Sensitivity to Thyroid Hormone Indices Are Closely Associated With NAFLD

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Background: Previous studies on the association between thyroid function and non-alcoholic fatty liver disease (NAFLD) have contradicted. Acquired resistance to thyroid hormone theory might provide a reasonable explanation for these contradictions. We aimed to analyze the association between sensitivity to thyroid hormone indices with NAFLD.

Methods: A total of 4,610 individuals from the health medical center of the First Hospital of China Medical University were included in this study. The previously used thyroid feedback quantile-based index (TFQIFT4) was calculated. Also, we substituted free triiodothyronine (FT3) into the TFQI formulas to get the TFQIFT3 index. NAFLD was defined using abdominal ultrasound.

Results: Study results showed that FT3/FT4 and TFQIFT3 were positively correlated with the triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels (P<0.05) and negatively correlated with high-density lipoprotein cholesterol (HDL-C) level (P<0.05). In contrast, TFQIFT4 was positively correlated with HDL-C level (P<0.05). After adjustment for multiple confounders, FT3, FT3/FT4, and TFQIFT3 were positively associated with the risks of dyslipidemia and NAFLD (P<0.05). TFQIFT3 and FT3/FT4 performed better than TFQIFT4 on ROC analyses for NAFLD prediction, although the diagnostic sensitivity and specificity at the optimal cut-points were low. However, no association was observed between TFQIFT4 with the risks of dyslipidemia and NAFLD.

Conclusion: TFQIFT3 and FT3/FT4 can be used as new indicators for predicting dyslipidemia and NAFLD, although with low sensitivity and specificity at the optimal cut-points, while TFQIFT4 has insufficient evidence in predicting dyslipidemia and NAFLD.

Keywords: thyroid function, sensitivity to thyroid hormone indices, thyroid feedback quantile-based index, dyslipidemia, non-alcoholic fatty liver disease
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) includes a broad range of conditions from fat accumulation within the liver (simple steatosis), liver inflammation (non-alcoholic steatohepatitis, NASH) through to liver fibrosis and cirrhosis, the latter having an increased risk for progression to hepatocellular carcinoma. What is more, emerging evidence has shown that NAFLD is an increased risk for progression to hepatocellular carcinoma. What is more, emerging evidence has shown that NAFLD is related to extrahepatic complications such as obesity, type 2 diabetes, cardiovascular diseases, kidney diseases, malignancy, and all-cause mortality (1). Despite this alarming evidence, the nomenclature and the definition of NAFLD have not been updated to reflect the latest knowledge. The heterogeneity of the population with NAFLD concerning its causal factors and the comorbidities represents an essential impediment to discovering highly effective medications. Thus, to more accurately reflect the heterogeneity of the disease, the international consensus panel has recently advised using metabolic associated with fatty liver disease (MAFLD) instead of NAFLD (2). Nevertheless, for the sake of this study, we will continue the use of NAFLD, which has been used in our previous data and has been widely accepted in the literature.

The liver plays an essential role in lipid metabolism, including the synthesis and transportation of cholesterol and triglycerides (3). Disorder of hepatic lipid metabolism may precipitate the fat retention within the liver and subsequent development of dyslipidemia and NAFLD. Thyroid function is one of the most important factors regulating liver lipid metabolism. Epidemiological data showed that the prevalence of NAFLD was 27.4–33.1% in the population with euthyroidism, 35.7–36.3% in the population with hypothyroidism, and 11.95–21.5% in the population with hyperthyroidism (4–6). Several studies also demonstrated that free thyroxine (FT₄) and free triiodothyronine (FT₃) serum levels were negatively associated with the risk of NAFLD and thyroid-stimulating hormone (TSH) serum levels were positively associated with the risk of NAFLD in the population with thyroid dysfunction (7–11). Furthermore, systematic reviews confirmed the positive association between hypothyroidism and NAFLD risk (12, 13). On the other side, thyroid dysfunctions both in the form of overt and subclinical hypothyroidism were more common among patients with NAFLD (14–16).

