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Thyroid stimulating hormone (TSH) and free thyroxine concentrations are associated with lipids metabolism in euthyroid new-onset type 2 diabetic subjects.

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Abstract

Thyroid disease associated with abnormal lipid profile, which may lead to atherosclerosis. Although several observations indicate that serum Thyroid Stimulating Hormone (TSH) levels in the high normal range are related to Cardiovascular (CVD) risk factors in the general population. However, it remains to be elucidated that the association between thyroid hormones within the normal range and lipids in patients with type 2 diabetes. Thyroid hormones, TSH levels, antithyroid antibodies, anthropometric parameters, lipid profile, glucose and blood pressure were measured in 404 euthyroid new-onset type 2 diabetic subjects. Pearson's correlation analysis and multiple linear regression analysis were used to assess the influence of thyroid function parameters on the lipid profiles. The result showed that Total Cholesterol (TC), Low Density Lipoprotein-Cholesterol (LDL-C), Apolipoprotein B (ApoB) and Apolipoprotein A1 (ApoA1) increased linearly with the elevation of TSH within the normal range. Multiple regression analysis demonstrated high normal TSH level was positively correlated with the TC, LDL-C, ApoA1 and ApoB, serum Free Thyroxine (FT4) level was negative correlated with TC, Triglyceride (TG) and ApoB. The change of thyroid function, even within reference range of thyroid function tests, high normal TSH and low FT4 might exert adverse effects on the lipid profile resulting in hypercholesterolemia and hypertriglyceridemia, two well-known CVD risk factors.

Keywords: Lipids, Thyroid hormones, Euthyroid, Type 2 diabetes.

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Introduction

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice and have been shown to mutually influence each other [1]. Type 2 Diabetes Mellitus (T2DM) is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with hyperglycaemia and disturbance of lipid metabolism which contribute to cardiovascular diseases. The prevalence rate of thyroid dysfunction is much higher among diabetic population and estimated to be from 6.9% to 16%, with overt and subclinical hypothyroidism being the most common disorder. But we found that most of T2DM patients have normal thyroid function in these studies [2,3].

Thyroid hormone has multiple effects on the regulation of lipid metabolism [4]. Interestingly, the concept was emerging nowadays that effects of low thyroid function on dyslipidemia and atherosclerotic cardiovascular disease susceptibility might extend into the euthyroid range. A series of studies reported that serum Thyroid Stimulating Hormone (TSH) levels within the normal reference range were related to increased Total Cholesterol (TC), Triglyceride (TG), and Low-Density Lipoprotein Cholesterol (LDL-C) [5,6], although not all investigations confirm these associations [7,8]. Latest research found that TSH might up-regulate hepatic3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) expression, which suggested a potential direct role of TSH in the cholesterol biosynthesis in the liver [9]. Furthermore, the thyroid hormones play an important role in regulating lipid metabolism. Numerous studies have confirmed the presence of an inverse relationship between serum thyroxin and cholesterol levels [10]. Even within the reference range, serum Free Thyroxine (FT4) levels near the upper limit were associated with different metabolic markers in euthyroid patients with

coronary artery disease [11]. Recently, several studies have reported that relative low thyroid functions within normal range were more frequent and might lead to blood lipid metabolism disorders, insulin resistance and obesity in subjects with diabetes [12,13]. However, only a few studies can be found which concerned the relationship between thyroid within the normal range and lipids in T2DM while the prevalence and complication of diabetes are increasing rapidly in our country. And in most of these studies, TSH, FT4 and Free Triiodothyronine (FT3) were not measured together.

Therefore, the aim of this study was to investigate the potential associations between diabetes, thyroid hormone levels within the normal range and dyslipidemia in new-onset type 2 diabetic patients. We hoped this study would lead to a better understanding the role of thyroid parameters in blood lipid metabolism in diabetes mellitus.

