ORIGINAL RESEARCH

Association Between Sensitivity to Thyroid Hormones and Metabolic Dysfunction-Associated Fatty Liver Disease in Euthyroid Subjects: A Cross-Sectional Study

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Objective: Thyroid hormones (THs) exert instrumental effects in regulating lipids metabolism. Whereas, research investigating the relationship between sensitivity indices to THs and metabolic dysfunction-associated fatty liver disease (MAFLD) have contradicted this. This study was designed to approach the correlation between sensitivity indices to THs and MAFLD in euthyroid subjects.

Methods: An overall sample of 6356 euthyroid participants were enrolled in a Chinese hospital. Free triiodothyronine to free thyroxine ratio (FT3/FT4), thyrotropin triiodothyronine resistance index (TT3RI), thyrotropin thyroxine resistance index (TT4RI), thyroid stimulating hormone index (TSHI) and thyroid feedback quantile-based indices (TFQI$_{FT3}$ and TFQI$_{FT4}$) were collected as sensitivity indicators to THs. Participants were split into two groups based on whether they suffered with MAFLD or not. And participants were categorized into quartiles based on sensitivity indicators to THs. The effects of sensitivity indices to THs on MAFLD were analyzed using regression analysis. Bootstrap was performed to assess the mediation effect of triglyceride glucose (TyG) index on the relationship between sensitivity parameters to THs and MAFLD.

Results: The incidence of MAFLD in euthyroid subjects was 34.47%. As FT3/FT4, TT3RI and TFQI$_{FT3}$ levels rose, so did the MAFLD prevalence. After adjustment for confounders, logistic regression analyses indicated that the high-level FT3/FT4 and TFQI$_{FT3}$ still remained risk factors for MAFLD. The relevance of FT3/FT4 and MAFLD was stronger among those whose age ≤ 40 years and had non-visceral obesity. And the interrelation between TFQI$_{FT3}$ and MAFLD was stronger in subjects whose age ≤ 40 years. Mediation analyses suggested that TyG index had a noteworthy indirect impact on the relationship between FT3/FT4, TFQI$_{FT3}$ and MAFLD.

Conclusion: Increased FT3/FT4 and TFQI$_{FT3}$ were significantly related to MAFLD prevalence in populations with normal thyroid function. TyG index partly mediated the relevance between FT3/FT4, TFQI$_{FT3}$ and MAFLD.

Keywords: thyroid hormone sensitivity, metabolic dysfunction-associated fatty liver disease, triglyceride glucose index, mediation effect

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a multisystem disorder, defined as the presence of fatty degeneration of the liver besides one of the following three criteria, namely racial adjusted overweight/obesity, type 2 diabetes mellitus (T2DM) or the disturbance of metabolism.[1] The clinical epidemiology research has demonstrated that the worldwide morbidity of MAFLD was approximately 25.0%.[2] And the incidence rate of MAFLD exceeded 50% in individuals who are overweight or obese.[3] Accumulating evidence suggested that MAFLD patients had more significant cirrhosis and hepatic cellular cancer (HCC) compared to non-alcoholic fatty liver disease (NAFLD) patients.[4,5] Besides, numerous previous studies found that MAFLD was correlated with greater rates of overweight,[3] glucose dysregulation,[6]

atrial fibrillation,[6] cardiovascular diseases (CVD) mortality[7] and all-cause mortality.[8,9] The prevalence of MAFLD has led to a continuous increase of the social medical burden. Therefore, better awareness of the underlying hazard factors for MAFLD contributes to improving preventive and therapeutic measures.

Thyroid hormones (THs) have been suggested to interact on liver lipid homeostasis through a set of processes, including stimulating the entry of free fatty acids (FFA) into the liver for esterification to triacylglycerol (TG) and increasing mitochondrial β-oxidation of fatty acids to affect liver lipid accumulation.[10,11] Impaired lipid metabolism and hepatic steatosis were shown in both subclinical and clinical hypothyroidism patients.[12,13] The effect of THs on hepatic steatosis still existed despite changes within the norm but the results were not entirely consistent.[14–17] Furthermore, THs individually might not be enough to comprehensively expound thyroid gland status. Based on this situation, thyroid hormone sensitivity indicators were presented, which better reflected thyroid homeostasis.[18–20] Laclaustra et al[18] proposed thyroid feedback quantile-based index (TFQI), namely central sensitivity to THs, which could be used to evaluate the reaction of hypophysis to THs. Studies demonstrated that TFQI, thyroid-stimulating hormone index (TSHI), as well as thyrotrophic thyroxine resistance index (TT4RI) levels were correlated with metabolic syndrome (Mets), advanced hepatic fibrosis and other diseases in populations with euthyroidism.[20–23] Additionally, as a peripheral sensitivity index to THs, free triiodothyronine to free thyroxine (FT3/FT4) could predict NAFLD independent of metabolic indicators in euthyroid subjects.[24,25] At present, large-sample studies on the effects of sensitivity indices to THs on MAFLD were limited. This study aimed to gain insight into correlations between sensitivity indices to THs and MAFLD in euthyroid populations.