However, results from euthyroid patients were inconsistent. From a large cohort study, higher-normal serum FT₃ and lower-normal serum TSH levels were independently related to a higher incidence of NAFLD (17). Thus, a mild acquired resistance to thyroid hormone might exist in the euthyroid population with NAFLD. So far, however, there has been little research on the association between sensitivity to thyroid hormone indices with the risk of NAFLD. Thyroid Feedback Quantile-based Index (TFQI) was proposed by Laclaustra, a novel index of central sensitivity to thyroid hormone. Laclaustra found that TFQI was related to cardiometabolic health characteristics in the general population (18). Therefore, this cross-sectional study aimed to investigate the direct association of central sensitivity to thyroid hormone (evaluated by TFQI) and peripheral sensitivity to thyroid hormone (evaluated by FT₃/FT₄) with dyslipidemia and NAFLD, trying to overcome current contradictions about the association between circulating thyroid hormone levels and hepatic alterations.

METHODS

Subjects and Study Design

The participants consisted of 7,689 adults (age ≥ 14 years old) who completed health examinations at the health medical center of the First Hospital of China Medical University from January 1, 2017, to December 31, 2018. Exclusion criteria: 1) Age < 14 years old (n = 0); 2) Missing data (n = 499); 3) Patients with history of thyroid diseases (n = 292); 4) Thyroid antibody abnormalities (n = 2288). After exclusion, 4,610 participants were included in the final retrospective cross-sectional analysis (Figure 1). The study was approved by the Ethics Committee of the First Hospital of China Medical University. An informed consent waiver was obtained for using de-identified data.

Data Collection

The participants were examined after overnight fasting for 8-12 h in the morning. 1) Gender, age (years), weight (kg), height (meter), waist circumference (WC), systolic blood pressure (SBP, mmHg), and previous medical history of the participants were measured and recorded. 2) Body mass index (BMI) was derived by dividing the weight in kilograms by the squared height in meters (kg/m²). 3) WC was determined at mid-abdomen (midpoint between subcostal and supraumbilical landmarks according to WHO protocol) (19). 4) BP was measured after at least five minutes of rest and averaged twice BP reading measured at an interval of two minutes.

Biochemical Measurements

An automatic biochemical analyzer (Hitachi, Japan) was utilized for biochemical parameters measurement, including fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC) levels. Hyper-triglyceridermia (hyper-TG), hyper-cholesterolemia (hyper-TC), hypo-high-density lipoprotein cholesterolemia (hypo-HDL), hyper-low-density lipoprotein cholesterolemia (hyper-LDL) were defined as TG ≥ 1.7 mmol/L, TC ≥ 5.2 mmol/L, HDLC < 1.0 mmol/L, and LDLC ≥ 3.4 mmol/L, respectively, and dyslipidemia if any one of them (20). Serum levels of FT₃, FT₄, TSH, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were determined by electrochemiluminescent immunoassays on Architect i2000SR (Abbott Laboratories, Chicago, IL, USA). The reference ranges of FT₃, FT₄, and TSH were 2.63-5.70 pmol/L, 9.01-19.05 pmol/L, and 0.35-4.94 mU/L, respectively. The thyroid antibody abnormality was defined as TPOAb ≥ 5.61 IU/ml and/or TgAb ≥ 4.11 IU/ml. TFQI is achieved by the algorithm TFQI = cumulative distribution function (cdFT₄) – (1 – cdTSH) (18). In order to investigate the role of FT₃ in this index, FT₄ in TFQITT₄ formulas was replaced with FT₃ to obtain TFQI. The value of TFQI ranged from -1 to 1. For TFQI, negative values indicated that the hypothalamus-pituitary-thyroid axis was more sensitive to the
change of thyroid hormones; positive values indicated low sensitivity; the value of 0 indicated a normal sensitivity.

