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The relationship between thyroid stimulating hormone within the reference range and coronary artery disease: impact of age

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Abstract. Studies on the relationship between thyroid stimulating hormone (TSH) within the reference range and coronary artery disease (CAD) have produced conflicting results. Furthermore, the effect of age on this relationship has never been explored. The aim of this study was to investigate the association between TSH levels and CAD among euthyroid subjects and whether age influenced this relationship. A total of 318 subjects who underwent coronary angiography were included. Serum TSH, T3, T4, lipid, blood glucose and creatinine levels were measured and compared between the groups with and without CAD. Age-stratified analysis and multivariate logistic regression analysis were performed. Levels of TSH, T3 and T4 did not differ significantly between CAD (n=196) and non-CAD group (n=122) (TSH: 1.77 ± 0.99 vs 1.89 ± 0.98 mIU/L, T3: 1.45 ± 0.36 vs 1.51 ± 0.35 nmol/L, T4: 100.06 ± 20.49 vs 103.95 ± 24.06 nmol/L, respectively) when comparisons were performed among all subjects. A significant between-group difference in levels of TSH was observed among subjects less than or equal to 65 years old (CAD group: n=121, non-CAD group: n=106), with higher TSH levels in CAD group (2.03 ± 0.94 vs 1.75 ± 0.97 mIU/L, adjusted $p=0.024$). Multivariate logistic regression analysis revealed that elevated level of TSH was an independent predictor for CAD (odds ratio: 1.512, $p=0.011$). No significant between-group difference in TSH levels was observed among subjects older than 65 years (CAD group: n=75, non-CAD group: n=16). The results showed that higher levels of TSH within the reference range were independently associated with the presence of CAD only among subjects less than or equal to 65 years old, suggesting age might influence the relationship.

Key words: Thyrotropin, Coronary artery disease, Age Factors

OVERT HYPOTHYROIDISM is known to predispose patients to cardiovascular diseases [1]. However, controversies exist regarding whether subclinical hypothyroidism (SCH), defined as a serum thyroid stimulating hormone (TSH) concentration above the normal range with normal serum free T4 and free T3 concentration, is associated with coronary artery disease (CAD) and its mortality. Some [2-5] but not all studies [6-8] showed a positive association between them. Recently, these associations have been further investigated among individuals with normal thyroid function.

One prospective study indicated TSH levels within the reference range were positively and linearly associated with cardiovascular mortality in women [9] and four cross-sectional studies [10-13] reported that relatively low thyroid function within the reference range was associated with the presence of CAD, while two others [14-15] did not confirm these findings. These results arouse the debate on whether there is a need to redefine the upper normal limit of TSH [16-17].

It has been reported that age influences the relationship between SCH and CAD [18], with increased risks for CAD in younger but not older individuals. However, few studies have explored the role of age in the link between thyroid function and CAD in euthyroid subjects so far. To address this issue, we conducted this study to investigate the relationship between TSH within the reference range and CAD and the modifica-

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tion effect of age.

(SPSS Inc., Chicago, IL, USA) in version 17.0.

Methods

Subjects

Patients who underwent coronary angiography because of chest pain during the period from January 2012 to October 2012 were retrospectively reviewed. The exclusion criteria were as follows: (1) Abnormal serum levels of TSH, T4 or T3; (2) History of thyroid dysfunction or under treatment with thyroid medication; (3) Acute or past myocardial infarction; (4) History of revascularization of coronary artery; (5) severe cardiac, hepatic or renal dysfunction; (6) Medication with amiodarone, sex hormones and steroid hormones. Finally, a total of 318 subjects were included. The project was approved by the local Ethics Committee.

Data collection

Information of past medications and risk factors for CAD, including smoking, hypertension and diabetes were obtained from medical records. The body mass index (BMI) was calculated by dividing the weight (Kg) with the square of height (m^2). Coronary angiography was carried out *via* the radial artery or femoral artery. Coronary angiographic findings were reviewed by two expert cardiologists and significant stenosis was defined as a diameter stenosis of 50% or greater.

Before angiography, fasting venous blood specimens were collected to measure lipid profile, blood glucose, creatinine and thyroid hormones. The lipid profile, blood glucose and creatinine were measured by an automatic biochemistry analyzer (Modular DPP, Roche, Switzerland) and commercial kits. The levels of T3, T4 and TSH were measured by using a chemiluminescence immunoassay (ADVIA Centaur XP, Siemens, USA). The laboratory reference ranges for TSH, T3, and T4 were 0.3-5.0 mIU/L, 0.92-2.79 nmol/L, and 24.5-171.6 nmol/L, respectively.

