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ABOUT COVER

Peer Review of *World Journal of Diabetes*, Tao-Hsin Tung, PhD, Researcher, Director, Epidemiologist, Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, Zhejiang Province, China. dongdx@enzemed.com .

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ORIGINAL ARTICLE

Observational Study

Association between sensitivity to thyroid hormones and non-high-density lipoprotein cholesterol levels in patients with type 2 diabetes mellitus

Xiao-Ye Duan, Jun-Ling Fu, Li-Na Sun, Zhi-Jing Mu, Shuang-Ling Xiu

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Abstract

BACKGROUND

Dyslipidemia and type 2 diabetes mellitus (T2DM) are chronic conditions with substantial public health implications. Effective management of lipid metabolism in patients with T2DM is critical. However, there has been insufficient attention given to the relationship between thyroid hormone sensitivity and dyslipidemia in the T2DM population, particularly concerning non-high-density lipoprotein cholesterol (non-HDL-C).

AIM

To clarify the association between thyroid hormone sensitivity and dyslipidemia in patients with T2DM.

METHODS

In this cross-sectional study, thyroid hormone sensitivity indices, the thyroid feedback quantile-based index (TFQI), the thyroid-stimulating hormone index (TSHI), the thyrotrophic T4 resistance index (TT4RI), and the free triiodothyronine (FT3)/free thyroxine (FT4) ratio were calculated. Logistic regression analysis was performed to determine the associations between those composite indices and non-HDL-C levels. Random forest variable importance and Shapley Additive Explanations (SHAP) summary plots were used to identify the strength and direction of the association between hyper-non-HDL-C and its major predictor.

RESULTS

Among the 994 participants, 389 (39.13%) had high non-HDL-C levels. Logistic regression analysis revealed that the risk of hyper-non-HDL-C was positively correlated with the TFQI (OR: 1.584; 95%CI: 1.088-2.304; P = 0.016), TSHI (OR: 1.238; 95%CI: 1.034-1.482; P = 0.02), and TT4RI (OR: 1.075; 95%CI: 1.006-1.149; P =

0.032) but was not significantly correlated with the FT3/FT4 ratio. The relationships between composite indices of the thyroid system and non-HDL-C levels differed according to sex. An increased risk of hyper-non-HDL-C was associated with elevated TSHI levels in men (OR: 1.331; 95%CI: 1.003-1.766; P = 0.048) but elevated TFQI levels in women (OR: 2.337; 95%CI: 1.4-3.901; P = 0.001). Among the analyzed variables, the average SHAP values were highest for TSHI, followed by TT4RI.

CONCLUSION

Impaired sensitivity to thyroid hormones was associated with high non-HDL-C levels in patients with T2DM.

Key Words: Non-high-density lipoprotein cholesterol; Sensitivity to thyroid hormones; Type 2 diabetes mellitus; Thyroid feedback quantile-based index; Free triiodothyronine/free thyroxine ratio

Core Tip: Reduced central thyroid hormone sensitivity was an independent risk factor of high non-high-density lipoprotein cholesterol (non-HDL-C), even after adjusting for multiple confounding factors. The patients with hyper-non-HDL-C were more susceptible to metabolic disorders and impaired sensitivity to thyroid hormones. Meanwhile, the relationships between thyroid hormone sensitivity and non-HDL-C levels were different in male and female, indicating a gender-related regulation of thyroid hormones on serum non-HDL-C levels. This study may provide new evidence for the role of reduced thyroid hormone sensitivity for non-HDL-C levels and lie the groundwork for future therapeutic strategies for diabetes-related cardiovascular disease risk.

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INTRODUCTION

Dyslipidemia and type 2 diabetes mellitus (T2DM) are chronic diseases with significant public health implications[1]. Atherogenic dyslipidemia is one of the major risk factors for atherosclerotic cardiovascular disease (ASCVD) in people with T2DM[2]. Patients with diabetes have approximately double the ASCVD risk of those without diabetes[3]. ASCVD, a vascular complication of T2DM, is a leading cause of mortality. Therefore, the management of lipid metabolism in patients with T2DM is crucial.

Thyroid hormones are not only essential determinants of overall energy expenditure but also important regulators of various aspects of lipid metabolism[4,5], including the synthesis, mobilization, and decomposition of fat and other processes through a complex regulatory mechanism[6]. Many studies have revealed a causal association between thyroid dysfunction and dyslipidemia[5,7,8]. However, previous studies have shown that thyroid hormone or thyroid-stimulating hormone (TSH) levels alone may not be sufficient to explain the relationship between the thyroid system and dyslipidemia[6-8], and the calculation of comprehensive indices can systematically reflect the regulation of thyroid hormone homeostasis[9]. The TSH index (TSHI), thyrotrophic T4 resistance index (TT4RI) and thyroid feedback quantile-based index (TFQI) have been well verified for evaluating central sensitivity to thyroid hormones, and the free triiodothyronine (FT3)/free thyroxine (FT4) ratio is an index that reflects the peripheral bioavailability of thyroid hormones[9,10]. An increasing number of studies have shown that higher values of these composite indices are associated with hyperuricemia, homocysteinemia, vitamin D deficiency, obesity, metabolic syndrome, diabetes, hypertension, reduced kidney function, and diabetes-related mortality, even in euthyroid populations[9-16]. These findings have led to new directions in research regarding the relationship between thyroid function and lipid metabolism. Liu *et al*[17] reported that the risk of dyslipidemia was positively correlated with the TFQI, TSHI, and TT4RI and negatively correlated with FT3/FT4 in patients with coronary heart disease. A recent study indicated that among euthyroid adults, reduced central and peripheral sensitivity to thyroid hormones was associated with high remnant cholesterol (RC) levels[10]. To our knowledge, no study has investigated the association between thyroid hormone sensitivity and dyslipidemia in the T2DM population; in particular, there is a lack of focus on non-high-density lipoprotein cholesterol (non-HDL-C)[17-21]. Non-HDL-C, calculated as total cholesterol (TC) minus high-density lipoprotein (HDL), includes all plasma lipoproteins, such as low-density lipoprotein cholesterol (LDL-C), triglyceride (TG)-rich lipoprotein (TRL), TRL-remnants, and lipoprotein(a)[22]. As non-HDL-C is a measure of all atherogenic cholesterol, it is not surprising that it strongly correlates with ASCVD risk and is also better at predicting ASCVD risk in patients on statin therapy and/or in those with T2DM [23]. Usually, maintaining the optimum level of LDL-C is the primary goal for dyslipidemia management in the general population. However, patients with T2DM who have extremely low LDL-C levels still remain at a very high risk of ASCVD[24]. In line with international guidelines, the 2020 Chinese Guideline on the Primary Prevention of Cardiovascular Diseases recommends non-HDL-C as an alternative treatment target to LDL-C[25]. Previous studies have

revealed that TSH levels within the reference range are positively associated with increased non-HDL-C. However, the relationship between thyroid hormone sensitivity and non-HDL-C has rarely been investigated. Thus, the effects of thyroid hormone and thyroid hormone sensitivity on non-HDL-C in individuals with T2DM remain unclear.