Materials and Methods

Study design and patients

All of the patients were from inpatients of Department of Endocrinology, the Affiliated Yantai Yuhuangding Hospital of Qingdao University from January 2015 to July 2016. We finally chose 404 individuals (212 males and 192 females). New-onset T2DM was diagnosed according to 1997 American Diabetes Association criteria and never received anti-diabetic treatment. Euthyroidism is defined as TSH within 0.27-4.2 mIU/L and FT4 and FT3 within the laboratory reference ranges. We divided those euthyroid patients into four categories: G1 (lower limits of TSH 0.27-1.19 mIU/L), G2 (TSH 1.2-1.89 mIU/L), G3 (TSH 1.9-2.49 mIU/L) and G4 (upper limits of TSH 2.5-4.2 mIU/L) according to epidemic ecological studies [14]. The exclusion criteria were dependent on self-reported history and the data from our measurements. Subjects with the following status were excluded: type 1 diabetes, latent immune diabetes of the adults, gestational diabetes, other type of diabetes, liver function disorders, renal diseases and hypothyroidism subclinical hypothyroidism, myocardial infarction or stroke within 6 months. None of the subjects were treated with any medications which were known to influence lipid metabolism or body weight during the previous three months. This study was approved by the ethics committee of the Yantai Yuhuangding Hospital and written informed consents were obtained from all subjects.

Anthropometric measurements

A complete physical examination was conducted on each individual under condition of empty bladder and stomach. The Body Mass Index (BMI) was calculated as the weight in kilograms divided by the height squared in meters. There was a 3 min interval between the two measurements for each participant, and the mean value of the two measurements was used as Systolic Bold Pressure (SBP) and Diastolic Blood Pressure (DBP).

Laboratory measurements

Blood samples were collected by venipuncture from all subjects following 12 h of fasting. The levels of TSH, FT4, FT3, anti-Thyroglobulin antibody (anti-TG) and anti-Thyroid Peroxidase antibody (anti-TPO) were measured by using chemiluminescence tests (Elecsys 2010, Roche, Basel, Switzerland) with intra-and inter-assay coefficients of variation of less than 5%. The laboratory reference ranges for TSH, FT4, and FT3 were 0.27-4.2 mIU/L, 12-22 pmol/L and 2.8-7.1 pmol/L, anti-TG (0-115 IU/ml), anti-TPO (0-34 IU/ml), respectively. HemoglobinA1c (HbA1c) levels were measured by high pressure liquid chromatography (ADAMSTM A1C-8160, Japan). The levels of Fasting Plasma Glucose (FPG), Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein (LDL) cholesterol, High-Density Lipoprotein (HDL) cholesterol, Apolipoprotein B (ApoB) and Apolipoprotein A1 (ApoA1) were determined using an auto biochemical analyzer (MODULAR-000GS; Roche, Basel, Switzerland). FFA was measured by Fatty Acid Assay Kit (Beijing nine strong Biotechnology Co., Ltd, China).

Statistical analysis

The descriptive data were presented as the mean ± Standard Deviation (SD). Before proceeding with the statistical analysis, all of the parameters were tested for a normal distribution using the Kolmogorov-Smirnov test. Parameters that were not normally distributed were transformed to an approximate normal distribution. Differences in proportions of variables were determined by chi-squared analysis. Statistical analysis was performed with ANOVA followed by a multiple comparison test for subgroups by LSD. The relationships between thyroid hormones and lipid parameters were examined by Pearson's correlation analyses. To adjust for sex, age and FPG, a partial correlation analysis was performed while evaluating the relationship between TSH, FT4 and lipid. A multiple linear regression analysis using lipid profile as the dependent variable and TSH, FT4 and other parameters as the independent variable was performed to estimate the influence of TSH and FT4 on lipid metabolism. The statistical analyses were performed using SPSS software (18.0 for Windows, SPSS Inc., Chicago, USA). Statistical significance was defined as $P<0.05$.

Results

Baseline characteristics

A total of 212 men and 192 women participated in the study. Table 1 showed the clinical characteristics of 404 new-onset diabetic patients with euthyroidism. 56% of the participants were moderately overweight (BMI>25 kg/m^2) and 13.7% were obese (BMI>30 kg/m^2). Fasting blood glucose levels in 83.5% of patients were less than 10 mmol/L. The average HbA1c level was 8.56 ± 1.39%, suggesting that the level of the average blood glucose in all patients is moderately elevated while no significant metabolic disorders. Forty-six subjects were positive for either anti-TG or anti-TPO. Nineteen of these

subjects were positive for anti-TPO only, twenty-one of subjects were positive for anti-TG only and six subjects were positive for both antithyroid antibodies.