**Abdominal Ultrasonography and NAFLD Definition**

Abdominal ultrasonography (USG) was used to test liver disease. All participants underwent abdominal USG (Siemens Acuson X300, German). NAFLD was defined by at least two of the following positive ultrasound finding (1. The liver near-field echogenicity is enhanced diffusely and is stronger than that of the kidney; 2. The structure of the intrahepatic duct is blurring; 3. The liver far-field echogenicity weakened gradually), and no history of heavy drinking (weekly alcohol intake ≤ 210g in males and ≤ 140g in females) (21).

**Statistical Analysis**

The data were processed using SPSS 22.0 statistical software. Continuous variables with normal distribution were shown as means ± standard deviation (SD), and the independent T-test was performed to compare groups. While continuous variables with skewed distribution were shown as medians (interquartile ranges), non-parametric Mann-Whitney tests were conducted to compare groups. All categorical variables were expressed as relative numbers, and the χ2 tests were used to compare groups. Kendall’s tau-b was used to calculate the correlation coefficient. Correlation is generally defined as very weak if correlation coefficient (r) <0.2, weak if r ≥0.2 and <0.4, moderate if r ≥0.4 and <0.6, strong if r ≥0.6 and <0.8, and very strong if r ≥0.8. To evaluate the association between thyroid parameters with lipid profiles and NAFLD, logistic regression models were used. Model 1 adjusted for demographic factors, including gender and age; model 2 adjusted all the factors adjusted in model 1 plus metabolic factors, including BMI, WC, SBP, and FPG. To evaluate the performance of the indices, we examined the receiver operating characteristics curves (ROC), which plots sensitivity against 1-specificity, and calculated the cut-points from ROC results. All calculated P values were two-sided, and a P value < 0.05 was taken to indicate a significant difference.

**RESULTS**

**Clinical Characteristics of the Participants**

The clinical baseline data of participants are shown in Table 1. A total of 4,610 participants were included in the final analysis, 2681 men (58.2%) with an average age of 47.88 ± 11.19 years. The incidence of dyslipidemia was 62.4%, higher in men than in women (66.9% vs. 33.1%, P < 0.001). Compared with the normal lipid profile group, the age, BMI, WC, SBP, FPG, FT₃, FT₃/FT₄, TFQ₁, TG, TC, and LDL-C levels in the dyslipidemia group were significantly higher (P < 0.01), the FT₄ and HDL-C levels in the dyslipidemia group were significantly lower (P < 0.01). The difference of TSH and TFQ₁ between the two groups was not statistically significant (P = 0.568, P = 0.130, respectively).

Table 2 showed that NAFLD incidence in the participants was 48.9%, higher in men than in women (75.5% vs. 24.5%, P < 0.001). Compared with the control group, the age, BMI, WC,
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; FT3/FT4, FT3 to FT4 ratio; TSH, thyroid stimulating hormone; TFQIFT3, the thyroid feedback quantile-based index calculated by FT3; TFQIFT4, the thyroid feedback quantile-based index calculated by FT4; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Age (years) 48.87±10.23 46.93±11.95 <0.001
Gender (Men/Women) 27.09±0.37 23.45±2.97 <0.001
BMI (kg/m²) 89.43±6.02 78.75±6.97 <0.001
WC (cm) 182.3±20.17 175.2±19.82 <0.001
SBP (mmHg) 4.39±0.54 4.42±0.54 <0.001
FT3 (pmol/L) 3.43±0.90 3.23±0.87 <0.001
TG (mmol/L) 4.94±0.90 4.28±0.87 <0.001
FT4 (pmol/L) 1.32±0.37 1.23±0.38 <0.001
TC (mmol/L) 3.10±0.80 3.41±0.79 <0.001
LDL-C (mmol/L) 2587 (62.4) 1926 (951) <0.001
FPG (mmol/L) 5.34 (4.99,5.91) 4.94 (4.59,5.49) <0.001
SBP (mmHg) 133.67±17.99 124.22±18.92 <0.001
WC (cm) 89.43±9.02 78.75±9.67 <0.001

TABLE 2 | Comparison of clinical characteristics between participants with and without NAFLD.