Therefore, the purpose of this study was to clarify the association between thyroid hormone sensitivity and non-HDL-C in patients with T2DM and to further explore these associations in different sexes in an attempt to provide new evidence for the role of impaired thyroid hormone sensitivity for serum atherogenic non-HDL-C levels.

MATERIALS AND METHODS

Study design and participants

A total of 1147 patients with T2DM were recruited from the Department of Endocrinology, Xuanwu Hospital, Capital Medical University, from January 2020 to December 2021. All participants met the 1999 World Health Organization diagnosis and classification criteria for T2DM. The exclusion criteria were as follows: (1) Age ≤ 35 years; (2) Oncological, infectious, serious liver or renal disease; (3) Lack of data on TSH, FT3, FT4, TC, or HDL cholesterol (HDL-C); and (4) A history of surgery for thyroid diseases, antithyroid therapy and hormone replacement. After exclusion, 994 participants were included in the final analysis (Figure 1).

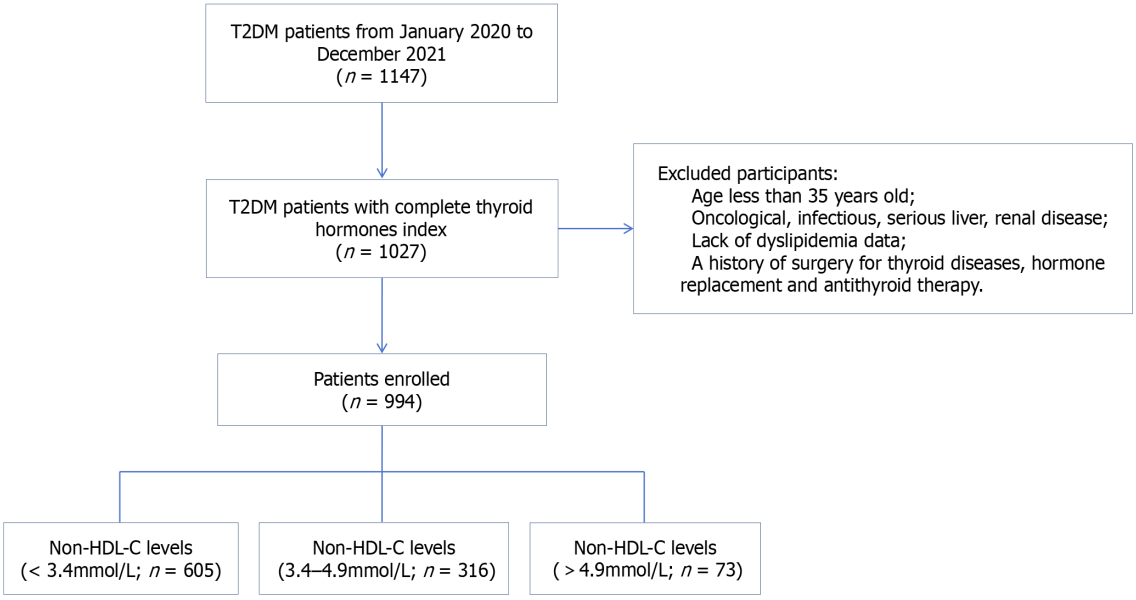

Figure 1 Flow chart of patient recruitment. Non-HDL-C: Non-high-density lipoprotein cholesterol; T2DM: Type 2 diabetes mellitus.

Clinical and biochemical measurements

Blood samples from the participants were obtained after overnight fasting and were measured in the biochemistry laboratory of Xuanwu Hospital of Capital Medical University. Biochemical parameters, including fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), TC, TG, HDL-C, low-density lipoprotein (LDL), uric acid, albumin, prealbumin, 25-hydroxyvitamin D [25(OH)D] and hemoglobin, were measured. Fasting blood insulin and fasting blood C-peptide levels were also measured.

All study subjects fasted for 10 h, and elbow venous blood was collected in the morning to determine FBG, TG, TC, LDL-C, and HDL-C levels. The HbA1c values were determined *via* liquid chromatography tandem mass spectrometry. Fasting insulin and C-peptide levels were measured *via* radioimmunoassay. The level of TSH was measured using a third-generation immunoassay. FT3 and FT4 levels were measured *via* a competitive immunoassay. The reference ranges for FT3, FT4, and TSH were 2.3-4.2 pg/mL, 0.89-1.76 ng/dL, and 0.55-4.78 mLU/L, respectively.

Hyper-non-HDL-C, hypertriglyceridemia, hypercholesterolemia, hypo-HDL cholesterolemia, and hyper-low-density lipoprotein cholesterolemia were defined as non-HDL-C ≥ 3.4 mmol/L, TG ≥ 1.7 mmol/L, TC ≥ 5.2 mmol/L, HDL-C < 1.0 mmol/L, and LDL-C ≥ 3.4 mmol/L[5]. Hypertension was defined as a systolic blood pressure (SBP) ≥ 130 mmHg, a diastolic blood pressure (DBP) ≥ 85 mmHg or specific treatment for previously diagnosed hypertension[13].

