position of the detection target changes or not. Probes with pressure sensors are another advantage. The signal on the probe can feedback the pressure to the operator in real time, thus improving the stability and accuracy of the detection. LiSA was calculated according to the attenuation of 3.5-MHz ultrasound in two-dimensional ultrasound echo signals of the liver. The final LiSA value was the median of individual measurements, and the interquartile range < 40 dB/m was used as a quality criterion. The classification of liver ultrasonic attenuation parameters in this study refers to the French multi-center clinical study by Sasso et al.¹² Using liver biopsy as the gold standard, the cut-off value of CAP for diagnosing fatty liver in patients with chronic hepatitis B, chronic hepatitis C and NAFLD was as follows: $S \geq S1$ ($\geq 10\%$): 238 dB/m; $S \geq S2$ ($\geq 34\%$): 259 dB/m; $S \geq S3$ ($\geq 67\%$): 292 dB/m¹². Due to the high correlation between LiSA and CAP, the stratification method of LiSA in this study was as follows: group A (LiSA \leq 238dB/m, no hepatic steatosis); group B (238dB/m < LiSA \leq 291dB/m, mild and moderate hepatic steatosis); group C (LiSA > 291dB/m, severe liver steatosis).

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences 24.0. Before proceeding with the statistical analysis, all the parameters were tested for a normal distribution using the Kolmogorov–Smirnov test. Normal-distribution variables were expressed as the mean \pm standard deviation. Normal-distribution variables between the two groups were compared with the independent sample *t*-test. One-way analysis of variance was used for comparison among the three groups. Nonnormally distributed variables were expressed as the median (inter-quartile range). Nonnormally distributed variables between the two groups were compared with the Mann–Whitney test, while the Kruskal–Wallis test was used for the comparison of the three groups. Categorical variables were compared using the chi-Square (χ^2) test. The relationships between LiSA and clinical parameters were evaluated using Spearman correlation coefficient. Multiple linear regression analysis was used to assess the independent correlation between thyroid hormone levels and LiSA. Two-tailed *P* value < 0.05 indicated a statistically significant difference.

Results

Anthropometric and Biochemical Characteristics of the Study Population

A total of 139 participants who met the inclusion criteria were included in this study, including 24 lean, 66 overweight, and 49 obese participants. The anthropometric and clinical characteristics as well as laboratory measurements of the participants are shown in Table 1. Patients with obesity had higher LiSA compared with overweight and lean individuals ($P < 0.001$). The serum fT3 and TSH levels were significantly higher in obese participants than in lean individuals ($P < 0.05$). The serum T3, T4, and fT4 levels were not significantly different among three groups. The anthropometric parameters, including BMI, WC, and SBP, were significantly higher in overweight/obesity individuals than in lean individuals ($P < 0.05$). TC, one of the

Table 1 Clinical and Laboratory Characteristics of Lean, Overweight and Obese Subjects

Characteristic	Lean Subjects (n=24)	Overweight Subjects (n=66)	Obese Subjects (n=49)	P-value
Male/female	10/14	31/35	23/26	0.894
Age (year)	49.1±6.1	45.3±12.3	43.9±11.4	0.180
BMI(kg/m ²)	22.1±1.6	26.0±1.0	32.4±4.6	<0.001 ^b
WC (cm)	81.2±5.3	89.4±5.3	105.7±8.4	<0.001 ^b
SBP (mmHg)	121.7±15.7	127.9±16.0	135.2±15.7	0.003 ^b
DBP (mmHg)	76.0±9.9	78.0±11.0	80.9±11.8	0.171
LiSA (dB/m)	228.2±40.9	251.5±68.8	288.5±58.4	<0.001 ^b
HbA1c(%)	7.0±1.9	6.9±1.7	6.5±1.4	0.429
HOMA-IR	1.9 (1.5, 2.7)	3.5 (2.2, 4.8)	5.6 (4.4, 8.3)	<0.001 ^b
TG(mmol/L)	1.2(0.8, 1.5)	1.3(0.8, 2.0)	1.6(1.2, 2.5)	0.117
TC(mmol/L)	4.4±1.3	4.8±1.4	5.2±1.3	0.048 ^a
HDL-C(mmol/L)	1.2±0.2	1.2±0.2	1.2±0.2	0.868
LDL-C(mmol/L)	2.9±1.0	3.2±1.1	3.5±1.0	0.064
T3(nmol/L)	1.5 (1.5, 1.7)	1.5(1.3, 1.8)	1.7 (1.5, 1.8)	0.102
T4(nmol/L)	114.5 (109.3, 131.4)	111.3 (102.8, 125.2)	118.2 (106.5, 130.3)	0.184
TSH(mIU/L)	1.5 (1.1, 1.7)	1.7 (1.2, 2.1)	1.8 (1.3, 2.5)	0.045 ^a
ft3(pmol/L)	5.6 (5.2, 5.9)	5.6 (5.3, 6.1)	5.9 (5.5, 6.3)	0.039 ^a
ft4(pmol/L)	11.9 (10.4, 12.7)	11.2 (10.3, 12.9)	11.5 (10.5, 12.3)	0.570