The relationship between thyroid hormones and lipid parameters

Correlation between thyroid hormones and lipid parameters in all the subjects were shown in Tables 2 and 3. Because serum lipid parameters did not fit a normal distribution, log transformations were applied to the values of TC, HDL, ApoB and FFA. The results showed that TSH levels were positively associated with serum TC, TG, LDL-C, ApoA1 and ApoB levels ($r=0.264$, $P<0.001$ for TSH and TC; $r=0.221$, $P<0.001$ for TSH and LDL-C; $r=0.169$, $P=0.001$ for TSH and ApoA1; $r=0.276$, $P<0.001$ for TSH and ApoB). We did not find a relationship between TSH and TG, HDL-C and FFA. The correlations remained significant between TSH and TC, LDL-C, ApoA1 and ApoB after we adjusted for age, gender and FPG. Significant negative correlations were identified between FT4 and serum TC, TG, LDL-C and ApoB levels ($r=-0.135$, $P=0.007$ for FT4 and TC; $r=-0.117$, $P=0.018$ for FT4 and TG; $r=-0.113$, $P=0.023$ for FT4 and LDL-C; $r=-0.135$, $P=0.007$ for FT4 and ApoB). The correlations remained significance between FT4 and TC, TG, LDL-C and ApoB after adjusted for age, gender and FPG. There were no significant relationship between FT3 and lipid (Data not shown in the article).

A multiple linear regression analysis using lipid profile as the dependent variable and TSH, FT4 and other parameters as the independent variable (Table 4). The results revealed that TSH independently associated with TC ($\beta=0.258$, $P<0.0001$), LDL-C ($\beta=0.226$, $P<0.0001$), ApoA1 ($\beta=0.132$, $P=0.006$) and ApoB ($\beta=0.263$, $P<0.0001$), while FT4 independently associated with TC ($\beta=-0.105$, $P=0.030$), TG ($\beta=-0.104$, $P=0.029$) and ApoB ($\beta=-0.106$, $P=0.030$).

Comparison of clinical characteristics among different TSH categories within the normal range

Clinical characteristics of the subjects in different TSH categories were shown in Table 5. Only BMI in G3 was significantly higher than that in G2 ($P<0.05$). No significant differences existed concerning age, sex, levels of FBG, HbA1c, SBP, DBP, FT4 and FT3 among the four TSH categories. There was a significant increase in concentrations of TC and LDL-C in G3 and G4 compared to G1 and G2 respectively ($P<0.05$). ApoA1 and ApoB levels were significantly higher in G4 than that in G1 and G2 ($P<0.05$). And more importantly, TC, LDL-C, ApoA1 and ApoB increased significantly in G4 (TSH 2.5-4.2 mIU/L) than those in G2 and G3 when compared with those in G1. This trend maintained substantially in HDL-C levels, which in G4 were higher than that in G1, but no significant differences among the four TSH categories. TG in G3 was significantly higher than that in G1 and G2 respectively ($P<0.05$), but also no significant differences between these groups. No significant differences existed among the levels of FFA of the four TSH categories.

Comparison of Clinical characteristics among the subjects with antithyroid antibody positivity

We aimed to compare laboratory parameters and lipid of euthyroid patients who have only positive antithyroid. Of the 404 patients, 46 (11.38%) were antithyroid antibody positive and 358 (88.62%) were negative. FT4 levels in antibody positive patients were significantly lower than those in antibody negative patients (15.87 ± 2.32 pmol/L *vs.* 16.68 ± 2.20 pmol/L; $P<0.05$). TSH and FT3 levels were not significantly different between groups. Lipid including TC, LDL-C, TG, ApoA1 and ApoB levels in antibody positive patients were higher than those in antibody positive patients. However, the differences were not significant (Table 6).