Definition of variables

Central indices of thyroid hormone sensitivity were calculated with the following formulas: TFQI = cumulative distribution function (CDF) FT4 - (1 - CDF TSH). TSHI = Ln TSH (μIU/mL) + 0.1345 × FT4 (pmol/L). TT4RI = FT4 (pmol/L) × TSH (μIU/mL). Central thyroid hormone sensitivity indicators reflect the response of the hypothalamus-pituitary-thyroid axis to changes in peripheral FT4. Negative values indicate higher central sensitivity, and positive values indicate lower

central sensitivity to changes in FT4. For TSHI, TT4RI, and TFQI, the higher the values, the lower is the central sensitivity to thyroid hormones[9].

The peripheral index of thyroid hormone sensitivity was calculated as follows: FT3/FT4 ratio = FT3 (pmol/L)/FT4 (pmol/L). Higher values indicate greater peripheral sensitivity to thyroid hormones.

The fasting RC level was calculated as TC - (HDL-C + LDL-C) (mmol/L)[10].

Non-HDL-C was calculated as TC - HDL-C (mmol/L). Homeostasis Model Assessment of insulin resistance (HOMA-IR) was calculated as the fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5.

Statistical analysis

For continuous variables, the data are presented as the means ± SDs or medians (upper and lower ranges). Data for categorical variables are expressed as numbers (%). One-way ANOVA, the Kruskal-Wallis H (K) test or the chi-square test was used for comparisons between variables where appropriate. The results of the logistic regression analysis are presented as ORs and 95%CIs. Pearson's and partial correlation coefficients were used to explore the associations of non-HDL-C with the thyroid-associated variables adjusted for sex, age, body mass index (BMI) and HbA1c. To further evaluate the potential associations of hyper-non-HDL-C with impaired thyroid hormone sensitivity, a logistic regression model was performed, and stratification was performed according to sex. IBM SPSS Statistics software, version 24.0 (IBM Corp., Armonk, NY, United States), and GraphPad 7.0 software were used for analyses of the data. Two-tailed *P* values < 0.05 were considered statistically significant. The Shapiro-Wilk test was used for the normality test. Random forest variable importance and Shapley Additive Explanations (SHAP) summary plots were used to identify the strength and direction of the association between hyper-non-HDL-C and its major predictor.

RESULTS

Baseline characteristics of the participants

A total of 994 adults included in this study were divided into three groups (non-HDL-C < 3.4 mmol/L, 3.4-4.9 mmol/L and > 4.9 mmol/L). The characteristics of the participants according to different non-HDL-C levels are shown in Table 1. The median age was 65.8 years (range 35.0-89.0), and 447 patients (44.9%) were males. Among all individuals with T2DM, 533 (54.1%) had fatty liver, 561 (56.8%) had hypertension, and 155 (27.5%) had cardiovascular disease.

Among them, 389 patients (39.13%) had high non-HDL-C levels (≥ 3.4 mmol/L). Compared with the normal non-HDL-C group (< 3.4 mmol/L), there was no significant difference in BMI, SBP, DBP or the incidence of hypertension. The levels of fasting plasma glucose (FPG), HbA1c, and HOMA-IR were significantly increased in the very high non-HDL-C level group (> 4.9 mmol/L) and decreased in the normal non-HDL-C group. These findings suggested poorer glycemic control in high non-HDL-C group. However, the levels of estimated glomerular filtration rate (eGFR) and 25(OH)D were significantly reduced in the very high non-HDL-C level group and significantly elevated in the normal non-HDL-C group ($P < 0.05$). TSH, TFQI, TSHI, TT4RI, TG, TC, LDL-C and RC levels tended to increase with increasing HDL level ($P < 0.05$), whereas the levels of FT3 and FT3/FT4 were significantly lower in the high non-HDL-C group than in the normal non-HDL-C group ($P < 0.05$; Table 1).

As shown in Figure 2, central thyroid hormone sensitivity indices, including the TFQI, TSHI, and TT4RI, were significantly elevated in patients in the high non-HDL-C group, whereas the peripheral thyroid hormone sensitivity index FT3/FT4 was significantly lower ($P < 0.05$).

Correlations between non-HDL-C levels and thyroid-associated variables

The correlations between non-HDL-C levels and thyroid-associated variables are presented in Table 2. TSH, TT4RI, TSHI, and the TFQI were positively associated with non-HDL-C levels, whereas the FT3/FT4 ratio was negatively associated with non-HDL-C levels in all participants. FT3 and FT4 were negatively correlated with the levels of non-HDL-C in men, whereas TSHI, TT4RI were positively correlated. However, non-HDL-C levels were negatively associated with the FT3/FT4 ratio and positively associated with the TFQI in women (all $P < 0.05$).

We also analyzed the correlations between lipid profiles such as TG, TC, HDL, LDL and RC and thyroid-associated variables (Table 3). Lipid profiles, especially TG, TC and RC, were significantly associated with thyroid hormone sensitivity indices before and after adjusting for age, sex, BMI, and HbA1c. LDL levels were negatively associated with FT3 and the FT3/FT4 ratio and positively associated with TSHI, whereas HDL levels were negatively associated with FT3, TSH, the FT3/TF4 ratio, the TT4RI and the TSHI.

Relationship between hyper-non-HDL-C and impaired sensitivity to thyroid hormones

To investigate the relationship between hyper-non-HDL-C and impaired sensitivity to thyroid hormones, we performed logistic regression analyses (Table 4). The risk of hyper-non-HDL-C was positively correlated with the TFQI (OR: 1.584; 95%CI: 1.088-2.304; $P = 0.016$), TSHI (OR: 1.238; 95%CI: 1.034-1.482; $P = 0.02$), and TT4RI (OR: 1.075; 95%CI: 1.006-1.149; $P = 0.032$) but was not significantly correlated with the FT3/FT4 ratio. Even after adjusting for age, sex, BMI, and HbA1c, the associations between hyper-non-HDL-C and impaired central sensitivity to thyroid hormones were significant. However, the relationships between composite indices of the thyroid system and non-HDL-C levels differed according to sex. An increased risk of hyper-non-HDL-C was associated with elevated TSHI levels in men (OR: 1.331; 95%CI: 1.003-1.766; $P = 0.048$) but elevated TFQI levels in women (OR: 2.337; 95%CI: 1.4-3.901; $P = 0.001$).

