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Original Article

Serum cholesterol levels in middle-aged euthyroid subjects with positive thyroid peroxidase antibodies

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Abstract: Objective: This study was designed to investigate serum cholesterol levels in middle-aged euthyroid subjects with positive thyroid peroxidase antibodies (TPOAbs). Methods: We screened 1607 euthyroid subjects aged 35-65 years old. All the subjects were divided into 2 groups (i.e., TPOAb-positive group, n=205; TPOAb-negative group, n=1402) according to the level of TPOAb. The subjects were then subgrouped according to serum thyroid stimulating hormone (TSH) levels; those with a TSH level of 0.3-0.99 mIU/L, 1.0-1.89 mIU/L, and 1.9-4.80 mIU/L were classified into the low-normal, mid-range, and high-normal TSH subgroups, respectively). Each TSH group further subdivided into TPOAb-positive and TPOAb-negative subgroup. Data regarding the subjects' height, body weight, blood pressure, and levels of serum TSH, TPOAb, fasting plasma glucose, total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) were collected. Results: Compared with TPOAb-negative subjects, TPOAb-positive patients had higher levels of TSH, TC, and HDL-C (P=0.001, P=0.012, and P=0.049 respectively) with a tendency for increased LDL-C levels (P=0.053). In the low-normal TSH subgroup, subjects with and without TPOAb had similar levels of TSH, TC, HDL-C, and LDL-C (P>0.05). In mid-range TSH subgroup, TPOAb-positive patients had higher HDL-C levels compared to TPOAb-negative subjects (P=0.008) and a tendency for increased TC levels (P=0.121). In the high-normal TSH subgroup, TPOAb-positive patients had higher TSH and TC levels compared to TPOAb-negative subjects (P<0.001 and P=0.046 respectively). Conclusions: High TPOAb levels above the normal range appears in euthyroid population, dyslipidemia have begun.

Keywords: Thyroid peroxidase antibody, thyroid-stimulating hormone, total cholesterol, high density lipoprotein cholesterol

Introduction

Dyslipidemia is caused by congenital or acquired factors, which could cause abnormal quality and quantity of lipids and their metabolic substances in blood and other tissues or organs. Dyslipidemia without obvious symptoms is usually found using tests or the corresponding cardiocerebrovascular events; therefore, understanding the influential factors and pathogenesis of dyslipidemia, early detection, and intervention are very important for the prevention and treatment of atherosclerosis (AS) and reducing cardiovascular events and mortality.

There are many ways of detecting lipids clinically, including basic laboratory tests for total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). Seventy percent of serum TC is composed of LDL-C. The level of TC is usually parallel to that of LDL-C, and both of them raised got the most attention in the development and progression of AS [1, 2]. Elevated TG levels could also cause AS [3], possibly by influencing the structure of LDL or HDL. Based on the traditional view, HDL could transport cholesterol from the surrounding tissues (including atherosclerotic plaque) to the liver for decomposition. In addition, according

Table 1. Concentrations of clinical characteristics in TPOAb-positive group and TPOAb-negative group (n=1607)

Characteristics	TPOAb-positive group (n=205)	TPOAb-negative group (n=1402)	*P* values
TSH (mIU/L)	2.18±1.08	1.65±0.81	<0.001
TPOAb (IU/mL)	183.08±242.06	0.37±0.51	<0.001
BMI (kg/m^2)	22.38±2.22	22.18±2.19	0.342
SBP (mmHg)	115.43±11.77	114.45±11.15	0.32
DBP (mmHg)	74.60±7.95	74.94±8.16	0.633
FPG (mmol/L)	4.94±0.42	4.87±0.44	0.106
TC (mmol/L)	4.99±0.77	4.80±0.72	0.012
TG (mmol/L)	0.88±0.43	0.88±0.38	0.808
LDL-C (mmol/L)	3.15±0.63	3.01±0.60	0.053
HDL-C (mmol/L)	1.48±0.31	1.41±0.30	0.049

to recent studies, HDL could also play a role in the resistance to atherosclerosis through antioxidant and anti-inflammatory effects and protection of endothelial function [4, 5]. HDL-C was negatively associated with coronary heart disease (CHD) in several epidemiological studies. Gordon et al. found that a 1 mg/dL (0.026 mmol/L) increment in the HDL-C level was associated with a significant CHD risk decrement of 2% and 3% in men and women, respectively [6, 7].