Table 1. *Clinical and laboratory characteristics of all subjects.*

Characteristics	N=404
Age (year)	58.81 ± 9.94
Sex (F/M)	212/192
BMI (kg/m^2)	26.57 ± 3.23
FBG (mmol/L)	8.06 ± 2.25
HbA1c (%)	8.56 ± 1.39
SBP (mmHg)	135.14 ± 19.21
DBP (mmHg)	79.05 ± 11.42
TSH (mIU/L)	1.87 ± 0.86
FT4 (pmo/L)	16.55 ± 2.22
FT3(pmo/L)	4.56 ± 0.68
TC (mmol/L)	4.96 ± 1.02
TG (mmol/L)	1.77 ± 1.09
HDL-C (mmol/L)	1.19 ± 0.65
LDL-C (mmol/L)	3.12 ± 0.83
ApoA-1 (g/L)	1.24 ± 0.18
ApoB (g/L)	0.99 ± 0.26
FFA (mmol/L)	0.36 ± 0.17

Note: Data are presented as means ± SD or absolute number. BMI: Body Mass Index; FBG: Fasting Blood Glucose; HbA1c: Hemoglobin A1c; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TSH: Thyrotropin; FT4: Free Thyroxine; FT3: Free Triiodothyronine; TC: Total Cholesterol; TG: Triglyceride; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; FFA: Free Fatty Acid.

Table 2. *Association between TSH and lipid in all T2DM patients.*

Variables	TSH			
	R	P	R1	P1
TC (mmol/l)	0.264	<0.001	0.252	<0.001
TG (mmol/l)	0.090	0.070	0.099	0.043
HDL-C (mmol/l)	0.089	0.073	0.068	0.172

LDL-C (mmol/l)	0.221	<0.001	0.213	<0.001
ApoA1 (g/L)	0.169	0.001	0.114	0.004
ApoB (g/L)	0.276	<0.001	0.262	<0.001
FFA (mmol/L)	0.078	0.118	0.082	0.102

Note: Log10-transformed TG, HDL-C, ApoB and FFA were used for statistical analysis. The relationships between TSH and lipids were examined by Pearson correlation. P: before adjustment for sex, age and FPG, P1: after adjustment for sex, age and FPG.

Table 3. *Association between FT4 and lipid in all T2DM patients.*

Variables	**FT4**			
	R	**P**	**R1**	**P1**
TC (mmol/l)	-0.135	0.007	-0.124	0.013
TG (mmol/l)	-0.007	0.018	-0.13	0.009
HDL-C (mmol/l)	-0.018	0.715	0.005	0.923
LDL-C (mmol/l)	-0.113	0.023	-0.104	0.037
ApoA1 (g/L)	-0.065	0.189	-0.043	0.495
ApoB (g/L)	-0.135	0.007	-0.128	0.010
FFA (mmol/L)	-0.039	0.439	0.035	0.485

Note: Log10-transformed TG, HDL-C, ApoB and FFA were used for statistical analysis. The relationships between TSH and lipids were examined by Pearson correlation. P: before adjustment for sex, age and FPG, P1: after adjustment for sex, age and FPG.

Table 4. *Multiple linear regression of TSH and FT4 with lipid in patients.*

	TSH		**FT4**	
Variables	B	**P**	**B**	**P**
TC (mmol/l)	0.258	<0.001	-0.105	0.030
TG (mmol/l)	0.058	0.220	-0.104	0.029
HDL-C (mmol/l)	0.081	0.104	-0.030	0.976
LDL-C (mmol/l)	0.226	<0.001	-0.089	0.070
ApoA1 (g/L)	0.132	0.006	-0.028	0.559
ApoB (g/L)	0.263	<0.001	-0.106	0.030
FFA (mmol/L)	0.050	0.300	-0.068	0.159

Note: The relationships between TSH, FT4 and lipids were examined by multiple regression analyses. Value of β: standardized regression coefficients. P-values less than 0.05 were considered statistically significant.