Materials and Methods
Study Subjects
The research protocol was carried out on the basis of the Helsinki Declaration with authorization of the Hebei General Hospital Ethics Committee. The data were collected from the Hebei Health Examination Center from January 1, 2020, to December 31, 2020. All subjects were screened and assessed based on inclusion criteria and exclusion criteria. And each participant has completed informed consent.

The euthyroid adult subjects were eligible for inclusion in this research. Exclusion requirements were as followings: (1) Those with a medical history of thyroid dysfunction or medical treatment that might affect thyroid gland function (n = 483). (2) Malignant tumors, severe hepatic and renal dysfunction, hypothalamus and pituitary disease (n = 131). (3) Pregnant or lactating women (n = 22). (4) Incomplete data (n = 604).

Data Collection and Measures
At the time of enrollment, the detailed variables were gathered, involving sex, age, body mass index (BMI), waist circumference (WC). Standard measurement of blood pressure was conducted, including systolic blood pressure (SBP) and diastolic blood pressure (DBP). The venous blood of the subjects was taken on an empty stomach on the next morning. Serum biochemicals were determined, which included serum uric acid (SUA), serum creatinine (Scr), TG, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), amino-transferase (AST), alanine aminotransferase (ALT), free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine (TT3), and tetraiodothyronine (TT4), TSH, fasting plasma glucose (FPG) and blood urea nitrogen (BUN). The fatty liver was diagnosed according to the findings of liver ultrasound, which was performed by trained technicians.

Diagnostic Criteria of MAFLD
MAFLD was diagnosed on the basis of abdominal ultrasound-diagnosed liver steatosis, combining with one of three standard factors below, that is, overweight/obesity, T2DM, or metabolism disorder. Metabolism disorder was recognised as having two or more lipid disorder indicators: WC ≥90 cm for male, and ≥80 cm for female; blood pressure (BP) ≥130/85 mmHg or step-down medication therapy; TG ≥1.70 mmol/L or taking lipid-lowering agents; HDL-C <1.0 mmol/L for male and <1.3 mmol/L for female or specific medication therapy; pre-diabetes (FPG; 5.6–6.9 mmol/L). We did not evaluate serum insulin and hypersensitive C-reactive protein (hsCRP) due to the lack of these data.[1]

Calculations of Sensitivity Indices to THs and Triglyceride Glucose (TyG) Index

FT3/FT4 = FT3(pmol/L)/FT4(pmol/L). For FT3/FT4, the higher values stand for higher peripheral sensitivity to THs.

TT3RI = FT3(pmol/L)×TSH(mIU/L).[21]

TT4RI = FT4(pmol/L)×TSH(mIU/L).[26]

TSHI = lnTSH(mIU/L)+0.1345 × FT4(pmol/L)[27] The lower levels of TT3RI, TT4RI and TSHI expressed higher central TH activity.

$TFQI_{FT3}$= cdfFT3−(1 − cdfTSH).[21]

$TFQI_{FT4}$= cdfFT4−(1 − cdfTSH).[18] $TFQI_{FT3}$ and $TFQI_{FT4}$ ranged from −1 to 1, which reflected the central sensitivity to THs. For $TFQI_{FT3}$ and $TFQI_{FT4}$, negative values represented higher sensitivity to THs, conversely positive values represented lower sensitivity.[25]

TyGindex = ln[fastingTG(mg/dL)×FPG(mg/dL)/2].[28]

Statistical Analysis

SPSS 23.0 statistic software was adopted for statistic analysis. If the quantitative information were normally distributed, the results were represented by average ± standard bias, and independent samples *t*-test was taken to compare between two sets of data. We expressed by the median (interquartile range) for continuous skewness distribution data, and the Mann–Whitney *U*-test was applied to compare between two sets of data. The counting data were represented as [n (%)], groups were measured through the use of chi-square test. Multivariate logistic regressions were utilized to evaluate the impact of sensitivity indices to THs on MAFLD status. Mediation analyses were applied to explored the mediators in the connection between sensitivity indicators to THs and MAFLD. There were significant differences when *P*-values <0.05. The subgroup analyses were taken to estimate the robustness of outcomes.

Results

Comparison of Basic Features Between MAFLD and Non-MAFLD Group

Data from 6356 euthyroid subjects were taken for the research with a mean age of 47.04 ± 12.19 years old, which included 2904 (45.69%) males and 3452 (54.31%) females. The detection rate of MAFLD was 34.47% (2191/6356) (Figure 1). Comparing with non-MAFLD cases, the MAFLD participants showed greater levels of FT3, FT3/FT4, TT3RI, $TFQI_{FT3}$, age, WC, BMI, SBP, DBP, BUN, SUA, Scr, AST and ALT, as well as worse metabolism property, including higher TC, TG, LDL-C, FPG, TyG index, and lower HDL-C (*P*<0.05). The levels of FT4, TSH, TT4RI, TSHI as well as $TFQI_{FT4}$ had no statistical difference between the MAFLD and non-MAFLD groups (*P*>0.05) (Table 1).