Table 1 Basic characteristics of the population

Characteristics	All (*n* = 994)	Non-HDL-C levels (mmol/L)			*P* value
		< 3.4 (*n* = 605)	3.4-4.9 (*n* = 316)	> 4.9 (*n* = 73)	
Age (years)	65.8 (35.0-89.0)	66.0 (36.0-89.0)	64.0 (35.0-86.0)	64.0 (36.0-83.6)	0.010
Sex (male/female)	447/547	278/327	140/176	29/44	0.576
Disease duration of T2DM (years)	13.0 (0.0-40.0)	13.0 (0.0-35.0)	13.0 (0.0-40.0)	11.0 (0.02-30.0)	0.336
BMI (kg/m^2)	25.6 (14.38-47.97)	25.6 (14.38-45.45)	25.6 (16.0-47.9)	25.6 (19.5-41.1)	0.743
SBP (mmHg)	130 (90-210)	130 (90-190)	130 (90-210)	130 (110-180)	0.294
DBP (mmHg)	80 (50-120)	80 (50-120)	80 (50-110)	80 (60-100)	0.162
FPG (mmol/L)	8.22 (2.88-24.52)	7.79 (3.12-24.17)	8.84 (2.88-23.49)	9.97 (3.25-24.52)	< 0.001
Fasting C peptide (ng/mL)	2.30 (0.01-16.34)	2.21 (0.01-13.35)	2.37 (0.17-16.34)	2.78 (0.27-6.93)	0.008
HOMA-IR	4.47 (0.04-279.63)	4.22 (0.05-243.20)	4.74 (0.47-279.63)	5.43 (0.04-34.27)	0.047
HbA1c (%)	8.1 (4.9-15.1)	7.8 (4.9-14.8)	8.7 (5.4-15.1)	9.2 (6.0-14.7)	< 0.001
Creatinine (μmol/L)	62 (28-266)	62 (30-241)	60 (28-230)	65 (30-266)	0.016
eGFR [mL/min (1.73 m^2)$^{-1}$]	101.1 (19.1-323.7)	100.7 (21.1-291.4)	103.5 (19.1-323.7)	95.0 (22.4-284.9)	0.009
UA (mmol/L)	324 (7-811)	324 (7-811)	321 (98-797)	338 (209-612)	0.126
UACR (mg/g)	4.0 (0.0-2404.2)	4.1 (0.0-1637.8)	2.6 (0.0-1796.2)	12.8 (0.1-2402.2)	0.013
25(OH)D (ng/mL)	16.80 (3.00-57.55)	17.52 (3.00-57.55)	16.57 (3.00-50.21)	14.73 (3.31-35.78)	0.039
Fatty liver, *n* (%)	533 (54.1)	304 (50.6)	180 (57.7)	49 (67.1)	0.002
Hypertension, *n* (%)	561 (56.8)	344 (57.2)	172 (54.8)	45 (61.6)	0.530
Cardiovascular disease, *n* (%)	155 (27.5)	111 (33.5)	34 (82.9)	10 (24.4)	0.002
Diabetic retinopathy, *n* (%)	238 (24.1)	142 (23.6)	68 (21.8)	28 (38.4)	0.011
Diabetic peripheral neuropathy, *n* (%)	411 (41.7)	248 (41.2)	123 (49.5)	40 (54.8)	0.055
Diabetic peripheral vascular disease, *n* (%)	157 (38.8)	89 (38.5)	55 (38.5)	13 (41.9)	0.931
Serum lipid level (mmol/L)					
TG	1.35 (0.24-21.80)	1.37 (0.24-8.59)	1.69 (0.39-9.99)	2.51 (0.63-21.80)	< 0.001
TC	4.25 (2.03-10.35)	3.74 (2.03-5.74)	5.07 (4.13-7.20)	6.53 (5.58-10.35)	< 0.001
LDL-C	2.51 (0.15-6.88)	2.08 (0.15-3.80)	3.28 (1.12-4.66)	4.32 (1.37-6.88)	< 0.001
HDL-C	1.10 (0.33-3.42)	1.10 (0.33-3.42)	1.10 (0.47-2.66)	1.09 (0.58-1.90)	0.896
non-HDL-C	3.10 (1.02-9.30)	2.56 (1.02-3.39)	3.95 (3.40-4.89)	5.3 (4.90-9.30)	< 0.001
RC	0.53 (-1.31-7.93)	0.45 (-1.31-2.40)	0.67 (-0.34-3.66)	1.13 (-0.33-7.93)	< 0.001
Thyroid function and indices of thyroid hormone sensitivity					
FT3 (pg/mL)	2.93 (0.91-4.49)	2.93 (0.91-4.19)	2.97 (1.01-4.49)	2.80 (1.15-3.97)	0.006
FT4 (ng/dL)	1.19 (0.72-1.59)	1.18 (0.72-1.92)	1.18 (0.75-1.96)	1.21 (0.76-1.59)	0.905
TSH (uIU/mL)	1.74 (0.01-9.89)	1.65 (0.07-9.89)	1.86 (0.07-9.48)	2.03 (0.16-9.12)	0.017
FT3/FT4	2.47 ± 0.47	2.47 ± 0.47	2.48 ± 0.45	2.34 ± 0.52	0.040
TT4RI	2.10 (0.01-12.23)	1.99 (0.10-9.89)	2.27 (0.1-12.23)	2.56 (0.20-8.43)	0.008
TSHI	0.72 (-4.43-2.42)	0.66 (-2.48-2.42)	0.79 (-4.43-2.42)	0.91 (-1.66-2.63)	0.010
TFQI	0.00 ± 0.35	-0.02 ± 0.36	0.03 ± 0.34	0.08 ± 0.34	0.026

The data are expressed as the means ± SDs, medians (upper and lower quartiles) or *n* (%). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; UA: uric acid; UACR: urinary albumin-creatinine ratio; FPG: fasting plasma glucose;

HbA1c: glycosylated hemoglobin; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; non-HDL-C: Non-high-density lipoprotein cholesterol; RC: remnant cholesterol; T2DM: Type 2 diabetes mellitus; HOMA-IR: Homeostasis Model Assessment of insulin resistance; 25(OH)D: 25-hydroxyvitamin D; FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