NAFLD group Control group P

| N (%) | 2252 (48.9) | 2358 (51.1) | – |
| Gender (Men/Women) | 1701 (551) | 980 (1378) | <0.001 |
| Age (years) | 48.87±10.23 | 46.93±11.95 | <0.001 |
| BMI (kg/m²) | 27.09±0.37 | 23.45±2.97 | <0.001 |
| WC (cm) | 89.43±6.02 | 78.75±6.97 | <0.001 |
| SBP (mmHg) | 4.39±0.54 | 4.42±0.54 | <0.001 |
| FPG (mmol/L) | 3.43±0.90 | 3.23±0.87 | <0.001 |
| FT3 (pmol/L) | 1.32±0.37 | 1.23±0.38 | <0.001 |
| FT4 (pmol/L) | 3.10±0.80 | 3.41±0.79 | <0.001 |

SBP, FPG, FT3, FT4, FT3/FT4, FTQIFT3, FTQIFT4, TSH, TC, and LDL-C levels in the NAFLD group were significantly higher, while the HDL-C levels in the NAFLD group were significantly lower (P < 0.01). There was no significant difference in FT4, TSH, and TFQIFT4 levels between the NAFLD group and the control group (P = 0.078, P = 0.320, P = 0.091, respectively).

Correlation Between Thyroid Parameters and Lipid Profiles

FT3 levels were positively correlated with TG, TC, and LDL-C levels and negatively correlated with HDL-C levels (r = 0.109, P < 0.001, r = 0.031, P = 0.002, r = 0.048, P < 0.001, r = -0.084, P < 0.001, respectively). However, FT4 levels were negatively correlated with TG levels and positively correlated with HDL-C levels (r = -0.044, P < 0.001 and r = 0.23, P = 0.022, respectively). While TSH levels were positively correlated with TG and TC levels (r = 0.20, P = 0.040, r = 0.25, P = 0.012) (Table 3). FT4/FT3 was positively correlated with TG, TC, and LDL-C levels (r = 0.120, P < 0.001, r = 0.029, P = 0.003, r = 0.043, P < 0.001, respectively) and negatively correlated with HDL-C levels (r = -0.089, P < 0.001), results from TFQIFT3 were similar with FT3/FT4. In contrast, TFQIFT4 was only positively correlated with HDL-C levels (r = 0.03, P = 0.003).

Association of Thyroid Parameters With Dyslipidemia and NAFLD

We performed gender and age-adjusted and multivariate-adjusted models with the inclusion of thyroid function parameters and sensitivity to thyroid hormone indices.
As far as we know, this is the first study to evaluate the association between central and peripheral sensitivity to thyroid hormone and NAFLD. A reductase, which initiates cholesterol biosynthesis (26). Thyroid hormones affect lipid metabolism manifold, such as synthesis, mobilization, and degradation (25). Thyroid hormones can stimulate 3-hydroxy-3-methylglutarylcoenzyme A reductase, which initiates cholesterol biosynthesis (26). Additionally, triiodothyronine (T3) can bind to specific thyroid hormone-responsive elements to activate the LDL receptor gene, thus upregulates LDL receptors (27). Moreover, Thyroid hormones can regulate cholesterol metabolism by increasing the expression of the regulatory sterol element-binding protein-2 (SREBP-2) (28). Furthermore, Thyroid hormones can also regulate HDL metabolism; previous studies revealed that thyroid hormones exchanged cholesteryl esters from HDL2 to the very low-density lipoproteins and TGs in the opposite direction by increasing cholesteryl ester transfer activity (26). Another effect of T3 is to stimulate lipoprotein lipase, which catabolizes the TG-rich lipoproteins, leading to a decrease of TG (26).