Table 5. *Clinical characteristics of different TSH categories in all T2DM patients.*

	G1 (0.27-1.19 mIU/L)	**G2 (1.2-1.89 mIU/L)**	**G3 (1.9-2.49 mIU/L)**	**G4 (2.5-4.2 mIU/L)**	**P**
N=404	93 (23.1%)	140 (34.6%)	82 (20.3%)	89 (22.0%)	
Age (y)	58.23 ± 9.09	59.10 ± 9.32	58.96 ± 10.60	58.82 ± 11.18	0.930
Sex (F/M)	53/40	79/61	41/41	39/50	0.214
BMI (kg/m^2)	26.30 ± 2.89	26.21 ± 3.12	27.18 ± 3.51†	26.83 ± 3.40	0.122
FPG (mmol/L)	7.99 ± 2.33	8.22 ± 2.18	8.11 ± 2.36	7.86 ± 2.17	0.664
HbA1c (%)	8.76 ± 1.42	8.67 ± 1.35	8.45 ± 1.42	8.33 ± 1.36	0.224
SBP (mmHg)	134.19 ± 19.82	133.15 ± 18.12	137.78 ± 19.18	136.82 ± 20.13	0.267
DBP (mmHg)	79.46 ± 10.88	79.00 ± 11.50	79.65 ± 11.42	78.14 ± 11.95	0.825
FT4 (pmo/L)	16.74 ± 2.09	16.64 ± 2.26	16.60 ± 2.09	16.16 ± 2.06	0.292
FT3 (pmo/L)	4.46 ± 0.65	4.60 ± 0.69	4.56 ± 0.64	4.59 ± 0.73	0.507
TC (mmol/L)	4.61 ± 0.97	4.80 ± 0.97	5.27 ± 0.90*†	5.29 ± 1.09*†	<0.001
TG (mmol/L)	1.71 ± 1.23	1.64 ± 0.84	2.03 ± 1.35*†	1.81 ± 1.03	0.075
HDL-C (mmol/L)	1.13 ± 0.26	1.15 ± 0.27	1.30 ± 0.35	1.21 ± 0.27	0.245
LDL-C (mmol/L)	2.88 ± 0.74	3.04 ± 0.83	3.30 ± 0.77*†	3.33 ± 0.89*†	<0.001
ApoA1 (g/L)	1.21 ± 0.16	1.22 ± 0.19	1.22 ± 0.17	1.30 ± 0.19*†	0.001
ApoB (g/L)	0.91 ± 0.21	0.96 ± 0.22	1.05 ± 0.22*†	1.07 ± 0.34*†	<0.001
FFA (mmol/L)	0.33 ± 0.16	0.36 ± 0.19	0.35 ± 0.14	0.38 ± 0.19	0.510

Note: Data are presented as means ± SD or absolute number (%). Log10-transformed TG, HDL-C, ApoB and FFA were used for statistical analysis. ANOVA followed by a multiple comparison test by LSD or the Chi-square test for categorical variables was performed to assess statistical significance of differences between all groups.*P<0.05 *vs.* G1; †P<0.05 *vs.* G2.

Table 6. *Clinical characteristics in antithyroid antibody positive patients.*

	Antithyroid antibody positive	Antithyroid antibody negative	P
N (F/M)	46 (13/33)	360 (202/158)	
Age (year)	59.69 ± 8.60	58.75 ± 10.11	0.546
BMI (kg/m^2)	26.22 ± 3.57	26.59 ± 3.18	0.462
FPG (mmol/L)	7.59 ± 2.31	8.13 ± 2.25	0.127
HbA1c (%)	8.44 ± 1.32	8.57 ± 1.39	0.507
SBP (mmHg)	136.22 ± 19.30	135.02 ± 19.17	0.779
DBP (mmHg)	77.11 ± 10.43	79.31 ± 11.50	0.248
TSH (mIU/L)	2.08 ± 0.98	1.84 ± 0.84	0.145
FT4 (pmo/L)	15.87 ± 2.32	16.68 ± 2.20	0.030*
FT3 (pmo/L)	4.39 ± 0.84	4.58 ± 0.75	0.118
TC (mmol/L)	5.14 ± 1.00	4.94 ± 1.02	0.190
TG (mmol/L)	1.83 ± 1.02	1.76 ± 1.09	0.335
HDL-C (mmol/L)	1.19 ± 0.26	1.18 ± 0.68	0.328
LDL-C (mmol/L)	3.30 ± 0.87	3.09 ± 0.82	0.108
ApoA1 (g/L)	1.28 ± 0.16	1.23 ± 0.18	0.088
ApoB (g/L)	1.09 ± 0.45	0.98 ± 0.22	0.066
FFA (mmol/L)	0.37 ± 0.16	0.36 ± 0.17	0.390

Note: Data are expressed as mean ± SD. Student's t-test for continuous variables was performed to assess statistical significance of differences between groups. Antithyroid antibody positivity includes anti-TG positivity (≥ 115 IU/ml) and/or anti-TPO positivity (≥ 34 IU/ml).*P<0.05.