Correlations Between Sensitivity Indices to THs Levels and Prevalence Rate of MAFLD

Examinees were classified as four groups (Q1-Q4) in accordance with the quartile range of the sensitivity indicators to THs. By comparing MAFLD prevalence in the Q1-Q4 groups, it was observed that MAFLD prevalence statistically significantly increased with an increase in FT3/FT4, TT3RI and $TFQI_{FT3}$ (*P*<0.05). And the incidence rate of MAFLD was highest in the fourth group for FT3/FT4, TT3RI and $TFQI_{FT3}$ (Figure 2).

Multivariable Regression Analyses of Relationship Between Sensitivity Indices to THs and MAFLD Prevalence

In multivariable regression analyses, FT3/FT4, TT3RI and $TFQI_{FT3}$ were highly correlated with MAFLD in both model 1 and model 2. The relevance of FT3/FT4, $TFQI_{FT3}$ and MAFLD remained available after adjustment for age, sex, WC, BMI, blood pressure, TC, TG, LDL-C, HDL-C, fasting blood glucose, BUN, SUA, Scr, AST and ALT. And the odds ratio in comparing MAFLD with non-MAFLD was 11.810 (95% CI 4.148~33.628, *P*<0.001) for FT3/FT4 and 1.395 (95% CI 1.161~1.676, *P*<0.001) for $TFQI_{FT3}$ (model 3). Nevertheless, the relevances were not discovered between TT3RI, TT4RI, TSHI, $TFQI_{FT4}$ and MAFLD after adjustment for the above confounding factors (Table 2).
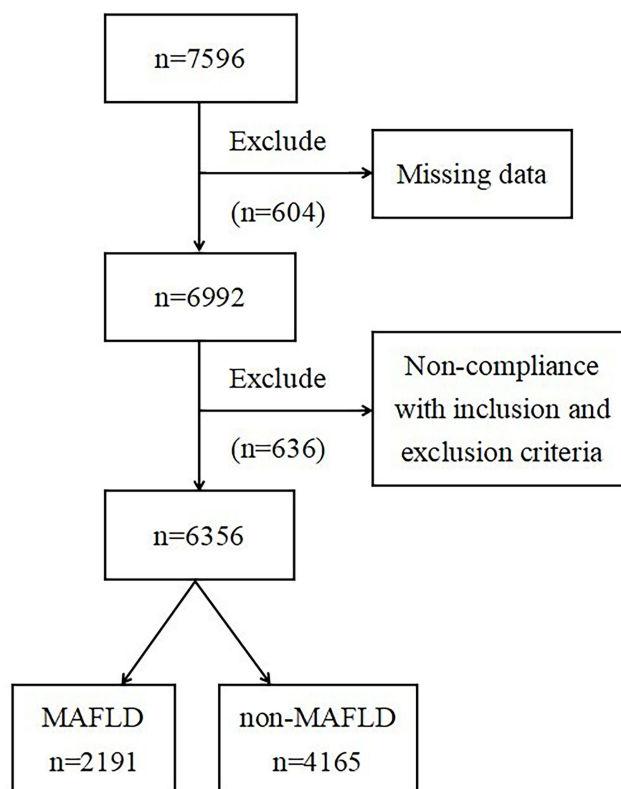
Figure 1 Flowchart of the inclusion and exclusion of participants.

The sensitivity indices to THs were explored as categorical variables (quartiles) to guarantee the robustness of results. The results suggested the significantly positively graded correlations between FT3/FT4, $TFQI_{FT3}$ and MAFLD risk. After adjustment for the above confounding factors, the high-levels of $TFQI_{FT3}$ and FT3/FT4 were still discovered to be risk factors for MAFLD. Moreover, the fourth group for FT3/FT4 (OR 1.533; 95% CI 1.250~1.879; $P<0.001$) and $TFQI_{FT3}$ (OR 1.521; 95% CI 1.239~1.866; $P<0.001$) had the greatest risk of MAFLD. And the Q2 group (OR 1.239; 95% CI 1.014~1.513;

Table 1 Comparison of Basic Demographic Characteristics of MAFLD and Non-MAFLD Population

	All Subjects (n = 6356)	MAFLD (n = 2191)	Non-MAFLD (n = 4165)	t/χ^2	P
Gender				596.400	<0.001
Male〔n(%)〕	2904 (45.69)	1462 (66.73)	1442 (34.62)		
Female〔n(%)〕	3452 (54.31)	729 (33.27)	2723 (65.38)		
Age (years)	47.04±12.19	50.24±11.08	45.35±12.41	15.479	<0.001
WC (cm)	85.97±11.65	94.91±9.31	81.26±9.87	53.424	<0.001
BMI (kg/m^2)	24.53±3.64	27.31±3.15	23.07±2.96	53.077	<0.001
SBP (mmHg)	121.63±17.91	129.67±16.64	117.4±17.09	27.444	<0.001
DBP (mmHg)	80.58±11.40	86.04±10.88	77.71±10.59	29.520	<0.001
TC (mmol/L)	5.09±0.96	5.28±0.98	4.99±0.94	11.474	<0.001
TG (mmol/L)	1.54±1.27	2.17±1.59	1.21±0.91	30.576	<0.001
LDL-C (mmol/L)	3.21±0.72	3.41±0.72	3.11±0.70	16.334	<0.001
HDL-C (mmol/L)	1.37±0.30	1.24±0.24	1.44±0.30	−28.107	<0.001
FPG (mmol/L)	5.69±1.42	6.23±1.74	5.41±1.11	22.916	<0.001
BUN (mmol/L)	4.82±1.22	5.07±1.19	4.69±1.22	11.865	<0.001