The presence of thyroid peroxidase antibodies (TPOAbs) is associated with thyroid lymphocytic infiltration. TPOAb is an important symbol of thyroid autoimmunity, and the TPOAb positive rate in the general population with a normal thyroid function could reach up to 10% [8, 9]. Positive TPOAb alone or in combination with elevated thyroid stimulating hormone (TSH) play important roles in the development of thyroid diseases according to some studies [10, 11]. Based on numerous studies, hypothyroidism could cause dyslipidemia [12, 13]. The risk of dyslipidemia also increased even with increasing TSH levels in euthyroid subjects [14, 15]. In addition, TPOAb also cause dyslipidemia, which is currently a major problem. This study was designed to investigate the effect of TPOAb on lipids in euthyroid subjects.

Materials and methods

Subjects

We screened 1607 euthyroid (TSH, 0.3-4.8 mIU/L) Chinese Han subjects (male: female, 1:3.7) aged 35-65 years with the collaboration of two hospitals in northern China (Xuzhou city and Linyi city) between January 2009 and January 2010. All subjects were divided into 2 groups according to the level of TPOAb: TPOAb-positive group (TPOAb ≥5.61 IU/mL, n=205) and TPOAb-negative group (TPOAb <5.61 IU/mL, n=1402). We then subgrouped the subjects according to serum TSH levels; subjects with a TSH level of 0.3-0.99 mIU/L, 1.0-1.89 mIU/L and 1.9-4.80 mIU/L were classified into the low-normal, mid-range, and high-normal TSH subgroups, respectively [16]. Each TSH group was subdivided further into TPOAb-positive and TPOAb-negative subgroups. We excluded the following subjects: those with thyroid-related diseases or a family history of thyroid-related diseases, being treated with thyroid disease-related drugs, with severe liver and kidney diseases, and with endocrine tumors.

Clinical, anthropometric, and laboratory measurements

Height and weight were measured, and body mass index (BMI) was calculated as weight/height^2 expressed in kg/m^2. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice after a 30-minute rest with the patient in the sitting position. There was a 3-minute interval between the 2 measurements and the mean value was used.

Overnight fasting blood samples were obtained from all subjects in the study. We tested TSH, TPOAb, FPG, TC, TG, and HDL-C levels. Serum TSH and TPOAb levels were tested using a chemiluminescence immunoassay according to the manufacturer's instructions (ACCESS automated chemiluminescence immunoassay analyzer, Beckman Coulter, Pasadena, CA, USA). FPG levels were tested with hexokinase law (the first Japanese pharmaceutical kit). TC, TG, and HDL-C levels were measured by routine enzymatic methods (Olympus 400, Olympus Optical Company, Tokyo, Japan). LDL-C was calculated using the Friedewald formula: LDL-C=TC-HDL-C-TG/2.2 (mmol/L) [17].

Statistics analysis

All data were logged into an Excel spreadsheet and analyzed using SPSS 17.0 software. TSH

Table 2. Concentrations of clinical characteristics in TPOAb-positive group and TPOAb-negative group in low-normal TSH levels (TSH 0.3-0.99 mIU/L, n=339)

Characteristics	TPOAb-positive group	TPOAb-negative group	*P* values
	(n=28)	(n=311)	
TSH (mIU/L)	0.73±0.18	0.73±0.18	0.961
TPOAb (IU/mL)	185.02±204.83	0.37±0.56	<0.001
BMI (kg/m^2)	22.67±2.20	21.92±2.05	0.271
SBP (mmHg)	115.00±11.12	116.13±10.92	0.674
DBP (mmHg)	74.06±6.84	76.26±8.98	0.310
FPG (mmol/L)	5.00±0.30	4.93±0.46	0.670
TC (mmol/L)	4.68±0.80	4.76±0.64	0.726
TG (mmol/L)	1.03±0.58	0.83±0.38	0.237
LDL-C (mmol/L)	2.92±0.66	2.96±0.55	0.825
HDL-C (mmol/L)	1.29±0.29	1.38±0.31	0.398

