Correlation Between Serum TSH Levels Within Normal Range and Serum Lipid Profile

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ABSTRACT

The aim of the work was to investigate the correlation between serum TSH (thyrotropin) levels within normal range and serum lipids. A total of 1962 subjects with normal thyroid function were enrolled. The subjects were divided into four groups according to the quartiles of serum normal TSH levels, [Q_1 (0.27–1.68) mIU/l, Q_2 (1.69–2.35) mIU/l, Q_3 (2.36–3.07) mIU/l, and Q_4 (3.08–4.20) mIU/l]. The effect of serum normal TSH levels on serum lipid profiles of different age or gender was analyzed. The total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels of the Q_3 group and TG levels of the Q_4 group were higher than those of the Q_1 group in youth ($p < 0.05$). The TC levels of the Q_3 group were higher than those of the Q_2 group in middle age ($p < 0.05$). The LDL-C levels of middle age or elderly were higher than those of youth at the same TSH levels ($p < 0.05$), while the TC levels of middle age were higher than those of youth in Q_1, Q_3, or Q_4 group ($p < 0.05$), and the TC and HDL-C levels of elderly were higher than those of youth in the Q_2 group ($p < 0.05$). The TG levels of the Q_3 group were higher than those of Q_1 group in males ($p < 0.05$). The LDL-C levels of the Q_3 group were higher than those of the Q_1 group in females ($p < 0.05$). In conclusion, the normal serum TSH levels were found to be closely related to serum lipid profiles, and with increasing TSH levels, serum lipids levels increased gradually.

Introduction

Thyroid-stimulating hormone (TSH) is secreted by the pituitary gland, which regulates the proliferation of thyroid cells, thyroid blood supply, and synthesis and secretion of thyroid hormones. These processes maintain normal thyroid function. TSH is the most sensitive indicator of thyroid function.

The thyroid function is closely related to the metabolism of blood lipids. The change in blood lipids in hypothyroidism and hyperthyroidism is usually the opposite. Some studies revealed that hypothyroidism might lead to hyperlipidemia, while hyperthyroidism leads to a decrease in blood lipids [1]. Hypercholesterolemia is the most common lipoprotein change in hypothyroidism. Salter et al. found that the expression of LDL receptor in liver cells of hypothyroid rats was significantly lower than that of normal control rats, and further studies on isolated hepatocytes showed that T_3 could directly increase the steady-state concentration of the mRNA for the LDL receptor by 25 %, which indicated that thyroid hormone may stimulate the synthesis and expression of LDL receptor in liver [2]. In addition, with the decrease of thyroid hormone levels, sterol regulatory element-binding protein 2 (SREBP-2) levels decline followed closely by a drop in LDL receptor mRNA, which caused a decrease in high affinity LDL cholesterol uptake in the liver leading to hypercholesterolemia [3, 4]. These results suggested that hypercholesterolemia in hypothyroidism may be due to the decrease of LDL receptor activity. With 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) as a rate-limiting enzyme of cholesterol synthesis, TSH could reduce the phosphorylation of HMG-CoA via AMP-ac-

tivated protein kinase (AMPK) in the liver, leading to increased HMG-CoA reductase activity, which increases cholesterol levels in the liver [5]. TSH can also directly upregulate the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in the liver, thus increasing the cholesterol content in liver and serum of rats after thyroidectomy [6].

The lipid peroxidation in patients with severe subclinical hypothyroidism was significantly higher than in those with normal thyroid function; this phenomenon is related to high risks of atherosclerosis [7]. Beibei et al. analyzed the correlations between serum TSH levels and serum lipids in 110 subjects with subclinical hypothyroidism and 1240 subjects with normal thyroid function by cluster sampling inclusion, indicating TSH as a risk factor for dyslipidemia independent of insulin resistance [8]. In a meta-analysis of a prospective cohort study, it was shown that subclinical hyperthyroidism and hypothyroidism may be associated with increased risks of death due to coronary heart diseases [9].

In contrast, Jiaoyue et al. found that after adjusting for age and other confounding factors, there is no correlation between TSH level and blood lipids [10]. However, a linear dose-dependent correlation between high TSH level in the normal range and dyslipidemia, possibly mediated by the effect of thyroid hormones on insulin sensitivity, was revealed in a large population-based study [11]. In patients with normal thyroid function and newly diagnosed asymptomatic coronary heart disease, the increased TSH level may have adverse effects on blood lipids and may also be a risk factor for hypercholesterolemia and hypertriglyceridemia [12]. Therefore, the present study aimed to explore the correlations between serum normal TSH levels and serum lipids.