Statistical analysis

Data were represented as mean $\pm$ standard deviation. Inter-group analysis was done by using independent *t* test, Mann-Whitney U test and chi-square test. Analysis of covariance was performed to adjust for age and sex. Multivariate logistic regression analysis was done to determine risk factors relating to CAD. Statistical significance was set at $p < 0.05$. All the above analyses were conducted with the use of SPSS software

Results

All subject analysis

A total of 38.4% of the patients did not have CAD, whereas 31.4% and 30.2% presented single-vessel and multivessel CAD, respectively. Levels of TSH, T3 and T4 were similar between CAD and non-CAD group (TSH: 1.77 ± 0.99 vs 1.89 ± 0.98 mIU/L, T3: 1.45 ± 0.36 vs 1.51 ± 0.35 nmol/L, T4: 100.06 ± 20.49 vs 103.95 ± 24.06 nmol/L, respectively). TSH levels between the group with single-vessel CAD and multivessel CAD also did not differ significantly (2.00 ± 0.99 vs 1.77 ± 0.96 mIU/L, $p = 0.096$). Age and percentage of male, diabetes, smoking and hypertension were significantly higher in CAD group compared with non-CAD group, while levels of high-density lipoprotein cholesterol (HDL-c) were relatively lower in CAD group. No significant differences on BMI, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c) and creatinine between the two groups were found. After adjusting for both age and sex, the above results did not change significantly except TG. The characteristics of the total subjects and comparisons were displayed in Table 1.

Age-stratified analysis

When analysis was restricted to participants less than or equal to 65 years old, levels of TSH were significantly higher in CAD group than in non-CAD group (2.03 ± 0.94 vs 1.75 ± 0.97 mIU/L, adjusted $p = 0.024$). Levels of T3 and T4 did not differ between two groups. No significant difference in TSH levels was observed between patients with single vessel CAD and multivessel CAD (2.13 ± 0.93 vs 1.89 ± 0.95 mIU/L, $p = 0.158$). Besides, significant between-group differences were observed with respect to age, HDL-c and percentage of smokers, hypertension and diabetes. Adjustment for age and sex did not significantly change the above results (Table 2).

To further assess the relationship between TSH and CAD among subjects less than or equal to 65 years old of age, these patients were divided into two categories based on the median value of TSH: G1 (TSH: 0.3-1.72 mIU/L) and G2 (TSH: 1.73-4.64 mIU/L). As shown in the Fig. 1, there were significantly more patients with CAD in G2 group as compared with G1 group (61.9% vs 44.7%, $p = 0.009$). Multiple logistic regression analysis showed elevated TSH level was an independent risk factor for CAD, with an adjusted odds ratio (OR)

Table 1 Clinical characteristics of total subjects

Variables	Overall (n=318)	Non-CAD (n=122)	CAD (n=196)	<i>p</i> value	<i>p'</i> value
Age (years)	59.42±10.60	54.81±10.17	62.29±9.87	0.000	
Male (%)	59.1	51.6	63.8	0.032	
BMI (kg/m ²)	24.82±3.23	24.71±3.27	24.89±3.21	0.641	0.105
Smoker (%)	35.5	26.2	41.3	0.006	0.028
Hypertension (%)	61.3	50	68.4	0.001	0.005
Diabetes (%)	18.6	11.5	23.0	0.010	0.007
FBG (mmol/L)	5.83±1.59	5.68±1.58	5.93±1.59	0.152	0.153
TC (mmol/L)	4.67±1.17	4.79±1.01	4.64±1.02	0.256 ^a	0.642 ^a
LDL-c (mmol/L)	2.73±0.82	2.84±0.82	2.74±0.83	0.379 ^a	0.523 ^a
TG (mmol/L)	1.67±1.77	1.50±0.74	1.60±1.31	0.096 ^a	0.035 ^a
HDL-c (mmol/L)	1.27±0.34	1.37±0.40	1.24±0.28	0.005 ^a	0.017 ^a
Creatinine (μmol/L)	66.31±13.12	64.99±14.17	67.12±12.39	0.181	0.962
TSH (mIU/L)	1.84±0.98	1.77±0.99	1.89±0.98	0.227	0.063
T3 (nmol/L)	1.49±0.36	1.45±0.36	1.51±0.35	0.135	0.371
T4 (nmol/L)	102.45±22.80	100.06±20.49	103.95±24.06	0.147	0.233

BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; TSH, thyroid stimulating hormone; *p* value, unadjusted; *p'* value, adjusted for age and sex; ^a, Comparisons were made after excluding 67 subjects who were on statin therapy