Table 2 Correlations between non-high-density lipoprotein cholesterol levels and thyroid parameters in patients with type 2 diabetes mellitus

Variables		All		Male		Female	
		r	*P* value	r	*P* value	r	*P* value
FT3 (pg/mL)	Model 1	-0.090[a]	0.005	-0.153[a]	0.001	-0.062	0.147
	Model 2	-0.128[a]	< 0.001	-0.187[a]	< 0.001	-0.095	0.027
	Model 3	-0.113[a]	< 0.001	-0.168[a]	< 0.001	-0.082	0.059
FT4 (ng/dL)	Model 1	-0.008	0.795	-0.115[b]	0.015	0.014	0.737
	Model 2	-0.013	0.693	-0.118[b]	0.013	0.012	0.78
	Model 3	-0.024	0.451	-0.14[a]	0.003	0	0.991
TSH (uIU/mL)	Model 1	0.073[b]	0.022	0.141[a]	0.003	0.007	0.867
	Model 2	0.079[b]	0.014	0.143[a]	0.002	0.016	0.714
	Model 3	0.093[a]	0.004	0.154[a]	0.001	0.024	0.575
FT3/FT4	Model 1	-0.051	0.107	-0.019	0.694	-0.075	0.078
	Model 2	-0.076[b]	0.017	-0.037	0.441	-0.101[b]	0.019
	Model 3	-0.033	0.301	-0.003	0.942	-0.052	0.228
TT4RI	Model 1	0.076[b]	0.018	0.121[b]	0.01	0.037	0.394
	Model 2	0.079[b]	0.013	0.121[b]	0.011	0.044	0.308
	Model 3	0.088[a]	0.006	0.129[a]	0.007	0.046	0.286
TSHI	Model 1	0.085[a]	0.008	0.129[a]	0.006	0.052	0.224
	Model 2	0.087[a]	0.006	0.129[a]	0.007	0.058	0.175
	Model 3	0.103[a]	0.001	0.14[a]	0.003	0.069	0.111
TFQI	Model 1	0.078[b]	0.014	0.029	0.539	0.121[a]	0.004
	Model 2	0.074[b]	0.02	0.024	0.612	0.121[a]	0.005
	Model 3	0.065[b]	0.044	0.014	0.777	0.109[b]	0.011

[a]$P < 0.01$.
[b]$P < 0.05$.
Model 1 was an unadjusted analysis. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, body mass index, and glycosylated hemoglobin. FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

SHAP was employed to assess the importance and contribution of thyroid-related variables within the optimal random forest models for hyper-non-HDL-C, with a prioritized list vividly illustrating their respective impacts (Figure 3). Among the analyzed features, the average SHAP values were highest for TSHI, followed by TT4RI (Figure 3A). The distribution of the SHAP scores was also analyzed for each feature (Figure 3B). As shown in the SHAP summary plot, the red dots indicate high feature values; however, the blue dots represent low feature values. SHAP values above zero suggested higher non-HDL-C values, whereas values below zero indicated lower non-HDL-C values. For example, a higher TSHI, TT4RI and TFQI (depicted in red) correlated with higher SHAP values, suggesting that they were all risk factors for hyper-non-HDL-C. Regarding the TSHI in the different sex models (Figure 4), an increase in the TSHI was strongly associated with an increase in its contribution to the model predictions. In terms of contributors in the sex models, the TT4RI ranked second in the male model and third highest in the female model. Compared with these factors, the other features had smaller contributions. The rankings of these other features also varied between different sex models.

Table 3 Relationships between lipid profiles and thyroid-associated variables

Variables		TG		TC		LDL-C		HDL-C		RC	
		r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
FT3 (pg/mL)	Model 1	-0.092[a]	0.004	-0.116[a]	< 0.001	-0.086[a]	0.007	-0.093[a]	0.004	-0.037	0.246
	Model 2	-0.114[a]	< 0.001	-0.149[a]	< 0.001	-0.106[a]	0.001	-0.083[a]	0.009	-0.081[b]	0.011
	Model 3	-0.099[a]	0.002	-0.137[a]	< 0.001	-0.094[a]	0.003	-0.097[a]	0.003	-0.068[b]	0.035
FT4 (ng/dL)	Model 1	-0.007	0.838	0.001	0.971	0.008	0.8	0.03	0.352	-0.032	0.312
	Model 2	-0.01	0.764	-0.003	0.928	0.006	0.84	0.03	0.349	-0.039	0.224
	Model 3	-0.02	0.535	-0.012	0.717	-0.002	0.948	0.037	0.249	-0.048	0.139
TSH (uIU/mL)	Model 1	0.074[b]	0.021	0.045	0.157	0.04	0.206	-0.080[b]	0.013	0.083[a]	0.01
	Model 2	0.077[b]	0.016	0.05	0.12	0.043	0.177	-0.082[b]	0.01	0.09[a]	0.005
	Model 3	0.082[b]	0.01	0.063	0.05	0.056	0.084	-0.08[b]	0.012	0.095[a]	0.003
FT3/FT4	Model 1	-0.082[b]	0.01	-0.093[a]	0.003	-0.065[b]	0.041	-0.141[a]	< 0.001	0.008	0.802
	Model 2	-0.095[a]	0.003	-0.114[a]	< 0.001	-0.078[b]	0.015	-0.134[a]	< 0.001	-0.021	0.519
	Model 3	-0.061	0.06	-0.082[b]	0.011	-0.045	0.167	-0.163[a]	< 0.001	0.01	0.749
TT4RI	Model 1	0.079[b]	0.013	0.052	0.102	0.046	0.147	-0.066[b]	0.039	0.078[b]	0.014
	Model 2	0.081[b]	0.011	0.055	0.087	0.048	0.133	-0.068[b]	0.034	0.082[b]	0.01
	Model 3	0.081[b]	0.012	0.065[b]	0.043	0.057	0.075	-0.061	0.057	0.083[b]	0.01
TSHI	Model 1	0.099[a]	0.002	0.061	0.056	0.048	0.135	-0.066[b]	0.039	0.095[a]	0.003
	Model 2	0.1[a]	0.002	0.063[b]	0.049	0.049	0.126	-0.067[b]	0.036	0.098[a]	0.002
	Model 3	0.103[a]	0.001	0.079[b]	0.014	0.064[b]	0.047	-0.059	0.065	0.102[a]	0.002
TFQI	Model1	0.087[a]	0.006	0.074[b]	0.02	0.059	0.066	-0.003	0.922	0.061	0.054
	Model2	0.085[a]	0.008	0.071[b]	0.026	0.056	0.078	< 0.001	0.989	0.057	0.076
	Model3	0.068[b]	0.035	0.068[b]	0.035	0.052	0.106	0.02	0.529	0.043	0.181

[a]$P < 0.01$

[b]$P < 0.05$.