(Continued)

Table 1 (Continued).

	All Subjects (n = 6356)	MAFLD (n = 2191)	Non-MAFLD (n = 4165)	t/χ²	P
SUA (μmol/L)	335.24±91.42	382.96±90.05	310.16±81.63	32.594	<0.001
Scr (μmol/L)	65.82±12.75	69.58±13.12	63.84±12.09	17.454	<0.001
AST (U/L)	22.28±11.06	25.45±13.66	20.61±8.98	16.932	<0.001
ALT (U/L)	22.12±18.01	30.61±22.64	17.65±12.95	29.024	<0.001
TyG index	8.64±0.66	9.09±0.64	8.41±0.54	44.878	<0.001
FT3 (pmol/L)	5.10±0.51	5.26±0.50	5.02±0.50	17.892	<0.001
FT4 (pmol/L)	11.55±1.50	11.51±1.50	11.57±1.50	−1.372	0.170
TSH (μIU/mL)	2.24±1.08	2.23±1.04	2.24±1.10	−0.287	0.774
FT3/FT4	0.45±0.07	0.46±0.07	0.44±0.07	12.881	<0.001
TT3RI	11.37±5.51	11.68±5.45	11.20±5.54	3.318	0.001
TT4RI	25.54±12.13	25.41±11.61	25.60±12.39	−0.593	0.553
TSHI	2.25±0.48	2.25±0.47	2.25±0.49	−0.052	0.959
TFQI$_{FT3}$	0.00±0.40	0.09±0.38	−0.05±0.39	13.504	<0.001
TFQI$_{FT4}$	−0.01±0.38	−0.01±0.38	0.00±0.38	−0.873	0.383

P=0.036) and Q4 group (OR 1.268; 95% CI 1.037~1.549; P=0.021) but not the Q3 group for TT3RI had higher MAFLD risk in comparison with the first group after controlling for confounders. However, no graded positive correlation between TT3RI quartiles and MAFLD risk was found (Table 3). Consistently, the relevance was not discovered between TT4RI, TSHI, TFQI$_{FT4}$ and MAFLD incidence after adjusting for confounders (all P>0.05, Figure 3).

Subgroup Analyses of the Correlations of FT3/FT4, TFQI$_{FT3}$ with MAFLD

Subgroup analyses were conducted to ascertain whether or not there were diverse relationships between FT3/FT4, TFQI$_{FT3}$ and MAFLD with various age, sex, BMI, visceral obesity, and TG. FT3/FT4 with MAFLD risk was more relevant in individuals ≤40 years old and without visceral obesity. Simultaneously, there was a higher correlation between TFQI$_{FT3}$ and MAFLD among people younger than 40 years old. No other notable interactions were found in subgroup analyses (Table 4).
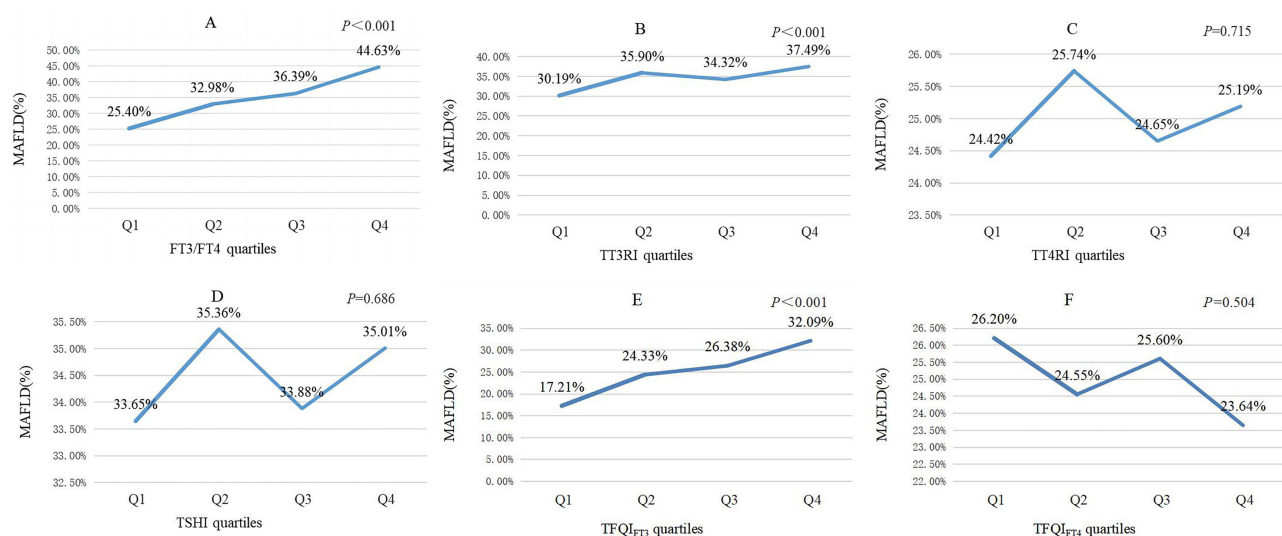