Table 2 Clinical characteristics of subjects less than or equal to 65 years old

Variables	Non-CAD (n=106)	CAD (n=121)	<i>p</i> value	<i>p'</i> value
Age (years)	52.44±8.62	56.20±7.00	0.000	
Male (%)	53.8	63.6	0.132	
BMI (kg/m ²)	24.75±3.38	25.41±3.25	0.138	0.053
Smoker (%)	28.3	43.8	0.016	0.054
Hypertension (%)	48.1	66.9	0.004	0.006
Diabetes (%)	12.3	22.3	0.047	0.028
FBG (mmol/L)	5.73±1.72	6.01±1.72	0.225	0.328
TC (mmol/L)	4.82±1.05	4.59±1.02	0.116 ^a	0.250 ^a
LDL-c (mmol/L)	2.85±0.86	2.71±0.82	0.253 ^a	0.319 ^a
TG (mmol/L)	1.53±0.77	1.70±1.50	0.346 ^a	0.061 ^a
HDL-c (mmol/L)	1.39±0.41	1.21±0.28	0.002 ^a	0.001 ^a
Creatinine (μmol/L)	64.87±14.22	66.61±11.89	0.317	0.926
TSH (mIU/L)	1.75±0.97	2.03±0.94	0.028	0.024
T3 (nmol/L)	1.46±0.35	1.51±0.33	0.309	0.818
T4 (nmol/L)	99.77±20.87	104.02±24.84	0.294	0.313

BMI, Body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; TSH, thyroid stimulating hormone; *p* value, unadjusted; *p'* value, adjusted for age and sex; ^a, Comparisons were made after excluding 39 subjects who were on statin therapy

of 1.512 (95% CI: 1.100-2.078, *p*=0.011). Other significant risk factors for predicting CAD were age (OR: 1.080, 95% CI: 1.038-1.124, *p*=0.000), hypertension (OR: 1.883, 95% CI: 1.033-3.432, *p*=0.039) and HDL-c (OR: 0.243, 95% CI: 0.087-0.681, *p*=0.007) (Table 3).

Among subjects older than 65 years, no significant differences in TSH, T3 and T4 between CAD group and non-CAD group were observed (TSH: 1.66±1.0 vs 1.89±1.09 mIU/L, adjusted *p*=0.772; T3: 1.52±0.39 vs

1.35±0.36 nmol/L, adjusted *p*=0.145; T4: 103.83±22.89 vs 101.96±18.32 nmol/L, adjusted *p*=0.524; respectively). The comparisons of other variables were shown in Table 4. When the median value of TSH was used as a cut-off to divide the subjects into two groups, the percentage of CAD was similar between the two groups (82.6% vs 82.2%, *p*=0.961). The results of multiple logistic regression analysis were showed in Table 5. The results should be interpreted with caution, espe-

Fig. 1 The frequency (%) of coronary artery disease according to the categories of TSH among subjects less than or equal to 65 years old

Table 3 Multivariate logistic regression analysis for coronary artery disease among subjects less than or equal to 65 years old

Variables	Odds ratio	95%CI	<i>p</i> value
Age	1.080	1.038-1.124	0.000
Smoking	1.845	0.895-3.800	0.097
Hypertension	1.883	1.033-3.432	0.039
HDL-c	0.243	0.087-0.681	0.007
TSH	1.512	1.100-2.078	0.011
Sex	1.212	0.588-2.499	0.602
Diabetes	1.664	0.751-3.689	0.210

HDL-c, high density lipoprotein-cholesterol

Table 4 Clinical characteristics of subjects older than 65 years

Variables	Non-CAD (n=16)	CAD (n=75)	<i>p</i> value	<i>p'</i> value
Age (years)	70.50±3.46	72.13±4.32	0.160	
Male (%)	37.5	64.0	0.050	
BMI (kg/m ²)	24.44±2.52	24.04±2.97	0.625	0.719
Smoker (%)	12.5	37.3	0.055	0.241
Hypertension (%)	62.5	70.7	0.558	0.370
Diabetes (%)	6.3	24.0	0.176	0.139
FBG (mmol/L)	5.56±0.36	5.80±1.36	0.521	0.357
TC (mmol/L)	4.45±0.51	4.73±1.05	0.413 ^a	0.091 ^a
LDL-c (mmol/L)	2.73±0.47	2.81±0.85	0.793 ^a	0.422 ^a
TG (mmol/L)	1.27±0.35	1.41±0.85	0.829 ^a	0.307 ^a
HDL-c (mmol/L)	1.19±0.24	1.32±0.29	0.194 ^a	0.032 ^a
Creatinine (umol/L)	65.50±13.80	67.95±13.21	0.506	0.773
TSH (mIU/L)	1.89±1.09	1.66±1.0	0.423	0.772
T3 (nmol/L)	1.35±0.36	1.52±0.39	0.130	0.145
T4 (nmol/L)	101.96±18.32	103.83±22.89	0.761	0.524