Subjects and Methods

Subjects

A total of 2885 subjects participating in the national survey on thyroid diseases and iodine nutrition status 2014 in Gansu Province, China were selected. After screening by inclusion and exclusion criteria, a total of 1962 subjects (including 1077 males and 885 females) were included in this study.

Inclusion criteria were as follows: Subjects aged ≥ 18 years, Han nationality, at least 5 years of residence in the same community (village), and normal thyroid function, were recruited in the present study.

Exclusion criteria were as follows: Patients with previous thyroid dysfunction, whether or not treated with drugs; patients with thyroid dysfunction diagnosed for this study; patients with hypothalamic and pituitary diseases, diabetes, and other endocrine diseases, malignant tumors, severe liver and kidney diseases, acute cerebrovascular diseases, hereditary hyperlipidemia; pregnant or lactating women.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written and oral information of the protocol was explained to them before screening, and informed consent was obtained from each eligible participant.

Methods

Baseline information of the subjects

The baseline data with respect to demographics, education level, drinking and smoking history, disease history, and family history of the patients were collected. Also, the height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured. The height and weight of each subject were measured by professional medical staff; the subjects were required to take off their shoes and wear thin clothing. Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). The WC was measured at the umbilical plane, while SBP and DBP were measured using an electronic sphygmomanometer after a 10-minute rest. After fasting for 8 hours at night, 5 ml urine samples were collected in the morning to measure the urinary iodine concentration (UIC).

Determination of serum biochemical indicators

After fasting for 8 hours at night, the venous blood samples were collected in the morning. The fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured using the Bs-220Automatic Biochemical Analyzer (Mairui Biotechnology Co. Ltd, China). The reagent was purchased from Meigao Medical Technology Co. Ltd (China).

The serum TSH levels of every subject were measured by chemiluminescence immunoassay (Cobas 601 Analyzer, Roche diagnostics, Switzerland). The reference range of serum TSH was 0.27–4.20 mIU/l, and the limit of detection was 0.002 mIU/l. The intra-assay and inter-assay coefficient of variation were 1.9–9.5 % and 1.1–6.3 %, respectively. The urinary iodine concentration was determined by inductively coupled plasma mass spectrometry (Agilent 7700x, Agilent Technologies, USA). The intra-assay coefficients of variation were 2.3, 2.5 and 2.4 %, and inter-assay coefficients of variation were 2.7, 1.4 and 2.3 %, respectively.

Grouping of the subjects

Among the different age groups (youth: 18–44 years; middle age: 45–59 years; elderly: ≥ 60 years) or different gender groups, the subjects were divided into four groups according to the quartiles of serum normal TSH levels (0.27–4.20) mIU/l, [Q_1 (0.27–1.68) mIU/l, Q_2 (1.69–2.35) mIU/l, Q_3 (2.36–3.07) mIU/l, and Q_4 (3.08–4.20) mIU/l]. The effect of serum TSH levels within the normal range on serum lipid profiles of different ages or different gender were analyzed.

TC ≥ 5.2 mmol/l; TG ≥ 1.70 mmol/l; LDL-C ≥ 3.4 mmol/l; and HDL-C < 1.04 mmol/l were considered as diagnosis of dyslipidemia [13].

Statistical analysis

All data were analyzed using SPSS25.0. Measurement data of normal distribution are expressed as mean ± standard deviation ($\bar{x} \pm s$), and the independent sample *t*-test was used to compare the dif-

ferences between two groups. The data of urinary iodine concentration showed a skew distribution, which was expressed as median (p25, p75), and nonparametric test was used to compare the differences between groups. After adjusting for confounding factors, an analysis of covariance (ANCOVA) was used for comparison between multiple groups and LSD-*t* for the pairwise comparison. The enumeration data were expressed as frequency and percentage. The chi-square test was used to compare the differentiation between inter-group rates. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of all subjects

A total of 1962 subjects (1077 males and 885 females) were included. The TSH levels of females were higher than those of males ($p<0.05$). The BMI, SBP, DBP, FPG, TG, and LDL-C levels were significantly higher in men than women ($p<0.05$), while the HDL-C levels were lower ($p<0.05$). Moreover, no significant difference was observed in age, UIC, and TC levels between men and women (▶ **Table 1**).