Notes: Data represent mean ± standard deviation or median (interquartile range 25–75%). ^aP<0.05, ^bP<0.01.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LiSA, steatosis analysis; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ft3, free triiodothyronine; ft4, free thyroxine.

lipid metabolic indexes, increased in obese participants ($P < 0.05$). HOMA-IR, representing insulin resistance, increased in overweight/obese individuals than in lean individuals ($P < 0.001$). No significant differences were found in sex, age, DBP, HbA1c, TG, HDL-C, LDL-C, T3, T4, and ft4 levels among the three groups ($P > 0.05$).

Anthropometric and Biochemical Characteristics of Three Groups According to the Different Levels of LiSA

All participants were further divided into 3 groups according to the different levels of LiSA (Table 2), among which 59 were in group A (LiSA ≤ 238dB/m), 39 were in group B (238dB/m < LiSA ≤ 291dB/m), and 41 were in group C (LiSA > 291dB/m). Table 2 shows that the levels of BMI, WC, SBP, DBP, HbA1c, HOMA-IR, TG, TC, and LDL-C gradually increased with the increasing LiSA levels ($P < 0.05$). Group C participants with severe liver steatosis were more likely to be young ($P < 0.05$). Increased LiSA levels were also significantly associated with increased ft3 levels ($P < 0.001$). No significant differences were found in sex, HDL-C, T3, T4, TSH, and ft4 levels among the three groups ($P > 0.05$).

Relationships Between LiSA and the Anthropometric and Laboratory Measurements in Lean, Overweight/Obese Participants

Spearman correlation analysis was performed between LiSA and the clinical characteristics in lean and overweight/obese participants (Table 3). The results showed that LiSA was positively associated with HbA1c in lean participants ($P < 0.05$). LiSA was not associated with other variables in lean participants ($P > 0.05$). LiSA was positively associated with BMI, WC, SBP, DBP, HbA1c, HOMA-IR, TG, TC, LDL-C, and ft3 in overweight/obese participants ($P < 0.05$). LiSA was not associated with other variables in obese participants ($P > 0.05$). The scatter plot illustrates the correlations between LiSA and clinical indicators (Figure 1A–J).

Table 2 Clinical and Laboratory Characteristics of Subjects with Different Degrees of LiSA

Group	Group A(n=59) ≤ 238dB/m	Group B(n=39) 238dB/m<LiSA≤291 dB	Group C(n=41) LiSA>291dB/m	P-value
Male/female	28/31	17/22	19/22	0.931
Age (year)	45.8±10.7	48.8±11.1	41.8±11.2	0.018 ^a
BMI(kg/m ²)	25.3±2.8	28.0±3.9	30.5±6.1	<0.001 ^b
WC(cm)	88.4±8.5	96.1±9.3	100.4±12.8	<0.001 ^b
SBP (mmHg)	125.0±18.0	130.2±13.9	135.4±14.6	0.008 ^b
DBP (mmHg)	75.9±11.5	77.7±9.8	83.8±10.6	0.002 ^b
HbA1c(%)	6.4±1.4	6.7±1.6	7.3±1.7	0.019 ^a
HOMA-IR	2.4(1.8, 4.0)	4.3 (2.8, 5.4)	6.2(4.3, 8.9)	<0.001 ^b
TG(mmol/L)	1.1 (0.7, 1.6)	1.5 (1.0, 2.0)	2.0 (1.4, 3.2)	<0.001 ^b
TC(mmol/L)	4.4±1.4	4.7±1.1	5.6±1.3	<0.001 ^b
HDL-C (mmol/L)	1.2±0.2	1.3±0.2	1.2±0.2	0.273
LDL-C (mmol/L)	2.9±1.0	3.1±0.9	3.8±0.9	<0.001 ^b
T3(nmol/L)	1.6(1.5, 1.8)	1.6 (1.4, 1.8)	1.6 (1.4, 1.8)	0.719
T4(nmol/L)	115.7 (106.2, 131.6)	114.1(102.8, 130.6)	112.2(104.3, 127.7)	0.761
TSH(mIU/L)	1.5 (1.1, 2.1)	1.7 (1.2, 2.8)	1.7 (1.2, 2.3)	0.159
ft3(pmol/L)	5.5 (5.2, 5.9)	5.6 (5.2, 6.0)	6.1 (5.7, 6.6)	<0.001 ^b
ft4(pmol/L)	11.8 (10.8, 12.8)	11.6 (10.3, 12.4)	10.9 (9.9, 12.2)	0.208