It is biologically plausible that thyroid hormones exert significant effects on the development of NAFLD. As we mentioned above, thyroid hormones had multiple effects on lipid metabolism at both systemic and hepatic levels by virtue of their roles in regulating the circulating level of lipoprotein, TG, and TC, as well as hepatic TG accumulation and metabolism (7, 29). Recent studies showed that the expression of hepatic lipogenic genes was regulated by thyroid hormones, what is more, several genes whose expression is changed in NAFLD were also regulated by thyroid hormones (30, 31). Additionally, decreased hepatic levels of thyroid hormones and defective intrahepatic deiodinase expression were found in NAFLD (32). On the other side, the previous study showed that excessive hepatic fatty acids in NAFLD may damage the activity of thyroid hormone receptors (33). Moreover, this apparent local hypothroid status promotes hepatic triglyceride accumulation by decreasing hepatic lipase activity (34). Furthermore, in vivo studies have shown

**DISCUSSION**

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**TABLE 3 | Correlation between thyroid parameters and lipid profiles.**

|          | FT₃     | FT₄     | TSH     | FT₃/FT₄ | TFQIFT₃ | TFQIFT₄ |
|----------|---------|---------|---------|---------|---------|---------|
| TG       | r       | 0.109   | -0.044  | 0.020   | 0.120   | 0.095   | -0.016  |
|          | p       | <0.001  | <0.001  | <0.001  | <0.001  | <0.001  | <0.001  |
| TC       | r       | 0.031   | -0.004  | 0.025   | 0.029   | 0.040   | 0.016   |
|          | p       | 0.002   | 0.711   | 0.012   | 0.003   | <0.001  | 0.096   |
| HDL-C    | r       | -0.084  | 0.023   | 0.016   | -0.089  | -0.049  | 0.030   |
|          | p       | <0.001  | 0.022   | <0.001  | <0.001  | <0.001  | 0.003   |
| LDL-C    | r       | 0.048   | -0.003  | 0.013   | 0.043   | 0.044   | 0.009   |
|          | p       | <0.001  | 0.769   | 0.180   | <0.001  | <0.001  | <0.001  |

Kendall's tau-b was used to calculate the correlation coefficient (r). TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FT₃, free triiodothyronine; FT₄, free thyroxine; TSH, thyroid stimulating hormone; FT₃/FT₄, FT₃ to FT₄ ratio; TFQIFT₃, the thyroid feedback quartile-based index calculated by FT₃; TFQIFT₄, the thyroid feedback quartile-based index calculated by FT₄. Bold values emphasized that P<0.05.
that not only thyroid hormone administration but also thyroid hormone agonists ameliorates hepatic fat accumulation (35-37).

TSH level is one of the essential risk factors in the pathogenesis of NAFLD, independent of FT3 and FT4. Tahara et al. found that the serum TSH level was significantly associated with the risk of NAFLD, while FT4 was not significantly related to the risk of NAFLD in the subclinical hypothyroidism population (7). Chung et al. found that NAFLD was positively associated with TSH serum level. They revealed that subclinical hypothyroidism was closely related to the risk of NAFLD in a TSH dose-dependent manner, even within the normal upper TSH level range (38). Liu et al. showed that the serum levels of TSH in patients with NAFLD.
NASH or without NASH were different significantly. Furthermore, the NASH prevalence in patients with subclinical hypothyroidism was significantly higher than in the euthyroidism patients. In multivariate analyses, they concluded that elevated serum TSH levels predicted the risk of NASH independently (39). Additionally, Kim et al. reported that even within the normal range of T4, an increase in the TSH level was closely related to the biopsy-proven NASH and advanced fibrosis (40).

As we mentioned above, positive associations of FT3 and TSH level with the risk of NAFLD, negative associations of FT4 level with the risk of NAFLD suggest that the role of thyroid hormone in the development and progression of NAFLD is complex. This association is at odds with the physiological effects of thyroid hormones, which are considered capable of activating lipolysis. Thus, we speculate that the contradictory results may reflect the close association between sensitivity to thyroid hormone with NAFLD.