Table 3. Concentrations of clinical characteristics in TPOAb-positive group and TPOAb-negative group in mid-range TSH levels (TSH 1.0-1.89 mIU/L, n=723)

Characteristics	TPOAb-positive group	TPOAb-negative group	*P* values
	(n=65)	(n=658)	
TSH (mIU/L)	1.47±0.26	1.43±0.25	0.332
TPOAb (IU/mL)	162.58±233.49	0.36±0.48	<0.001
BMI (kg/m^2)	22.52±2.28	22.32±2.15	0.568
SBP (mmHg)	115.45±10.01	114.13±11.30	0.442
DBP (mmHg)	72.98±6.80	75.01±7.84	0.087
FPG (mmol/L)	5.00±0.43	4.88±0.46	0.121
TC (mmol/L)	5.00±0.93	4.80±0.72	0.121
TG (mmol/L)	0.83±0.43	0.87±0.39	0.341
LDL-C (mmol/L)	3.15±0.77	3.03±0.59	0.381
HDL-C (mmol/L)	1.55±0.34	1.39±0.31	0.008

and TG levels were analyzed after the logarithmic transformation. Continuous clinical biochemical variables were presented as $\bar{x}$±s. A t-test was used to compare group means. Differences with a P<0.05 were considered statistically significant.

Results

General clinical characteristics

Compared to TPOAb-negative subjects, TPOAb-positive patients had higher levels of TSH, TC, and HDL-C (P=0.001, P=0.012, and P=0.049, respectively) and a tendency for increased LDL-C levels (P=0.053); TG levels were not significantly different between groups (P>0.05; **Table 1**).

In the low-normal TSH subgroup, BMI, SBP, DBP, and levels of TSH, FPG, TC, TG, LDL-C, and HDL-C were not significantly different TPOAb-positive patients TPOAb-negative subjects (P>0.05; **Table 2**).

In the mid-range TSH subgroup, TPOAb-positive patients had higher HDL-C levels (P=0.008) and a tendency for increased TC levels (P=0.121) compared to TPOAb-negative subjects; the TSH, TG and LDL-C levels were not significantly different between groups (P>0.05; **Table 3**).

In the high-normal TSH subgroup, the TSH and TC levels were higher in TPOAb-positive patients compared to TPOAb-negative subjects, (P<0.001 and P= 0.046, respectively), and TG, LDL-C, and HDL-C levels were not significantly different between groups (P>0.05; **Table 4**).

Discussion

In this study, we found that TPOAb-positive patients had higher serum TC and HDL-C levels than TPOAb-negative subjects in the middle-aged euthyroid population. In some studies, it has been suggested that positive TPOAb may cause abnormal lipid metabolism. In a Turkish study, TPOAb was negatively correlated with HDL-C levels, independent of thyroid function, in different thyroid functional statuses (i.e., overt hypothyroidism, subclinical hypothyroidism, and euthyroid) [18]. Mazaheri et al. found that when compared with TPOAb-negative subjects, only euthyroid patients with TPOAb levels >1000 IU/mL may experience lower HDL-C levels [19]. Topaloglu et al. found that there was a positive correlation between TPOAb levels and levels of TC and LDL-C, and a negative correlation between TPOAb levels and HDL-C levels in euthyroid premenopausal women [20]. However, in another previous study, subclinical hypothyroidism patients with and without TPOAbs had similar levels of TC, HDL-C, and LDL-C [21]. In addition, no statistically significant relationships were found between the presence of TPOAb and any type of lipid profile, even after adjusting for age, sex, smoking, and other confounding factors.