Notes: Group A (LiSA ≤ 238dB/m), group B (238dB/m < LiSA ≤ 291dB/m), group C (LiSA > 291dB/m). ^aP<0.05, ^bP<0.01.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LiSA, steatosis analysis; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ft3, free triiodothyronine; ft4, free thyroxine.

Multivariate Regression Analysis Regarding the Relationship Between Thyroid Hormone and LiSA in Overweight/Obese Participants

A stepwise multiple linear regression model was performed to evaluate the relationship between these variables and LiSA. The multivariate model consisted of LiSA as the dependent variable and BMI, WC, SBP, DBP, HbA1c, HOMA-IR, TG, TC, LDL-C, and ft3 as independent variables that had significant relationships with LiSA in the Spearman correlation analysis. The residuals plots for the linear regression model are shown in [Figure 1K](#) and [L](#). The results revealed that ft3 ($\beta = 0.353$, $P < 0.001$), WC ($\beta = 0.312$, $P = < 0.001$) and HbA1c ($\beta = 0.208$, $P = 0.009$) were independently associated with LiSA in overweight/obese participants ([Table 4](#)).

Discussion

The present study explored the relationship of thyroid hormone (ft3) and LiSA in Chinese overweight/obese subjects using case-control study design. We found that obese subjects have higher LiSA, ft3 and TSH levels than lean participants of similar age and sex. Spearman's correlation analyses showed that ft3 were significantly and positively correlated with LiSA. Multivariable linear regression analyses also illustrated that LiSA was positively associated with ft3 level in overweight/obese subjects after adjusting potential confounding factors. This study was novel in specifically addressing the relationship between thyroid hormone and LiSA in Chinese overweight/obese subjects.

Many studies have reported the correlation between thyroid hormone (ft3,ft4,T3,T4,TSH) and obesity-related anthropometric parameters (BMI, WC, waist-to-height ratio, visceral fat area, etc.),^{19–23} although the relationship and opinions in different studies differs.²⁴ Thyroid hormone plays an important role in the balance of energy metabolism in the body, and leptin may be a potential link between thyroid hormone and obesity metabolic pathway. Leptin can promote the conversion of ft4 to ft3 by affecting the activity of deiodinase in peripheral tissues.^{25–27} The positive correlation between leptin and the concentration ratio of ft3/ft4 was reported in both normal and obese subjects.²⁸ Fat accumulation of the body is an energy overload state, and the elevated ft3 levels may be an adaptive change of the body.

Table 3 Spearman Correlation Analysis of Factors Associated with LiSA in Lean, Overweight and Obese Subjects

Variable	Lean Subjects		Overweight and Obese Subjects	
	r	P	r	P
Male/female	0.208	0.330	-0.034	0.722
Age (year)	0.347	0.096	-0.052	0.582
BMI(kg/m ²)	0.343	0.101	0.367	<0.001 ^b
WC (cm)	0.316	0.309	0.392	<0.001 ^b
SBP (mmHg)	0.085	0.705	0.309	0.001 ^b
DBP (mmHg)	0.269	0.226	0.260	0.009 ^b
HbA1c(%)	0.491	0.017 ^a	0.274	0.002 ^b
HOMA-IR	0.258	0.235	0.495	<0.001 ^b
TG(mmol/L)	0.002	0.994	0.456	<0.001 ^b
TC(mmol/L)	0.196	0.359	0.268	0.004 ^b
HDL-C(mmol/L)	0.178	0.405	-0.096	0.309
LDL-C(mmol/L)	0.201	0.346	0.265	0.004 ^b
T3(nmol/L)	-0.054	0.803	0.049	0.604
T4(nmol/L)	-0.030	0.891	-0.075	0.425
TSH(mIU/L)	0.306	0.146	0.075	0.427
ft3(pmol/L)	0.166	0.439	0.376	<0.001 ^b
ft4(pmol/L)	-0.293	0.164	-0.150	0.109

Note: ^aP<0.05, ^bP<0.01.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LiSA, steatosis analysis; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ft3, free triiodothyronine; ft4, free thyroxine.