TSH, FT4, and FT3 are closely regulated and influenced by each other. Compared with a single index, the calculation of composite indices can systematically reflect the regulation of thyroid hormone homeostasis. Our results showed that FT3/FT4 was significantly positively associated with the risks of hyper-TG, hyper-TC, hyper-LDL, and NAFLD. FT4 can be converted to FT3 by deiodinase in the peripheral. Thus FT3/FT4 can be considered as an indicator of peripheral deiodinase activity. A previous study by Bilgin and Pirgon suggested that the augmented conversion from FT4 to FT3 by increasing deiodinase activity was a compensatory mechanism for fat excessively accumulation to ameliorate energy expenditure (41). Consistent with our study, Gokmen et al. found that the patients with NAFLD had significantly elevated FT3/FT4, and FT3/FT4 is a independent predictor of NAFLD in euthyroid patients and hyperthyroid patients (42).

In 2019, Lclaustra et al. proposed a new sensitivity to thyroid hormone index (TFQI) to detect mild levels of acquired thyroid hormone resistance in the population; the result showed that TFQI was more stable than the TSH index and TSH T4 index in evaluating sensitivity to thyroid hormone. That study also showed that TFQI values were related to obesity, diabetes, metabolic syndrome, and diabetes-related mortality (18). As we know, the prevalence of NAFLD is related to multiple metabolic risk factors, such as obesity, diabetes, and so on (4). NAFLD is also a strong determinant for the development of metabolic syndrome (43); what is more, metabolic abnormalities in metabolic syndrome, including diabetes, obesity, and hyperlipidemia, are critical metabolic risk factors for NAFLD (44, 45). Thus, in the present study, we proposed that TFQI might be related to NAFLD and might be a diagnostic predictor for NAFLD. In our study, sensitivity to thyroid hormone
evaluation by the TFQI\textsubscript{FT3} was significantly positively associated with the risk of hyper-TG, hyper-TC, hyper-LDL, and NAFLD. Moreover, TFQI\textsubscript{FT3} and FT\textsubscript{3}/FT\textsubscript{4} performed better than TFQI\textsubscript{FT4} on ROC analysis; although, TFQI\textsubscript{FT3} and FT\textsubscript{3}/FT\textsubscript{4} yielded low diagnostic sensitivity and specificity. In comparison, no association was found between TFQI\textsubscript{FT4} with the risk of dyslipidemia and NAFLD. Although the exact mechanisms remain unclear, the following aspect might be the possible explanation: serum level of FT3, which is mainly converted from serum FT\textsubscript{4} by deiodinase, can be considered as a compensatory mechanism for fat accumulation to improve energy expenditure and reflect better sensitivity of thyroid hormone (41). Thyroid function is also race-specific; in the present study, we only included Chinese participants. Therefore, the contradictory results in our study may be partly due to interethnic variations.

There are still some limitations in the present study: 1) The present study was designed cross-sectionally. Thus we only found the association between sensitivity to thyroid hormone indices with risk of NAFLD, and the design limited our ability to collect the follow-up data and evaluate the causality of associations; 2) Liver biopsy was not used to accurately detect NAFLD, while ultrasonography was utilized to diagnosed NAFLD, there was limited accuracy for detecting mild hepatic lipid accumulation; 3) this study included only Chinese patients who completed health examinations at a single medical center. Since the limitation mentioned, the present results above still need further confirmation by longitudinal prospective studies in multiple race populations.

CONCLUSIONS

The present study showed that TFQI\textsubscript{FT3} and FT\textsubscript{3}/FT\textsubscript{4} were independently associated with the risk of dyslipidemia and NAFLD after multiple adjustments. TFQI\textsubscript{FT3} and FT\textsubscript{3}/FT\textsubscript{4} performed better than TFQI\textsubscript{FT4} on ROC analyses for dyslipidemia and NAFLD prediction. Thus TFQI\textsubscript{FT3} and FT\textsubscript{3}/FT\textsubscript{4} can be used as new indicators for predicting dyslipidemia and NAFLD, although the diagnostic sensitivity and specificity at the optimal cut-points are very low, while TFQI\textsubscript{FT4} has insufficient evidence in predicting dyslipidemia and NAFLD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the First Hospital of China Medical University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

SL, JL, and ZW conducted a literature search, assisted with study design, data collection, data analysis, data interpretation, and draft the manuscript. WW and HG participated in study design, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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