Discussion

Thyroid hormone has multiple effects on the regulation of lipid digestion, absorption, synthesis, and catabolism [15]. Patients with overt hypothyroidism and subclinical hypothyroidism are known to be associated with the development of dyslipidemia compared to normal controls [16], which similar to the characteristic of lipid disorders in diabetes mellitus, yet most subjects with diabetes disease were euthyroid in the clinical setting. However the relationship between lipid profile and TSH and thyroid hormones within the euthyroid range in New-Onset T2DM is less studied. Because there is a consensus that diabetes patients should take statins or hypoglycemic drugs including insulin, which might change the lipid profiles, we chose to investigate those with newly onset type 2 diabetes to avoid the confounding effects of lipid-lowering drug and hypoglycemic drugs on lipid and blood glucose levels. Furthermore, to exclude the possible confounding effects of the diabetes complications, and to better understand the role of thyroid hormones in dyslipidemia of diabetes mellitus, we mainly focused on euthyroid new-onset type 2 diabetes in this study. Our results showed that TSH concentrations were positively and linearly correlated with TC and LDL-C levels in euthyroid new-onset type 2 diabetes, FT4 was negative correlated with TC, but the association between FT4 and LDL-C was less strong and lost statistical significant after controlling for age, gender, FPG and BMI. Similar result was also obtained in euthyroid non-diabetic populations. In a prospective population-based study [17], researchers demonstrated that within the normal range, the TSH level was associated with TC and LDL-C more strongly than FT4 among both men and women. The HUNT study also showed linear and significant increases in the serum TC and LDL-C levels with increased TSH level within the reference range [18]. The same result was found in one hundred seventeen females with type 2 diabetes that TSH was positively associated with TC and LDL-C [19].

The mechanisms of the regulation of cholesterol homeostasis include effects on biosynthesis, uptake and metabolism. Research demonstrated that TSH receptors are functionally present in both human and rat hepatocytes [20]. A recent study revealed that TSH promoted the expression of HMGCR, the rate-limiting enzyme in cholesterol synthesis in liver cells [9].

Based on these findings, we assumed that TSH, even within the normal range, might act through TSH receptor expressed on hepatocytes to up-regulate the expression of HMGCR resulting in increased TC levels in T2DM patients. Moreover, higher TSH was reported to increase plasma cholesterol ester transfer also resulting in increased TC levels in the context of chronic hyperglycemia in Triolo's study [21]. Thyroid hormone (FT3 and FT4) also induces the hepatic Sterol Regulatory Element-Binding Protein-2 (SREBP-2), which results in increased cholesterol synthesis [22]. Thus, decreased thyroid hormones especially FT4 lead to reduced hepatic cholesterol synthesis, and finally result in increased levels of circulating TC [23].

We also found negative correlation between serum FT4 level and TG in our study; this is consistent with the observations of Shon et al. [24] and Roos et al. [8] in euthyroid health subject. Different from previous studies in patients with diabetes and no diabetes [12,25], we found that TSH was not associated with TG. In the multiple linear regression analysis, our result found that FPG was significantly associated with TG. Possible reasons for the different results are that diabetic patients in our study do not receive antidiabetic drugs or hypolipidemic drugs, which may lead to high fasting blood glucose. So the association between FPG and TG was stronger, the relationship between TSH and TG became less strong and lost statistical significance. The potential mechanism of relationship between FT4 and TG can be explained in the following possibilities. One is that the elevation of TGs in hypothyroidism is caused by a reduced removal rate of TG from plasma due to a decrease in the activity of hepatic TG lipase [26]. Similar pathophysiological mechanisms may also be effective in euthyroid subjects with low-normal thyroid function [8]. Another is insulin resistance. Hypertriglyceridaemia are one of the main features of the dyslipidemia which closely related with type 2 diabetes and insulin resistance. Recently Study found that FT4 was negatively associated with HOMA-IR and fasting insulin levels in overweight and obese of euthyroid women [27]. A similar study in117 diabetic patient revealed a comparable inter-action between thyroid function and insulin sensitivity in contributing to diabetic dyslipidemia [19]. These data suggested that thyroid hormones may be part of the pathogenetic mechanism to explain lipid metabolic derangement early in the development of type 2 diabetes.