In our study, serum TSH levels of all subjects were within the normal range; however, TPOAb-

Table 4. Concentrations of clinical characteristics in TPOAb-positive group and TPOAb-negative group in high-normal TSH levels (TSH 1.9-4.80 mIU/L, n=545)

Characteristics	TPOAb-positive group	TPOAb-negative group	*P* values
	(n=112)	(n=433)	
TSH (mIU/L)	2.95±0.82	2.62±0.62	<0.001
TPOAb (IU/mL)	194.49±256.25	0.38±0.51	<0.001
BMI (kg/m^2)	22.25±2.21	22.12±2.28	0.648
SBP (mmHg)	115.53±12.94	113.74±11.00	0.257
DBP (mmHg)	75.68±8.68	73.94±7.90	0.084
FPG (mmol/L)	4.90±0.44	4.83±0.41	0.236
TC (mmol/L)	5.03±0.66	4.82±0.76	0.046
TG (mmol/L)	0.90±0.40	0.91±0.36	0.559
LDL-C (mmol/L)	3.18±0.53	3.03±0.63	0.100
HDL-C (mmol/L)	1.47±0.29	1.46±0.28	0.750

positive patients had higher TSH levels than TPOAb-negative subjects. Elevated TSH levels may be an important factor in lipid metabolism. According to the current research, not only hypothyroidism can cause hyperlipidemia [12, 13], but high TSH levels within the normal range can also cause dyslipidemia [14, 15]. Based on a large-scale cross-sectional study in Spain, a country with a strong adherence to the Mediterranean diet, involving 20783 subjects, the TSH levels were positively associated with TC and LDL-C levels and negatively associated with HDL-C levels [14]. TSH levels, even within the normal range, were positively and linearly correlated with TC levels in a domestic retrospective study [15]. With a 1 mIU/L TSH rise, the TC level would increase by 1.010 mmol/L. The subjects with relatively high TSH levels within the reference range were more likely to have hypercholesterolemia with an odds ratio of approximately 1.640. Currently, the exact mechanisms for the relationship between TSH and lipid are unclear. However, according to an animal study, TSH, by acting on the TSHR in liver cells, could activate downstream signaling pathways, which up-regulate the expression of the rate-limiting enzyme HMGCR in cholesterol synthesis, and increase TC synthesis [22]. In addition, TSH may play a regulatory role on blood lipids through other mechanisms (i.e., promotion of lipolysis and increasing serum free fatty acid levels [23] or acting on the extrahepatic signaling pathway [24]).

In order to weaken the influence of the TSH level on blood lipid metabolism, we further subdivided the subjects into low-normal, mid-range, and high-normal TSH subgroups (TSH 0.3-0.99 mIU/L, 1.0-1.89 mIU/L, and 1.9-4.80 mIU/L, respectively) [16] to enable a better observation of the possible effects of TPOAb on blood lipids. Based on the results in the mid-range TSH subgroup, subjects with and without TPOAb had similar levels of TSH, while the TC levels were increased in TPOAb-positive patients. TPOAb might be one of the leading causes, which elevated the TC levels, and these results were similar to the findings of Topaloglu et al. [20]. It was unclear how TPOAb affects serum lipid levels; however, interferon-γ (IFN-γ) may cause dyslipidemia without elevated TSH levels. In euthyroid patients with positive TPOAb, IFN-γ was significantly higher than the control group [25]. IFN-γ stimulated the formation of foam cells, induced cholesterol absorption, reduced cholesterol efflux, and therefore, resulted in an imbalance in cholesterol homeostasis according to several studies [26-28].

Interestingly, TPOAb-positive patients had higher HDL-C levels than TPOAb-negative subjects based on our results, which was inconsistent with previous studies [18-21]. This may be related to ethnic group differences, diet, lifestyle, sex, age composition, BMI, and other factors; however, the specific mechanism is still unclear.

Conclusion

According to this study, positive TPOAb can cause dyslipidemia in the euthyroid population. Compared to TPOAb-negative subjects, TPOAb-positive euthyroid patients had higher TC levels, which was consistent with previous reports, and the difference is that HDL-C level also rises.

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Disclosure of conflict of interest

None.

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