Figure 2 Comparisons of prevalence rate of MAFLD according to sensitivity to thyroid hormones quartiles (**A**) FT3/FT4 quartiles, (**B**) TT3RI quartiles, (**C**) TT4RI quartiles, (**D**) TSHI quartiles, (**E**) TFQI$_{FT3}$ quartiles, (**F**) TFQI$_{FT4}$ quartiles.

Table 2 Relationship Between Sensitivity Indices to Thyroid Hormones and MAFLD Prevalence in Different Models

Outcomes	Model I		Model II		Model III	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
FT3/FT4	254.910 (112.067~579.820)	<0.001	57.487 (22.073~149.721)	<0.001	11.810 (4.148~33.628)	<0.001
TT3RI	1.031 (1.020~1.041)	<0.001	1.018 (1.006~1.030)	0.004	1.006 (0.993~1.019)	0.393
TT4RI	1.004 (0.999~1.009)	0.084	1.001 (0.995~1.006)	0.746	0.998 (0.992~1.004)	0.528
TSHI	1.099 (0.980~1.231)	0.105	1.009 (0.882~1.155)	0.892	0.951 (0.822~1.101)	0.501
TFQI$_{FT3}$	2.555 (2.209~2.955)	<0.001	1.868 (1.576~2.215)	<0.001	1.395 (1.161~1.676)	<0.001
TFQI$_{FT4}$	0.897 (0.775~1.038)	0.145	0.864 (0.726~1.028)	0.099	0.862 (0.714~1.040)	0.122

Notes: Model 1 was adjusted for age and gender; Model 2 was adjusted for the covariates of model 1 plus WC, BMI, SBP, DBP; Model 3 was adjusted for the covariates of model 2 plus TC, TG, LDL-C, HDL-C, FPG, BUN, SUA, Scr, AST and ALT.

Table 3 Logistic Regression Analysis of FT3/FT4, TT3RI and TFQI$_{FT3}$ Quartiles for the Risk of MAFLD

Outcomes	Model I		Model II		Model III	
	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
FT3/FT4 (quartile)						
Q1 (≥0.26, and<0.40)	Ref	<0.001	Ref	<0.001	Ref	<0.001
Q2 (≥0.40, and<0.44)	1.478(1.258~1.736)	<0.001	1.343(1.112~1.623)	0.002	1.285(1.049~1.573)	0.015
Q3 (≥0.44, and<0.49)	1.863(1.589~2.183)	<0.001	1.589(1.317~1.915)	<0.001	1.336(1.090~1.636)	0.005
Q4 (≥0.49, and≤0.80)	2.624(2.238~3.077)	<0.001	2.002(1.661~2.414)	<0.001	1.533(1.250~1.879)	<0.001
P for trend	<0.001		<0.001		<0.001	
TT3RI (quartile)						
Q1 (≥2.48, and<7.31)	Ref	<0.001	Ref	<0.001	Ref	<0.001
Q2 (≥7.31, and<10.19)	1.443(1.231~1.691)	<0.001	1.299(1.078~1.565)	0.006	1.239(1.014~1.513)	0.036
Q3 (≥10.19, and<14.23)	1.361(1.161~1.595)	<0.001	1.080(0.896~1.302)	0.420	0.974(0.796~1.191)	0.794
Q4 (≥14.23, and≤33.97)	1.765(1.506~2.069)	<0.001	1.473(1.223~1.774)	<0.001	1.268(1.037~1.549)	0.021
P for trend	<0.001		<0.001		0.087	
TFQI$_{FT3}$ (quartile)						
Q1(≥-1.00, and<-0.28)	Ref	<0.001	Ref	<0.001	Ref	<0.001
Q2(≥-0.28, and<0.00)	1.670(1.415~1.970)	<0.001	1.455(1.200~1.764)	<0.001	1.320(1.075~1.620)	0.008
Q3(≥0.00, and<0.28)	1.917(1.626~2.259)	<0.001	1.596(1.317~1.934)	<0.001	1.300(1.059~1.596)	0.012
Q4(≥0.28, and≤1.00)	2.769(2.352~3.260)	<0.001	1.985(1.640~2.403)	<0.001	1.521(1.239~1.866)	<0.001
P for trend	<0.001		<0.001		<0.001	

Notes: Model 1 was adjusted for age and gender; Model 2 was adjusted for the covariates of model 1 plus WC, BMI, SBP, DBP; Model 3 was adjusted for the covariates of model 2 plus TC, TG, LDL-C, HDL-C, FPG, BUN, SUA, Scr, AST and ALT.