The prevalence of high TG (30.7 %) and low HDL-C (10.9 %) in men was significantly higher than that in women (18.5 %) and (2.4 %). There was no significant difference in the prevalence of high TC and high LDL-C between men and women. Also, the total prevalence of dyslipidemia in men was significantly higher than that in women (44.5 vs. 31.6 %) (▶ **Table 1**).

Comparison of serum lipids between different age groups with different serum TSH levels

After adjusting for gender, BMI, SBP, DBP, FPG, and UIC, the TC and LDL-C levels of Q_3 group were higher than those of Q_1 group ($p<0.05$), and the TG levels of Q_3 or Q_4 group were higher than those of Q_1 group in youth ($p<0.05$). The TC levels of the Q_3 group in middle age were higher than those of the Q_2 group ($p<0.05$), and no significant difference was detected in TG, HDL-C, and LDL-C levels between middle age with different TSH levels ($p>0.05$). Also, no significant difference was detected in serum lipids levels between the elderly with different TSH levels ($p>0.05$) (▶ **Table 2**).

The LDL-C levels of middle age or elderly were higher than those of youth at the same TSH levels (all $p<0.05$). The TC levels of middle age in Q_1, Q_3, or Q_4 group were higher than those of youth (all $p<0.05$), while the TC and HDL-C levels of elderly in the Q_2 group were higher than those of youth ($p<0.05$) (▶ **Table 2**). The TC levels of middle age in Q_3 or Q_4 group were higher than those of elderly ($p<0.05$), and TG levels in Q_2 group were higher than those of elderly ($p<0.05$) (▶ **Table 2**).

Comparison of serum lipids between total population or different gender groups with different serum TSH levels

After adjusting for age, BMI, SBP, DBP, FPG, and UIC, the TC, TG, and LDL-C levels in the Q_3 group were higher than those in the Q_1 group ($p<0.05$), and the TG levels of the Q_4 group were higher than those of Q_1 group in the total population ($p<0.05$). The TG levels of the Q_3 group were significantly higher than those of Q_1 group in males ($p<0.05$). The LDL-C levels of the Q_3 group were significantly higher than those in the Q_1 group in females ($p<0.05$) (▶ **Table 3**).

▶ **Table 1** Baseline characteristics of the subjects.

Variables	Total population	Males	Females
Cases (n)	1962	1077	885
Age (years)	40.32 ± 14.21	40.54 ± 14.17	40.04 ± 14.25
BMI (kg/m^2)	23.49 ± 3.25	24.23 ± 3.25	22.58 ± 3.25 *
SBP (mmHg)	123.74 ± 16.56	125.42 ± 14.78	121.68 ± 18.30 *
DBP (mmHg)	76.78 ± 10.92	78.96 ± 10.46	74.11 ± 10.87 *
FPG (mmol/l)	5.18 ± 0.90	5.23 ± 0.92	5.11 ± 0.86 *
UIC (μg/l)	223.40 (157.80, 309.40)	220.35 (157.93, 293.70)	229.90 (157.30, 322.60)
TC (mmol/l)	4.32 ± 0.92	4.34 ± 0.87	4.30 ± 0.97
TG (mmol/l)	1.46 ± 1.02	1.60 ± 1.07	1.29 ± 0.92 *
HDL-C (mmol/l)	1.50 ± 0.37	1.39 ± 0.34	1.64 ± 0.36 *
LDL-C (mmol/l)	2.53 ± 0.72	2.61 ± 0.70	2.44 ± 0.73 *
TSH (mIU/l)	2.39 ± 0.90	2.31 ± 0.87	2.49 ± 0.92 *
High TG [n (%)]	495 (25.2)	331 (30.7)	164 (18.5) *
High TC [n (%)]	311 (15.9)	171 (15.9)	140 (15.8)
High LDL-C [n (%)]	226 (11.5)	137 (12.7)	89 (10.1)
Low HDL-C [n (%)]	138 (7.0)	117 (10.9)	21 (2.4) *
Dyslipidemia [n (%)]	759 (38.7)	479 (44.5)	280 (31.6) *

* $p<0.05$: Compared with males.

▶ **Table 2** Comparison of serum lipids between different age groups with different serum TSH levels.