Model 1 was an unadjusted analysis. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, body mass index, and glycosylated hemoglobin. FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

DISCUSSION

The present study revealed that impaired sensitivity to thyroid hormones was significantly associated with non-HDL-C levels in the T2DM population. Our results indicated that reduced central thyroid hormone sensitivity (increased TSHI, TT4RI, and TFQI) was an independent risk factor for hyper-non-HDL-C, even after adjusting for multiple confounding factors. Moreover, the associations between thyroid hormone sensitivity indices and non-HDL-C levels differed between men and women, suggesting that sex-associated regulation of thyroid hormones impacted serum non-HDL-C levels.

Our study revealed that the levels of TSH, TFQI, TSHI, and TT4RI were significantly greater in individuals with hyper-non-HDL-C than in those with normal non-HDL-C, indicating the presence of central thyroid hormone resistance in participants with high non-HDL-C levels. Moreover, the FT3/FT4 ratio decreased, indicating impaired thyroid hormone sensitivity in peripheral organs. Furthermore, central thyroid hormone sensitivity indices (TFQI, TSHI, and TT4RI) were found to be independent risk factors for hyper-non-HDL-C in patients with T2DM. Moreover, we identified the strength and direction of the association between high non-HDL-C and its major predictor derived from random forest variable importance using SHAP and random forest model analyses. To our knowledge, no study has investigated the association between thyroid hormone sensitivity and non-HDL-C[4,5,17-19]. Non-HDL-C is a better marker of atherogenicity and represents the residual ASCVD risk in patients who have achieved target LDL-C goals[21-23]. Since non-HDL-C is known as 'bad cholesterol', it contains all atherogenic lipoproteins, which accumulate in the intima of the arteries, leading to the formation of atherosclerotic plaques[20]. According to international guidelines, the 2023 Chinese Guideline on the Primary Prevention of cardiovascular disease (CVD) recommends non-HDL-C as an alternative treatment target for LDL-C; however, clinicians often do not pay sufficient attention to this point[23]. Asvold *et al*[24] conducted a large sample cohort study with a follow-up of 11 years and reported that changes in TSH levels were associated with concomitant

Table 4 Logistic regression analysis of the relationship between non-high-density lipoprotein cholesterol and impaired sensitivity to thyroid hormones in patients with type 2 diabetes mellitus

Variables	All		Male		Female	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
FT3 (pg/mL)	0.91 (0.71-1.166)	0.456	0.698 (0.41-1.191)	0.187	1.002 (0.769-1.306)	0.987
FT4 (ng/dL)	0.919 (0.689-1.225)	0.564	0.194 (0.061-0.617)	0.005	1.012 (0.775-1.32)	0.932
TSH (uIU/mL)	1.091 (1.015-1.172)	0.018	1.136 (1.02-1.264)	0.02	1.037 (0.935-1.15)	0.49
FT3/FT4	1.01 (0.754-1.352)	0.949	1.369 (0.861-2.177)	0.184	0.846 (0.577-1.24)	0.392
TT4RI	1.075 (1.006-1.149)	0.032	1.086 (0.985-1.197)	0.097	1.055 (0.963-1.156)	0.252
TSHI	1.238 (1.034-1.482)	0.02	1.331 (1.003-1.766)	0.048	1.155 (0.918-1.452)	0.218
TFQI	1.584 (1.088-2.304)	0.016	0.961 (0.545-1.692)	0.89	2.337 (1.4-3.901)	0.001

Data were analyzed *via* logistic regression analysis adjusted for age, sex, body mass index and glycosylated hemoglobin. FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