Mesomeric Effect Analyses of TyG Index on Associations Between FT3/FT4, TFQI$_{FT3}$ and MAFLD

We carried out mediation analyses in order to discuss whether or not TyG index was a mediating factor in the link between FT3/FT4, TFQI$_{FT3}$ and MAFLD. The research indicated that FT3/FT4, TFQI$_{FT3}$ and TyG index presented positive correlations with MAFLD. Simultaneously, FT3/FT4 and TFQI$_{FT3}$ were significantly positively correlative with TyG index. The results expressed underlying mechanisms for TyG index to mediate the connections between FT3/FT4, TFQI$_{FT3}$ and MAFLD. As the findings reported, FT3/FT4 (β = 2.7820, 95% CI: 1.8979~3.6660) and TFQI$_{FT3}$ (β = 0.5250, 95% CI: 0.3688~0.6812) had prominent direct influences on MAFLD risk (Figure 4). As Figure 4A displays, TyG index (β = 3.5026, 95% CI: 2.9555~4.0902) incompletely mediated indirect influence of FT3/FT4 on the occurrence of MAFLD. The mediation ratio was 55.73%. TyG index (β = 0.6473, 95% CI: 0.5498~0.7463) also incompletely mediated indirect influence of TFQI$_{FT3}$ on MAFLD. The mediation proportion was 55.22% in this model (Figure 4B).
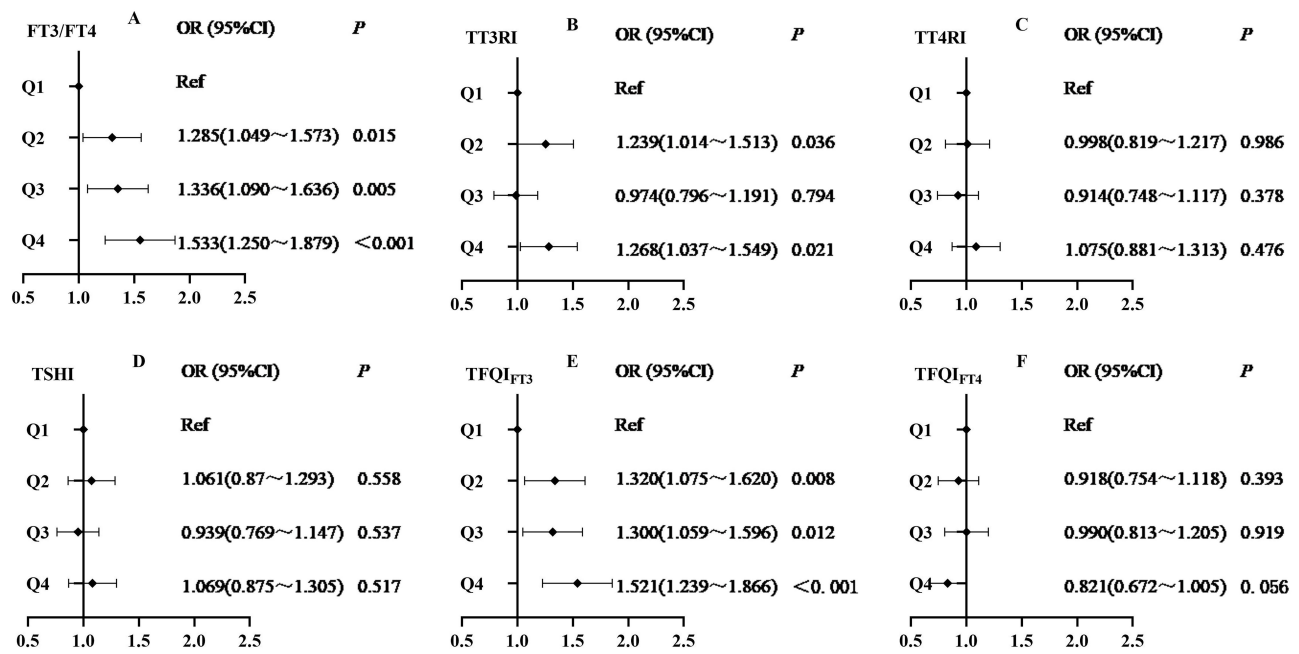
Figure 3 Logistic regression analysis of relationship between sensitivity indices to thyroid hormones quartiles and the risk of MAFLD (**A**) FT3/FT4 quartiles, (**B**) TT3RI quartiles, (**C**) TT4RI quartiles, (**D**) TSHI quartiles, (**E**) TFQI$_{FT3}$ quartiles, (**F**) TFQI$_{FT4}$ quartiles. The model was adjusted for age, gender, WC, BMI, SBP, DBP, TC, TG, LDL-C, HDL-C, FPG, BUN, SUA, Scr, AST and ALT.