Low FT4 levels associated with hypertriglyceridemia may subsequently increase the import of TG into the liver, thereby cause hepatic steatosis. One research in Chinese people has found that serum FT4 level even within the reference range was significantly associated with the risk for NAFLD [28]. Another study in American also found that lower plasma FT4 levels are associated with a higher prevalence of NAFLD and the increased levels of hepatic triglyceride content in patients with T2DM [29]. This result suggested that relatively low but clinically normal thyroid function may increase incidence of NAFLD in diabetic patients, thus increasing the incidence of cardiovascular disease.

Different from previous studies in diabetic patients, our study also found that the level of TSH was significantly correlated with ApoA1 and ApoB levels. Recent study showed that elevated ApoA1 levels acted as a risk factor for Cerebrovascular Disease (CVD), independent of conventional cardiovascular risk factors [30]. Another research indicated that significantly positive correlations between the serum levels of TSH and ApoA1 in euthyroid cardiovascular patients [31]. Because ApoA1 are structural components of HDL-C. However, the results of the present study didn't found the relationship between TSH and HDL-C, which indicated that TSH might regulate ApoA1 production without affecting the HDL-C levels. Our findings also agree with these results that show low normal thyroid function may contribute to higher circulating ApoB-containing lipoprotein levels [32,33]. Taken together, these findings suggested that higher TSH and FT4 in normal range could increase serum ApoA1 and ApoB concentrations may contribute to the increased risk of atherosclerosis and premature coronary artery disease in type 2 diabetes.

Some authors suggested that chronic autoimmune thyroiditis might be considered as a risk factor of atherosclerosis independent of thyroid function [34]. In this study, antithyroid antibody positivity was considered in association with thyroid function and lipids profile in diabetic subjects. We found that FT4 levels were significantly lower in antibody positive patients. TSH were higher in antibody positive group, however, the differences were not significant. Along with higher TSH and lower FT4 level in these antithyroid antibody positive groups, higher lipid concentrations were also observed, but the differences were not significant. This may attribute to the small sample size of patients who have positive antithyroid antibody. Larger scale studies were needed to further confirm the role of thyroid antibodies in atherosclerosis.

Several limitations of our study needed to be considered. The first limitation of this study is its small sample size. The second limitation is that thyroid status was classified in all patients based on one blood test. Thus, some individuals with transient TSH elevations might have been misclassified. The third, the causality between TSH and lipid levels cannot be fully established because we used a cross-sectional design. A well-designed prospective research study will be necessary to address the relationship between TSH and lipid levels. The last limitation is that some patients may be given hypoglycemic drugs therapy after hospitalization which may influence the accuracy of fasting insulin levels. We did not determine serum insulin level. Whether the relationship between thyroid hormone levels and blood lipid level is influenced by insulin resistance should be further verified. In the future, large-scale studies with longer follow-up periods will be needed to estimate the real impact of this association and its clinical significance.

In conclusion, our study firstly showed high-normal TSH level was positively correlated with the hypercholesterolemia and elevated apolipoprotein levels and low serum FT4 level was associated with hypertriglyceridaemia in euthyroid new-onset type 2 diabetic patients. All these suggested that relatively low but clinically normal thyroid function, as inferred from higher

TSH and lower FT4 in normal range, could also exert adverse effects on the lipid profile and increase atherosclerosis susceptibility in type 2 diabetic patients. In the treatment of diabetes with dyslipidemia, thyroid function especially the serum TSH level should be monitored and maintained in the relatively low-normal range. Further large prospective studies are needed to demonstrate the mechanisms of lipid metabolism and CVD related risk in new-onset type 2 diabetes with respect to thyroid function and antithyroid antibodies.

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Conflict of Interest Statement

The authors declare that there is no conflict interest in this work.

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