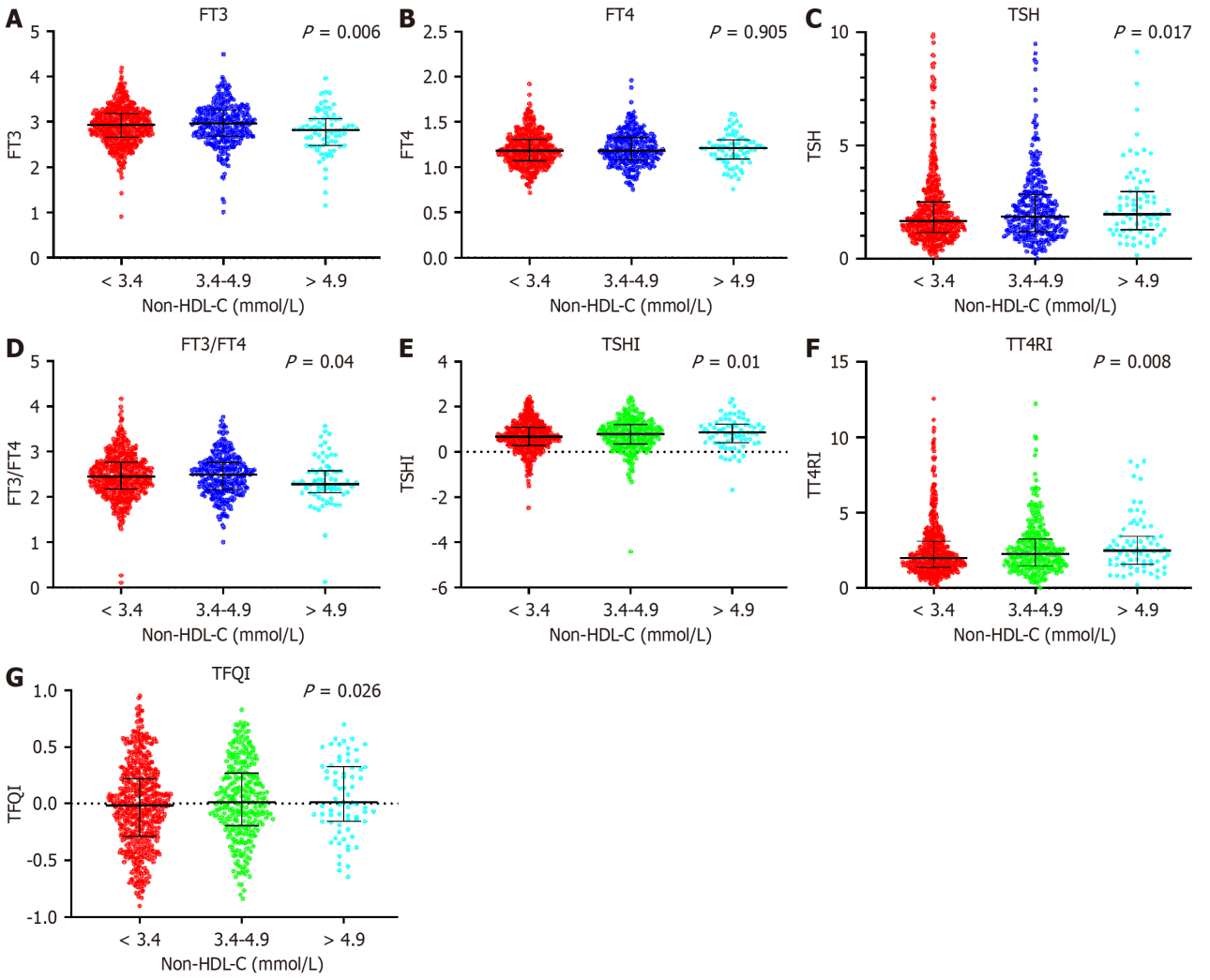

Figure 2 Comparison of thyroid-associated variables in different non-high-density lipoprotein cholesterol level groups. Data were analyzed by Student *t*-test or Mann-Whitney *U* test. A: Free triiodothyronine (FT3); B: Free thyrotropin (FT4); C: Thyroid-stimulating hormone (TSH); D: FT3/FT4; E: TSH index; F: Thyrotrophic T4 resistance index; G: Thyroid feedback quantile-based index. Non-HDL-C: Non-high-density lipoprotein cholesterol; FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

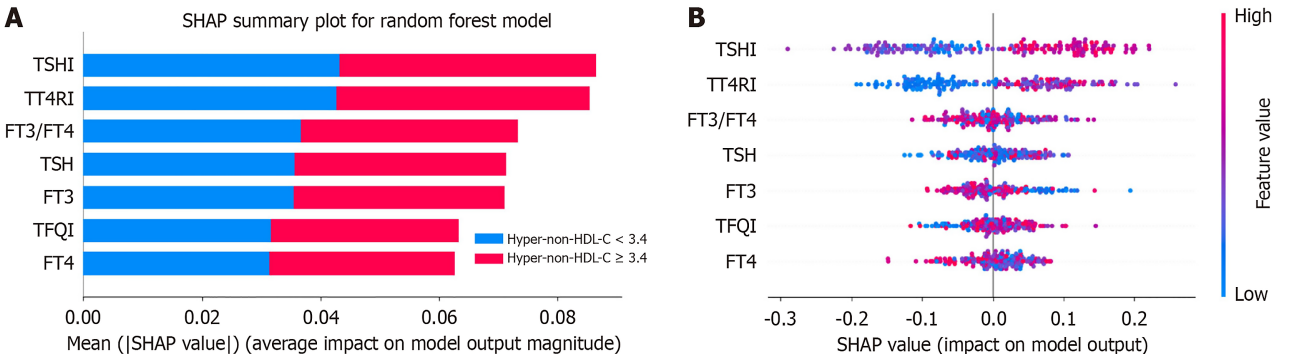

Figure 3 Feature importance of Shapley Additive Explanations values for the random forest model in detecting hyper-non-high-density lipoprotein cholesterol. A: Variables with the most significant impact on the prediction of hyper-non-high-density lipoprotein cholesterol (hyper-non-HDL-C) ranked in order of importance; B: Distribution of the influence of each variable on the prediction of hyper-non-HDL-C. The numerical characteristics of the variables are visually represented by colors, with larger values shown in red and smaller values shown in blue. Negative Shapley Additive Explanations values (spread to the left) suggest a decrease in the probability of hyper-non-HDL-C, whereas positive values (spread to the right) suggest an increase in probability. SHAP: Shapley Additive Explanations; FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index; Hyper-non-HDL-C: Non-high-density lipoprotein cholesterol.

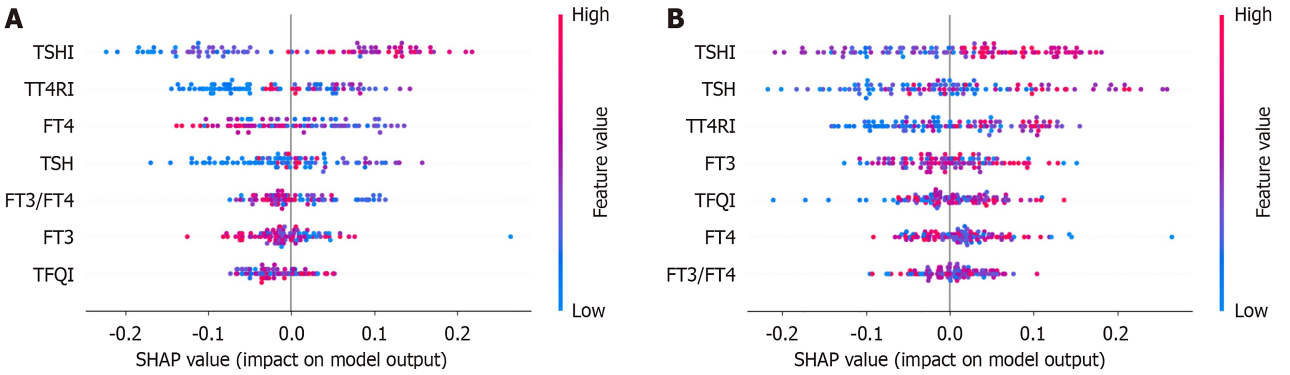

Figure 4 Feature importance of Shapley Additive Explanations values for the random forest model in detecting hyper-non-high-density lipoprotein cholesterol for men and women. A: The influence of each variable on the prediction of hyper-non-high-density lipoprotein cholesterol (hyper-non-HDL-C) in men; B: The influence of each variable on the prediction of hyper-non-HDL-C in women. The numerical characteristics of the variables are visually represented by colors, with larger values shown in red and smaller values shown in blue. Negative Shapley Additive Explanations values (spread to the left) suggest a decrease in the probability of hyper-non-HDL-C, whereas positive values (spread to the right) suggest an increase in the probability. SHAP: Shapley Additive Explanations; FT3: Free triiodothyronine; FT4: Free thyrotropin; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyrotrophic T4 resistance index; TFQI: Thyroid feedback quantile-based index.