NAFLD is known to frequently coexist with obesity and type 2 diabetes mellitus (T2DM), and they act synergistically to promote the deterioration of adverse clinical outcomes (hepatic and extra-hepatic).^{29,30} Obesity and T2DM are strongest risk factors for the progression of NAFLD to nonalcoholic steatohepatitis, liver fibrosis or cirrhosis.³¹ The links between these three diseases are complex, and the interactions are intricate. In our study, we showed a positive association between LiSA and WC and HbA1c, which is consistent with previous research reports and the logical relationship between these diseases. It indicates that weight management and blood glucose control are very important for the treatment of NAFLD.

Several studies reported the relationships between thyroid function parameters and the risk of NAFLD, but the results are somewhat controversial. Four studies supported a positive correlation between the ft3 level and the risk of NAFLD.^{32–35} In contrast, two studies did not find any significant relationship between them.^{36,37} These discrepancies among previous studies might be due to several reasons. Firstly, the region and ethnicity were different. The study by van den Berg et al³² were performed in Germany, while the other studies were performed in China. Secondly, the age of participants was varied among studies. In the study by Xu et al, all participants were equal to or more than 65 years.³⁶ In a study by Tao et al, the age was unrestricted.³⁷ In the study by Liu et al, the age of participants ranged from 35 to 60 years.³³ In the study by Ma et al, the mean (\pm SD) of age was 30.0 \pm 7.2 years old.³⁵ Thirdly, the disease characteristics of the study population were different among studies. In the studies by Tao et al,³⁷ Xu et al,³⁶ Ma et al³⁵ and van den Berg et al³² euthyroid participants were selected. In the study by Ding et al³⁴ patients with hepatitis B virus were enrolled. Fourthly, the study design was different among studies. The study by Liu et al was a randomized controlled trial exploring the impact of levothyroxine supplementation on the prevalence of NAFLD in patients with subclinical hypothyroidism,³³ and the remaining studies were cross-sectional studies.

Thyroid hormones included triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), free triiodothyronine (ft3), and free thyroxine (ft4). Thyroid hormones are mostly bound to thyroxine-binding globulin in peripheral blood. The main thyroid hormones that play a physiological role are FT4 and FT3, and the physiological activity of FT3 is three to four times that of FT4. In our study, we found no significant correlation between other thyroid