Group	Cases (n)	TC (mmol/l)	TG (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	FPG (mmol/l)	UIC (μg/l)
Youth										
Q_1 group	317	4.06 ± 0.83*	1.26 ± 0.82$^{*\#}$	1.48 ± 0.35	2.31 ± 0.61*	23.11 ± 3.37	117.31 ± 12.95	74.12 ± 10.61	4.94 ± 0.59	231.70 (164.45, 310.65)
Q_2 group	332	4.13 ± 0.80	1.35 ± 0.95	1.47 ± 0.36	2.36 ± 0.65	23.34 ± 3.55	119.07 ± 13.30	75.45 ± 10.52	4.98 ± 0.56	231.10 (162.80, 313.90)
Q_3 group	333	4.19 ± 0.80	1.39 ± 0.96	1.50 ± 0.33	2.39 ± 0.64	22.86 ± 3.51	118.72 ± 12.09	74.26 ± 10.06	4.94 ± 0.59	224.50 (164.55, 299.65)
Q_4 group	285	4.18 ± 0.90	1.41 ± 0.95	1.50 ± 0.40	2.38 ± 0.66	23.33 ± 3.64	119.25 ± 13.35	74.67 ± 9.85	5.03 ± 0.63	236.15 (169.78, 333.83)
Middle age										
Q_1 group	110	4.50 ± 0.88$^{\Delta}$	1.62 ± 0.78	1.49 ± 0.38	2.81 ± 0.83$^{\Delta}$	24.10 ± 2.87	127.99 ± 15.15	81.53 ± 10.64	5.35 ± 0.68	209.60 (152.95, 309.55)
Q_2 group	102	4.47 ± 0.89*	1.63 ± 1.07$^{\&}$	1.51 ± 0.32	2.75 ± 0.72$^{\Delta}$	23.83 ± 2.86	128.64 ± 13.80	80.94 ± 9.93	5.61 ± 1.69	204.40 (147.18, 305.73)
Q_3 group	110	4.75 ± 0.83$^{\Delta\&}$	1.64 ± 1.50	1.48 ± 0.31	2.92 ± 0.62$^{\Delta}$	24.09 ± 2.79	128.25 ± 14.70	80.45 ± 10.21	5.37 ± 0.62	227.60 (150.50, 295.20)
Q_4 group	145	4.70 ± 0.87$^{\Delta\&}$	1.73 ± 1.19	1.53 ± 0.36	2.87 ± 0.61$^{\Delta}$	24.03 ± 2.98	128.76 ± 16.46	81.05 ± 10.76	5.49 ± 1.16	200.00 (145.05, 330.20)
Elderly										
Q_1 group	63	4.73 ± 1.08	1.62 ± 0.97	1.52 ± 0.34	2.89 ± 0.73$^{\Delta}$	24.43 ± 2.92	141.75 ± 22.54	78.90 ± 12.36	5.78 ± 1.30	213.50 (162.40, 292.10)
Q_2 group	58	4.90 ± 1.47$^{\Delta}$	1.44 ± 1.03	1.64 ± 0.43$^{\Delta}$	2.93 ± 0.99$^{\Delta}$	23.41 ± 3.13	141.93 ± 18.80	81.10 ± 11.63	5.61 ± 0.88	220.40 (142.58, 303.43)
Q_3 group	48	4.55 ± 0.94	1.80 ± 1.04	1.51 ± 0.46	2.82 ± 0.81$^{\Delta}$	24.65 ± 3.06	143.10 ± 22.20	79.04 ± 10.81	5.76 ± 0.87	219.25 (156.60, 217.40)
Q_4 group	59	4.63 ± 1.08	1.88 ± 1.32	1.58 ± 0.60	2.86 ± 0.80$^{\Delta}$	24.66 ± 3.72	144.49 ± 17.36	81.12 ± 13.10	5.84 ± 1.85	208.10 (143.30, 270.00)

Youth: 18–44 years; Middle age: 45–59 years; Elderly: ≥ 60 years. Q_1 group: TSH (0.27–1.68) mIU/l; Q_2 group: TSH (1.69–2.35) mIU/l; Q_3 group: TSH (2.36–3.07) mIU/l; Q_4 group: TSH (3.08–4.20) mIU/l.
* $p < 0.05$: Compared with Q_3 group at the same age; $^{\#}$ $p < 0.05$: Compared with Q_4 group at the same age. $^{\Delta}$ $p < 0.05$: Compared with youth group at the same TSH level;$^{\&}$ $p < 0.05$ compared with elderly group at the same TSH level.

▶ **Table 3** Comparison of serum lipids between total population or different gender groups with different serum TSH levels.