BMI, Body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; TSH, thyroid stimulating hormone; *p* value, unadjusted; *p'* value, adjusted for age and sex; ^a, Comparisons were made after excluding 29 subjects who were on statin therapy

Table 5 Multivariate logistic regression analysis for coronary artery disease among subjects older than 65 years

Variables	Odds ratio	95%CI	<i>p</i> value
Age	1.168	0.978-1.396	0.087
Smoking	2.497	0.405-15.381	0.324
Hypertension	2.382	0.601-9.448	0.217
HDL-c	24.084	1.559-371.959	0.023
TSH	1.099	0.589-2.049	0.767
Sex	0.203	0.041-1.002	0.050
Diabetes	7.646	0.828-70.643	0.073

HDL-c, high density lipoprotein-cholesterol

cially for HDL-c, which was positively associated with CAD and its 95% confidence interval was very wide. This might be partly due to small number of non-CAD subjects older than 65 years (n=16).

Discussion

Studies on the relationship between normal range of thyroid function and CAD had produced inconsistent results [10-15]. The discrepancies might derive from the number of enrollment, heterogenous subjects and racial difference *et al.* However, the effect of age on this relationship was neglected and none of them performed an age-stratified analysis. In the present study, a significant and independent association between elevated TSH levels within the reference range and CAD was observed in younger individuals but not in all or older individuals. This finding suggested that age might play a role in the relationship of TSH and CAD.

The impact of age on the CAD risks in people with SCH has been investigated by some studies. It has been reported that in elderly individuals (at least 65 year old or older) high levels of TSH were not associated with an increased risk of CAD and its mortality [19-21]. Furthermore, in the study by Gussekloo *J et al.* [22], which included 599 subjects who were aged 85 years at enrollment and followed for a mean period of 3.7 years, individuals with higher TSH levels had a longer life span than controls, suggesting a protective effect of SCH in elderly individuals. Two meta-analyses showed that the association between SCH and CAD was stronger [23] or only existed [18] among individuals younger than 65 years old. A recent large intervention study lasting for a median period of 7.6 years indicated that treatment of SCH with levothyroxine resulted in a significant reduction of ischemia heart diseases events in younger individuals, but not in older people [24]. These results, along with ours, further supported that higher levels of TSH may have different effects for younger and older population, with more adverse effects on the former. The underlying mechanisms remained unknown. Different Thyroid physiology in older and younger had been documented, with a decreased thyroid hormone metabolism [25] and increased TSH levels [20, 26] in the elderly. This age-related change of thyroid function may be one of the mechanisms explaining the effect of age on CAD risks. Other possible explanations included different effects of increased TSH on vascular risks during aging and

more conventional risk factors in the older to mask the adverse effects of higher TSH levels.

The exact underlying mechanisms involved in the association between high TSH levels with the reference range and CAD remain uncertain. Our previous studies showed that TSH levels were positively associated with hypercholesterolemia independent of thyroid hormones among euthyroid subjects [27]. Other studies reported high levels of TSH with the reference range were associated with hypertension [28], impaired endothelial function [29], arterial stiffness [30], metabolic syndrome [31] and renal dysfunction [32]. These findings may partly explain why individuals with TSH levels in the upper part of the reference range are at high risk for CAD.

Some potential limitations should be addressed. First, a causal relationship cannot be established from this cross-sectional study. Second, we did not measure serum free T3 and free T4 levels, which were active forms of thyroid hormones. However, the aim of our study was to assess the relationship of TSH and CAD in euthyroid subjects and simultaneous measurements of TSH, total T3 and total T4 were enough to establish a euthyroid state. Third, because this was a retrospective and hospital-based study, selection bias existed. Fourth, the number of subjects in the elderly subgroup was relatively small, which may influence the statistic power of sub-analysis. Fifth, single measurement of thyroid hormones may result in misclassification since thyroid function is influenced by nonthyroidal illnesses [33]. However, because stringent exclusion criteria were used in this study, such potential confounding was minimized.

In conclusion, this study showed that high levels of TSH within the reference range were independently associated with the presence of CAD only among subjects less than or equal to 65 years old of age, suggesting a modification effect of age on this relationship. Correlation between levels of TSH and severity of CAD was not observed. Well-designed prospective studies should be necessary to fully clarify the relationship of high levels of TSH with the presence and severity of CAD and the role of age.

Conflict of Interest

The authors declare no conflicts of interest.

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