Discussion

A growing number of studies have revealed a correlation between THs and MAFLD in individuals with euthyroidism.[29–31] The characteristic of our paper was to explore possible correlations of thyroid function with MAFLD by using central and peripheral sensitivity indicators instead of THs. They could supply more messages about the associations between resistance to THs and MAFLD occurrence. Our results revealed that MAFLD prevalence was 34.47% in the euthyroid

Table 4 Subgroup Analysis of the Correlations of FT3/FT4 and TFQI$_{FT3}$ with MAFLD

| Characteristics	No	FT3/FT4			TFQI$_{FT3}$		
		OR (95% CI)	P	P for Interaction	OR (95% CI)	P	P for interaction
Sex				0.434			0.733
Male	2904	10.108 (2.517~40.590)	0.001		1.253 (0.980~1.603)	0.072	
Female	3452	16.587 (3.306~83.212)	0.001		1.562 (1.176~2.073)	0.002	
Age (years)				0.008			0.032
≤40	2199	48.735 (5.317~446.707)	0.001		1.523 (1.028~2.255)	0.036	
40–60	3294	3.676 (0.938~14.409)	0.062		1.341 (1.051~1.711)	0.018	
>60	863	22.325 (1.812~274.988)	0.015		1.223 (0.800~1.871)	0.353	
BMI (kg/m^2)				0.091			0.858
<24	2959	8.318 (0.980~70.575)	0.052		1.028 (0.699~1.512)	0.888	
24–28	2356	12.059 (3.023~48.114)	<0.001		1.492 (1.173~1.898)	0.001	
≥28	1041	5.664 (0.506~63.348)	0.159		1.330 (0.859~2.059)	0.201	
Visceral obesity				0.024			0.321
No	3406	19.072 (3.293~110.445)	0.001		1.503 (1.092~2.070)	0.012	
Yes	2950	7.553 (2.108~27.063)	0.002		1.267 (1.017~1.580)	0.035	
TG (mmol/L)				0.488			0.690
<1.7	4555	9.193 (2.394~35.312)	0.001		1.397 (1.109~1.761)	0.005	
≥1.7	1801	12.353 (2.255~67.670)	0.004		1.306 (0.959~1.780)	0.091	
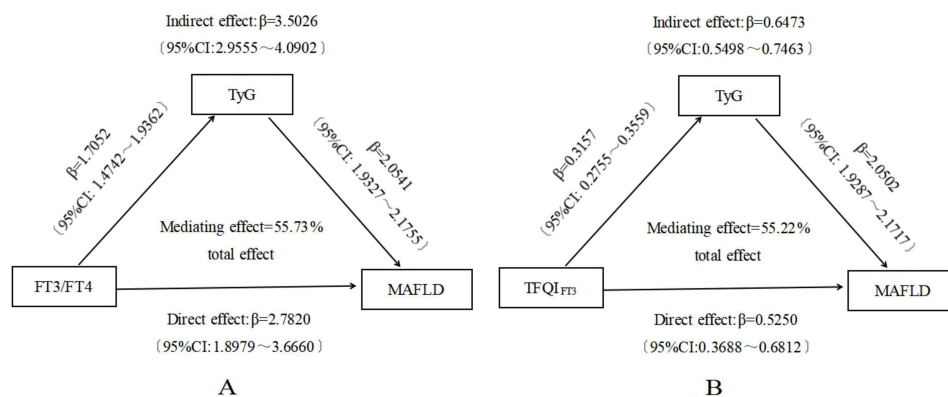
Figure 4 Mediation effect of TyG index on the associations between FT3/FT4, TFQI_FT3 and MAFLD prevalence (**A**) FT3/FT4; (**B**) TFQI_FT3.

population. A previous study based on nationwide health examination data demonstrated that from 2009 to 2017, the morbidity of MAFLD rose from 22.75% to 35.58% in China, which was similar to our findings.[6]

This research showed that the MAFLD group was characterized by higher TT3RI, TFQI_FT3 and FT3/FT4 levels in comparison with the non-MAFLD group. The morbidity of MAFLD raised with increasing TFQI_FT3 and FT3/FT4 levels when multiple potential confounders were adjusted. From the further analysis, subjects in the highest quartile of TFQI_FT3 and FT3/FT4 had the notably highest MAFLD risk compared to the three lower quartile groups, which conformed to the findings of Wan et al.[32] The research carried out by Lai et al[25] also expressed that TFQI_FT3 and FT3/FT4 were closely associated with abnormal blood lipid as well as hepatic steatosis in populations with euthyroidism. This result further provided feasibility for preventing the progression of MAFLD by altering thyroid sensitivity. Nevertheless, one recent research suggested that, for initially diagnosed T2DM individuals with euthyroidism, no associations were found between THs, sensitivity indices to THs and MAFLD after controlling for BMI and homeostatic model assessment for insulin resistance (HOMA-IR).[29] The heterogeneity of the criteria and population for euthyroidism might partly illustrate the differences among these studies. Our study expressed that the relevance of FT3/FT4 and MAFLD was stronger among those whose age ≤40 years and had non-visceral obesity. And the interrelation between TFQI_FT3 and MAFLD was stronger in subjects whose age ≤40 years. It might be related to the excessive consumption of fatty food and the lack of moderate physical exercise in young participants.[33]