changes in non-HDL-C and TG levels (all $P < 0.001$) irrespective of sex. Several studies have implied a close association between higher normal-range TSH and concentrations of total serum non-HDL-C parameters[19,26]. Thyroid hormones within the reference range combined with elevated TSH have been shown to be associated with pronounced lipid disorders and consequently an increased risk of atherosclerotic vascular disease[7,8]. Physiologically, thyroid hormones and TSH are inversely correlated owing to a negative feedback loop. However, high thyroid hormones can coexist with high TSH in individuals with resistance to thyroid hormones[9]. Reduced sensitivity to thyroid hormone in the general population has been shown to be a vital risk factor for various metabolic diseases, such as diabetes and hypertension[5,13,15]. These discoveries have also led to new directions in research regarding the relationship between thyroid function and lipid metabolism. Our findings suggest that the composite thyroid hormone sensitivity indices are better indices than the absolute values of FT3, FT4, and TSH, which could provide more information on thyroid function and directly relate thyroid hormone resistance to lipid metabolism.

Our study demonstrated that lipid profiles, especially TG, TC and RC, were also significantly associated with thyroid hormone sensitivity indices. However, HDL-C levels were negatively associated with peripheral thyroid hormone resistance. In line with previous studies, Liu *et al*[17] analyzed the associations between thyroid system indices and lipid profiles (TC, TG, HDL-C, LDL-C) and reported that the risk of dyslipidemia was positively correlated with TFQI, TSHI, and TT4RI and negatively correlated with FT3/FT4 in patients with coronary heart disease. A recent large sample study indicated that among euthyroid adults, reduced sensitivity to thyroid hormones was associated with high RC levels[10]. Therefore, sensitivity to thyroid hormones is associated with dyslipidemia, indicating that periodic screening of thyroid hormones in the T2DM population is recommended to aid early prevention of dyslipidemia.

In addition, our findings also revealed that elevated TFQI levels were associated with an increased risk of hyper-non-HDL-C in women. The TFQI is a new index for detecting acquired thyroid hormone resistance that was first proposed in 2019 by Laclaustra *et al*[9]. The performance of the TFQI was shown to be more stable than that of the TSHI and TT4RI[9]. Lipid abnormalities are especially relevant in women because they escalate rapidly with biological aging and endocrine changes related to menopause[26]. The menopausal transition and loss of estrogen possibly explain this association between TFQI and non-HDL-C in females, which might act as a trigger factor and impede metabolic function[27].

In this study, the patients with high non-HDL-C levels had not only higher TG, TC, LDL-C and RC levels but also significantly higher levels of FPG, HbA1c, and HOMA-IR, suggesting a poorer balance of glucose-lipid metabolism in individuals with high non-HDL-C. Similar findings have also been reported by Vazirian *et al*[28], indicating that elevated non-HDL-C serves as a significant predictor of glucose-lipid metabolism. In addition, patients with high non-HDL-C levels had worse renal function (lower eGFRs and higher creatinine levels compared with those in the normal group, $P < 0.05$). Among the previous studies that investigated the association of non-HDL-C and renal function, conclusions have been inconsistent[29,30]. Saland *et al*[30] reported that longitudinal increases in proteinuria and decreases in eGFR were independently associated with significant concomitant increases in non-HDL-C in children with chronic kidney disease. In another study, the prevalence of hyper-non-HDL-C was not related to chronic kidney disease stage[29]. Moreover, our data revealed that the 25(OH)D level was significantly reduced in the high non-HDL-C group compared with the normal non-HDL-C group. Most previous studies have shown no associations between vitamin D deficiency and elevated non-HDL-C[31,32]. Nwosu *et al*[33] reported significant inverse correlations between 25(OH)D and non-HDL-C cholesterol. In brief, patients with high non-HDL-C levels could face multiple endocrine and metabolic disorders, which is worth exploring in larger sample studies.

The novelty of this study lies in providing another layer of evidence for resistance to thyroid hormones as an independent risk factor for hyper-non-HDL in the T2DM population, which would be highly important for the T2DM population with an increased risk of ASCVD. The limitations of this study should be acknowledged. First, this was a cross-sectional study that utilized blood sample data from only a single point, which means that the direct causal relationship between non-HDL-C levels and thyroid hormone sensitivity cannot be inferred. However, this study supports the important hypothesis that thyroid hormone sensitivity may be useful for assessing the risk of dyslipidemia. In the future, more studies are needed to demonstrate causality. Second, information on the medication history of the participants was lacking, which might affect the data for thyroid hormone and non-HDL levels. Third, because our analysis was restricted to patients with T2DM selected only from Xuanwu Hospital, it is uncertain whether our findings can be generalized to other populations.

CONCLUSION

In conclusion, this is the first study to demonstrate an association of high non-HDL-C levels with reduced sensitivity to thyroid hormone in the patients with T2DM, providing new evidence for the role of reduced thyroid hormone sensitivity for non-HDL-C levels. Future investigations are needed to explore the underlying mechanism of this phenomenon and to lay the groundwork for future therapeutic strategies for diabetes mellitus-related CVD risk.

FOOTNOTES

Author contributions: Duan XY analyzed the data and wrote the manuscript; Fu JL, Sun LN and Mu ZJ contributed to the data collection; Xiu SL contributed to the data interpretation and reviewed the manuscript; all the authors read and approved the submitted version of the manuscript.

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