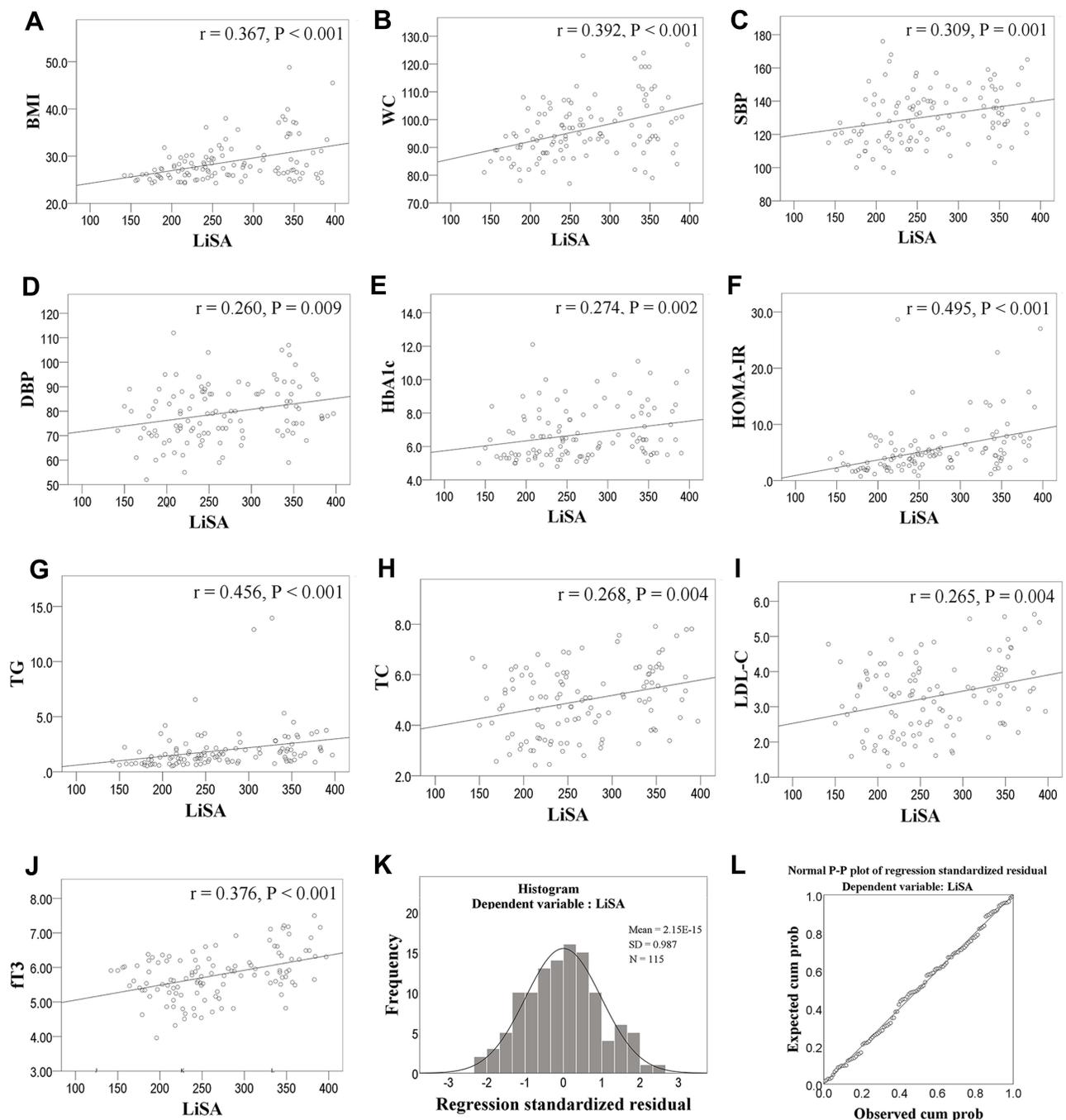


Figure 1 (A–J) Scatter plot showing significant Spearman correlation between LiSA and clinical indicators. **(K)** Histogram of residuals for the linear regression model. **(L)** Normal probability plot of regression standardized residual for the linear regression model.

hormones (fT4, T3, T4 and TSH) and LiSA. This is partly due to the relatively small sample size of our study. Studies with larger sample sizes and prospective studies are needed in our future research. In addition, FT3 plays a direct role in the physiological function, and its level is more directly related to the metabolic state of the body. Therefore, the statistical results of FT3 are more sensitive than other thyroid hormone indicators (fT4, T3, T4 and TSH).

Our study was unique and different from the previous studies. First of all, we selected lean participants as the control group, and found no correlation between LiSA and thyroid hormone, suggesting that the correlation between LiSA and thyroid hormones only existed in overweight/obese participants. In the second place, the lean group and overweight/

Table 4 Stepwise Multiple Linear Regression Analyses of Variables Associated with LiSA in Overweight and Obese Subjects

Variables	B	β	T	P	95% CI
fT3	34.735	0.353	4.441	<0.001	19.236–50.234
WC	1.980	0.312	3.919	<0.001	0.979–2.981
HbA1c	8.881	0.208	2.661	0.009	2.267–15.495

Abbreviations: fT3, free triiodothyronine; WC, waist circumference; HbA1c, hemoglobin A1c.

obese group in our research are similar in age, which greatly eliminates the influence of confounding factors of age differences. Thirdly, we conducted the subgroup analyses according to the degree of liver steatosis to further explore the clinical characteristics of different subgroup. In addition, we conducted the stepwise multivariate analyses to further evaluate the relationship of fT3 with LiSA and to eliminate the influence of other confounding factors. Last but not least, LiSA was used to evaluate the degree of NAFLD in our study, and the effectiveness and stability of LiSA are currently superior to other ultrasonic attenuation parameter.

Two major limitations in our research should be recognized. In the first place, the sample size in our study is relatively small, so the uncertainty caused by the correlation estimation of the small sample size will increase. Secondly, the present study cannot evaluate a direct causal relationship between thyroid hormones and LiSA, and further mechanism research and prospective cohort studies are necessary.

Conclusion

The present study is novel in specifically addressing the relationship between thyroid hormone and LiSA in Chinese overweight/obese subjects. Higher level of serum fT3 was independently associated with the degree of liver steatosis. The alterations in thyroid hormone levels may be an adaptation process of liver steatosis in obesity patients. Large-scale, multi-ethnic, multi-regional, population-based, prospective studies are still needed to confirm our findings.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

The study was approved by the Ethics Committee of Ningbo First Hospital and was conducted in accordance with the Declaration of Helsinki.

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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.

Disclosure

The authors declare no conflicts of interest in this work.

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