The underlying mechanisms of relationships between sensitivity indices to THs and MAFLD stay entirely unknown, but may contain chronic inflammation, dysregulation of mitochondrial homeostasis, endoplasmic reticulum stress and decreased insulin sensitivity.[34–38] Chronic inflammation was considered to be one of the key pathogenesis of MAFLD and could promote the incidence of MAFLD.[35] Studies revealed that low FT4 was related to higher levels of inflammatory biomarkers (eg, tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6 and interferon-γ).[38–40] Low-normal FT4 also could influence pro-inflammatory pathways and exacerbate liver fatty infiltration.[38] Alternatively, obesity was considered the main danger for the progress of MAFLD.[41,42] Laclaustra et al[18] proposed that TFQI was closely related to obesity. Due to obesity, fat accumulation occured in hepatic tissue, which led to the imbalance between pro-inflammatory and anti-inflammatory adipose cytokines.[43] Inflammation may also lead to mitochondrial damage, which induces incomplete lipid oxidation and the production of toxic lipid intermediates, ultimately promoting the development of liver steatosis to more serious diseases.[44] Abnormal lipid accumulation in hepatocytes was also usually correlated with disruption of the endoplasmic reticulum (ER) stress. High FT3 may upregulate the expression of endoplasmic reticulum-associated proteins, and cause ER stress and IR.[34] In response to ER stress, the unfolded protein response was triggered to cause inflammation, inflammasome activation, and the death of hepatocytes.[45,46] Furthermore, studies indicated that hepatic abnormal accumulation of lipids was consistent with insulin resistance.[47,48] IR was recognized as one of the potential pathogenic mechanisms of MAFLD. The expressions of β2 adrenergic receptor (β2AR) and peroxisome proliferatore-activated receptors (PPAR) triggered by THs could influence insulin sensitivity and promote the progression of MAFLD.[49,50] Loria et al[51] detected a positively significant correlation between FT3/FT4 and HOMA-IR in patients with NAFLD. Corica et al[19] also found that elevated central resistance to THs was markedly correlative with the severity of IR in

obese children before puberty. The reduced sensitivity to THs is also related to an increase in adipocyte fatty acid-binding protein (A-FABP), which promotes the progression of MAFLD by binding to free fatty acids (FFAs).[52] Besides, some investigators have speculated that THs may induce activation of hepatic stellate cells (HSC) as well as hepatic fibrogenesis to accelerate the development of liver fibrosis.[53]

TyG index, a product of FPG and fasting TG, was developed as an accurate alternative marker for IR.[54,55] Accumulating evidence has demonstrated that elevated TyG index could contribute to the incidence of T2DM,[56] MAFLD,[57,58] liver fibrosis[59] and CVD.[60] In our study, a strongly positive correlation between TyG index and MAFLD risk was found, which affirmed the above-mentioned viewpoint. FT3/FT4 and TFQI$_{FT3}$ were also positively correlative with TyG index. Further analyses of the mediation effect suggested that the relevance of FT3/FT4, TFQI$_{FT3}$ and MAFLD prevalence were partly mediated by TyG index in the population with euthyroidism, which further elucidated that IR might be the underlying pathway of correlations between sensitivity indices to THs and MAFLD risk.

Our research had a few underlying restrictions. Firstly, inferences regarding the causality between FT3/FT4, TFQI$_{FT3}$ and MAFLD could not be defined owing to the single-institution cross-section study design. Secondly, the homogeneous ethnicity of this cohort raised questions about universal applicability of our results. In the next, multiracial longitudinal researches are required to deeply explore related possibilities between FT3/FT4, TFQI$_{FT3}$ and MAFLD. Thirdly, it lacked histological confirmation in the diagnosis of fatty liver by abdominal ultrasound. Finally, data on eating habits, sports hobbies, and job categories have not been collected, so the results of this study had certain limitations in providing in-depth guidance on these aspects.

Conclusion

In summary, our study indicated that elevated FT3/FT4 and TFQI$_{FT3}$ levels significantly correlated with MAFLD prevalence in euthyroid participants. FT3/FT4 with MAFLD risk was more relevant in individuals less than 40 years old and without visceral obesity. Simultaneously, there was higher correlation between TFQI$_{FT3}$ and MAFLD among people younger than 40 years old. And TyG index partly mediated the associations between FT3/FT4, TFQI$_{FT3}$ and MAFLD. Based on these results, the prevention and treatment of MAFLD by improving sensitivity to thyroid hormones and IR may be applied in new clinical practice.

Data Sharing Statement

The raw stats can be obtained via E-mail at all times (Huanxin Liu: m13513317389@163.com).

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Disclosure

The authors report no conflicts of interest in this research.

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