Group	Cases (n)	TC (mmol/l)	TG (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)	Age (years)	BMI (kg/m²)	SBP (mmHg)	DBP (mmHg)	FPG (mmol/l)	UIC (μg/l)
Total											
Q_1 group	490	4.25 ± 0.91 *	1.39 ± 0.85 *#	1.49 ± 0.36	2.49 ± 0.73 *	40.34 ± 14.82	23.50 ± 3.25	122.85 ± 17.20	76.40 ± 11.29	5.14 ± 0.80	223.90 (159.53, 309.80)
Q_2 group	492	4.29 ± 0.96	1.42 ± 0.99	1.50 ± 0.36	2.50 ± 0.75	39.70 ± 14.00	23.45 ± 3.37	123.75 ± 16.07	77.25 ± 10.84	5.19 ± 0.99	223.40 (157.40, 309.10)
Q_3 group	491	4.35 ± 0.85	1.48 ± 1.12	1.50 ± 0.34	2.55 ± 0.70	39.56 ± 13.70	23.31 ± 3.38	123.24 ± 15.89	76.11 ± 10.51	5.12 ± 0.68	224.45 (161.33, 292.95)
Q_4 group	489	4.39 ± 0.94	1.56 ± 1.09	1.52 ± 0.42	2.58 ± 0.71	41.67 ± 14.22	23.70 ± 3.38	125.12 ± 17.00	77.34 ± 11.00	5.27 ± 1.06	221.30 (154.33, 317.45)
Males											
Q_1 group	301	4.29 ± 0.87	1.50 ± 0.86 *	1.40 ± 0.32	2.59 ± 0.72	40.86 ± 14.23	24.25 ± 3.17	124.47 ± 14.43	78.41 ± 10.90	5.21 ± 0.88	219.60 (157.60, 295.50)
Q_2 group	290	4.35 ± 0.89	1.55 ± 0.94	1.39 ± 0.33	2.60 ± 0.72	40.93 ± 13.79	24.14 ± 3.24	126.11 ± 14.89	79.34 ± 10.35	5.27 ± 1.15	222.65 (165.23, 303.03)
Q_3 group	253	4.37 ± 0.80	1.70 ± 1.35	1.39 ± 0.32	2.62 ± 0.67	39.33 ± 14.31	24.04 ± 3.15	124.82 ± 14.36	78.51 ± 9.79	5.18 ± 0.73	223.90 (159.85, 287.35)
Q_4 group	233	4.36 ± 0.93	1.69 ± 1.09	1.36 ± 0.39	2.63 ± 0.70	40.97 ± 14.42	24.52 ± 3.44	126.45 ± 15.49	79.71 ± 10.74	5.26 ± 0.81	214.30 (150.05, 292.20)
Females											
Q_1 group	189	4.18 ± 0.98	1.21 ± 0.79	1.63 ± 0.37	2.34 ± 0.71 *	39.52 ± 15.71	22.30 ± 3.02	120.27 ± 20.64	73.20 ± 11.20	5.02 ± 0.64	233.20 (165.00, 326.50)
Q_2 group	202	4.22 ± 1.04	1.23 ± 1.02	1.64 ± 0.36	2.37 ± 0.77	37.93 ± 14.15	22.46 ± 3.32	120.35 ± 17.10	74.26 ± 10.84	5.07 ± 0.66	228.40 (144.25, 315.40)
Q_3 group	238	4.34 ± 0.90	1.25 ± 0.72	1.61 ± 0.31	2.49 ± 0.72	39.80 ± 13.05	22.53 ± 3.45	121.55 ± 17.25	73.57 ± 10.66	5.05 ± 0.63	225.20 (161.05, 307.50)
Q_4 group	256	4.42 ± 0.96	1.44 ± 1.08	1.66 ± 0.41	2.53 ± 0.71	42.31 ± 14.04	22.94 ± 3.15	123.90 ± 18.21	75.18 ± 10.81	5.27 ± 1.24	235.00 (158.83, 351.78)

Q_1 group: TSH (0.27–1.68) mIU/l; Q_2 group: TSH (1.69–2.35) mIU/l; Q_3 group: TSH (2.36–3.07) mIU/l; Q_4 group: TSH (3.08–4.20) mIU/l. * $p < 0.05$: Compared with Q_3 group; # $p < 0.05$: Compared with Q_4 group.

Trends of mean serum lipids levels at different TSH levels

The subjects in the three age groups were grouped according to the quartiles of serum TSH levels within the normal range (0.27 mIU/l ≤ TSH ≤ 4.20 mIU/l). The altered trends of mean serum TC, TG, HDL-C, and LDL-C levels in the total population, different gender groups, or different age groups were compared.

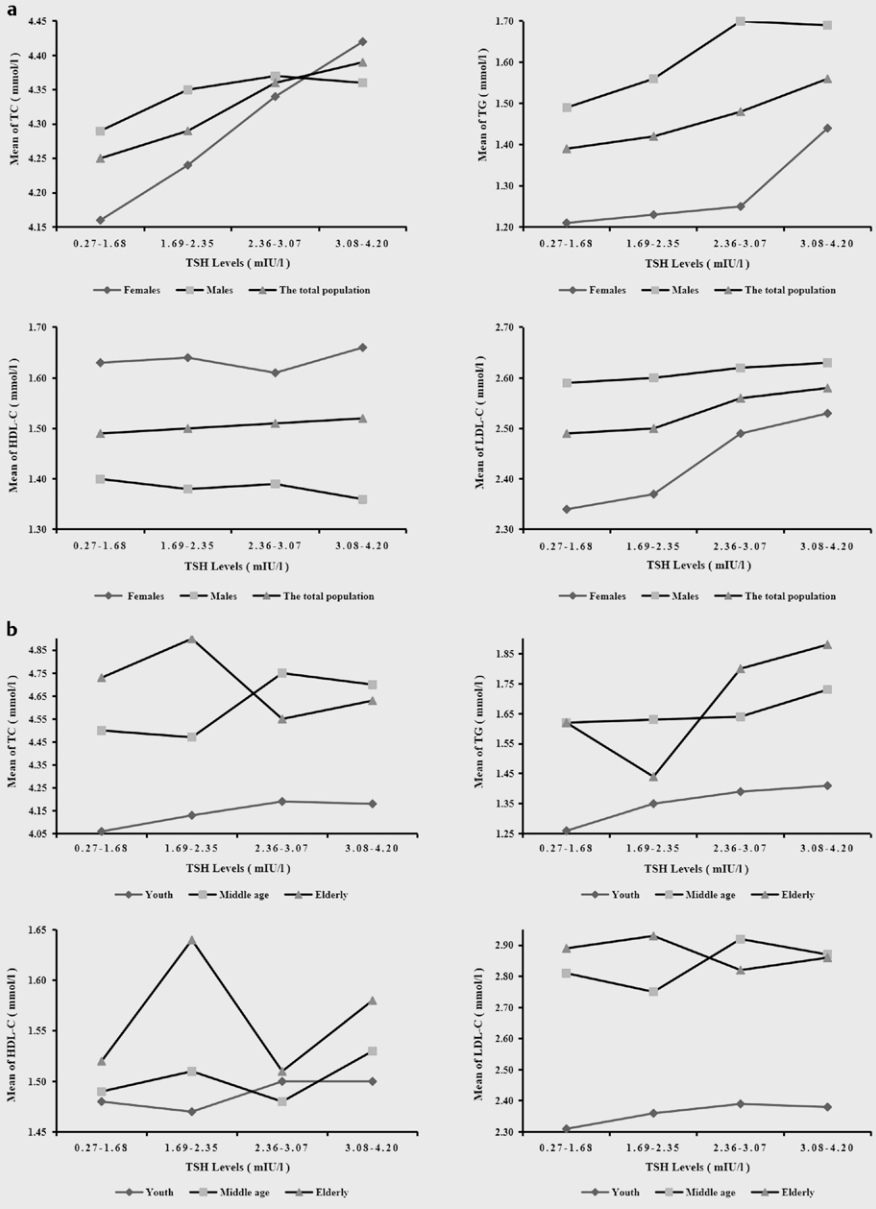
With the increasing serum TSH levels within the normal range, mean serum TC, TG, and LDL-C levels were increased, while HDL-C levels decreased. The trend was more significant in females than males or the total population (▶ **Fig. 1a**). With the increasing serum TSH levels within the normal range, mean serum TC, TG, and LDL-C levels were increased in youth. The trend was not significant in middle age or elderly groups (▶ **Fig. 1b**).

Trends of serum TSH levels in different age groups

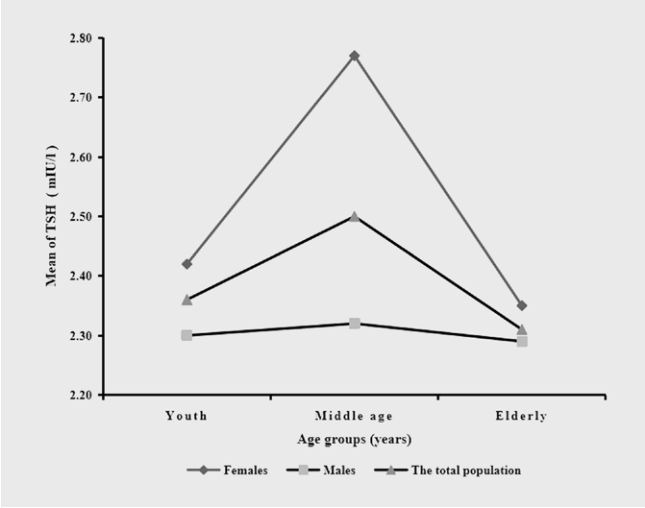
The TSH levels showed an increasing trend in an age-dependent manner. However, there was not a continuous increase with age, but a peak point. The TSH levels of females increased gradually with increasing age that peaked in the middle-aged group, followed by a downward trend. This phenomenon was not detected in males (▶ **Fig. 2**).

Discussion

The data from CHARLS (China Health and Retirement Longitudinal Study) and NHANES (US National Health and Nutrition Examination Survey) from 2011 to 2012 were compared among the population aged 45–75 years in China and USA. The prevalence of dyslipidem-



▶ **Fig. 1** Trends of mean serum lipids levels at different TSH levels. **a** Trends of mean serum lipids levels in the total population or different gender groups. **b** Trends of mean serum lipids levels in different age groups.



▶ **Fig. 2** Trends of serum TSH levels in different age groups.

ia in the Chinese population was found to be lower than that in the US (42.7 vs. 56.8 %), and the serum levels of TG, TC, and LDL-C in the Chinese population were lower than those in the US population [14], which suggested that lipid levels may be susceptible to environmental, regional, dietary, and genetic factors. The prevalence of dyslipidemia in rural Chinese adults was 32.21 % [15], and that in men was higher than that in women (42.85 vs. 26.16 %) [15]. The prevalence of high TC, high TG, low HDL-C, and high LDL-C was 5.11, 16.00, 19.27, and 4.76 %, respectively [15]. The prevalence of dyslipidemia among adults in northwest China was 52.72 % [16]. Similar to these results, the present study showed that the total prevalence of dyslipidemia in men was significantly higher than that in women (44.5 vs. 31.6 %), while the prevalence of high TG and low HDL-C was significantly higher than that in women. The higher prevalence of dyslipidemia in men may be related to eating habits, greater BMI, high work pressure, frequent social activities, or lack of physical exercise.

The serum TSH level is closely related to gender and age. NHANES III (National Health and Nutrition Examination Survey) in the USA indicated that serum TSH levels in both men and women increased with age, albeit the trend was obvious in women [17]. The current results also showed that the serum TSH levels in both males and females increased with age; however, the increase was not continuous and reached a peak. The serum TSH levels in women increased gradually with increasing age, reached a peak in the middle age, and then showed a downward trend, which was not obvious in men. The increasing trend may be related to menopausal status in women. The SardiNIA study indicated that the serum TSH levels of postmenopausal women were lower as compared to that in premenopausal women [18]. A longitudinal prospective study of hormone changes during the transition from premenopause to postmenopause indicated that the serum luteinizing hormone and follicle stimulating hormone were continuously increased and a concomitant fall in estrone and estradiol were observed in all women before menopause and in the two postmenopausal years, while Böttner et al. reported that estradiol can increase the secretion of TSH induced by thyrotropin-releasing hormone, and suggested that perimenopause may cause the corresponding endocrine changes of pituitary-thyroid axis [19, 20].

Silvia et al. found that serum TSH level was higher in women than in men [21]. Our study also found that serum TSH level was higher in women than in men, and the serum TSH level was higher in middle age than in youth or elderly. However, Lee et al. reported that serum TSH level was higher in those >60 years than those aged <60 years [22]. The reason for different results may be that serum TSH levels are affected by many other factors. For example, TSH secretion has obvious circadian rhythm, with excessive secretion at night and lower in the morning [23]. Concurrently, iodine intake [24] and estrogen [25] are also shown to affect serum TSH levels.

The changes in the serum TSH level in normal reference range were related to TC, TG, and LDL-C [26]. The TG level was higher in subjects with TSH at the upper limit of the normal range (2.5–4.5 mU/l) than in subjects with TSH at the lower limit of the normal range (0.3–2.5 mU/l) [27]. Jing et al. reported that the TG and LDL-C levels in the females with serum TSH level 4.001–4.940 mIU/l were higher than those with TSH levels 0.350–1.000 mIU/l, 1.001–2.500 mIU/l or 2.501–4.000 mIU/l; the TG levels in the males with TSH level 4.001–4.940 mIU/l was higher than those with TSH levels 0.350–1.000 mIU/l, 1.001–2.500 mIU/l or 2.501–4.000 mIU/l [28]. In the present study, the serum LDL-C levels in the females with serum TSH levels 2.36–3.07 mIU/l were significantly higher than those with TSH levels 0.27–1.68 mIU/l. The serum TG levels in males with TSH levels 2.36–3.07 mIU/l was higher than those with TSH level 0.27–1.68 mIU/l. These results indicated that even within the normal range, subjects with relatively high TSH levels might be more prone to dyslipidemia.

Reportedly, the associations between serum TSH levels and serum lipids were independent of thyroid hormones, and also greatly influenced by gender [29]. The increase in TSH level in the normal range might also be a risk factor for dyslipidemia, especially in women with normal high levels and subclinical hypothyroidism [30]. In the present study with increasing serum TSH levels within the normal range, serum TC, TG, and LDL-C levels were increased, while HDL-C levels decreased, especially in women, which was consistent with the results of the study by Hunt et al. [26]. For every 1 mIU/l increase in serum TSH concentration, the TG concentration increased by 0.095 mmol/l, and the serum TSH level of patients with hypertriglyceridemia was higher than that in those with normal TG level [31]. The correlation between serum TSH levels and serum lipids might be influenced by estrogen. Reduced estrogen production from ovaries might lead to increased serum TC and LDL-C and decreased HDL-C levels [32].

Besides gender, age can influence the correlation between thyroid function and lipid profiles [33]. Juan et al. divided the subjects with normal thyroid function into five subgroups based on the quartiles of TSH within the age-related reference range, which indicated that the serum TC and LDL-C levels of Q_5 group were higher than those of Q_1 group only in subjects aged <60 years, and no significant difference was observed in serum lipid levels between those aged >60 years with different TSH levels [34]. This study also showed that serum TC and LDL-C levels of the Q_3 group were higher than those of the Q_1 group, and the TG levels of the Q_3 or Q_4 group were higher than those of Q_1 group in youth. In addition,

serum TC levels of the Q_3 group were higher than those of the Q_2 group in the middle age. Also, no significant difference was detected in the serum lipids levels between the elderly with different TSH levels, which might be related to the relatively small sample size in the elderly group. The subjects of this study had normal thyroid function, while the elderly had more thyroid diseases [35], which might be the reason for the small sample size of the elderly.

TSH is the main regulator of lipid metabolism and is one of the major substances to maintain normal lipid. In addition, TSH can regulate the expression of hepatocyte genes and is closely related to the destruction of lipid homeostasis [36]. Furthermore, it has been found that the expression of TSHR is not only limited to the membrane of thyroid follicular cells but also in many parts of extra-thyroid tissues, such as fat cells and liver; thus, it is deemed as a major regulator of adipocyte differentiation [37].

Nevertheless, the current study has several limitations. First, we did not measure the levels of thyroid hormone in the subjects with normal TSH levels; hence, their potential association with serum lipids was not evaluated. Second, this was a cross-sectional study and was not designed as a long-term prospective study. Hence, most subjects visited our institution only once, due to which, we defined euthyroid on a single measurement of TSH, which might not reflect the correlations between the serum TSH levels within normal range and serum lipids. Finally, this study lacked the detection of cell levels, particularly the effect of TSH on lipid metabolism pathways in hepatocytes or adipocytes, which made it impossible to reveal the molecular mechanisms underlying the effect of serum normal TSH levels on serum lipids.

Conclusion

In conclusion, the current study showed that the serum normal TSH levels were closely related to serum lipid profiles. The serum lipids levels were higher in youth or middle age group with high TSH levels in the normal range. At the same normal TSH levels, the serum lipid levels of middle age or elderly were higher than those of youth. With the rising TSH levels, serum TC, TG, and LDL-C levels were increased gradually, and HDL-C levels decreased, especially in females.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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