Gender-Dependent Association Between Thyroid Hormones and Severity of Coronary Artery Disease by SYNTAX Score

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Abstract- Thyroid function has been shown to be associated with cardiovascular diseases. Moreover, sex can influence on the association between thyroid function and other diseases. We aimed to evaluate the relationship between thyroid hormones and the severity of coronary artery disease (CAD) and outcomes. In a prospective study, patients with chest pain undergoing diagnostic coronary angiography were evaluated. Patients were categorized based on the number of involved coronary arteries. Moreover, the severity of CAD was quantitatively calculated using the Syntax score (SS). All patients were also followed up for 3-month duration. The level of TSH in 150 patients was significantly higher in females than males (3.1 [1.7, 5] versus 1.8 [1, 3.3] mU/L; *P*=0.002). There was significant correlation between THS and the SS among females (ρ=0.477, *P*<0.001), but not males. Among both sexes, thyroid hormones were comparable between those with or without events during follow-up. The main predictors of high SS values included age (odds ratio [OR] 1.060, 95% confidence interval [CI] 1.018-1.104; *P*=0.005) and female (OR 2.941, 95% CI 1.198-7.218). The main predictors of multivessel disease were age (OR 1.077, 95% CI 1.026-1.132), female (OR 5.853, 95% CI 1.880-18.222), thyroxin (OR 0.733, 95% CI 0.547-0.981), and thyrotropin (OR 1.333, 95% CI 1.079-1.647). Thyroid hormones are associated with the presence and the severity of CAD, but it might be sex-related. However, thyroid hormone levels could not predict short-term outcomes of patients.

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Keywords: Coronary artery disease; SYNTAX score; Thyroid hormone; Sex; Prognosis

Introduction

Thyroid hormone plays an important role in our body metabolism and regulation of cardiovascular system (1,2). Thyroid function has been found to be associated with cardiovascular diseases, particularly atherosclerosis (3). The higher level of thyroid stimulating hormone (TSH), thyrotropin, have been correlated with systolic and diastolic hypertension (4), the less favorable values of lipid profile (5), the extent of coronary artery disease (CAD) evaluated by invasive coronary angiography (6), the presence of CAD (7), the prognosis of patients with CAD (8), and a higher risk of cardiovascular events (9). Thyrotropin is the most sensitive biomarker for evaluating the function of thyroid hormones (10), and it has been assessed in several studies to examine any associations between thyroid function and cardiovascular diseases.

Thyroid dysfunction is demonstrated to be associated with worse prognosis of patients with diabetes mellitus,

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nephropathy, metabolic syndrome, and heart failure, as well as pregnant individuals (11-13). Moreover, it has been found that sex can influence on the association between thyroid function and other diseases. Sex- and age-dependent relationships were observed between thyroid function and lipid profile (14,15), and between hypertension and hypothyroidism (16). There is no prospective study to evaluate the impact of sex on the association between CAD and thyroid hormones. Herein, in this study we tried to assess the relationship between the presence and the severity of CAD, measured by invasive coronary artery angiography (ICA) and the SYNTAX Score (SS), and the baseline levels of thyroid hormones. In addition, we evaluated the prognostic value of thyroid hormones at short-term follow-up period among patients with confirmed CAD.

Materials and Methods

Study protocol and population

In a prospective study, all patients with chest pain undergoing diagnostic ICA were entered into the study based on the defined criteria. Inclusion criteria comprised of individuals with chest pain suggestive of CAD who underwent ICA. The exclusion criteria were patients with an inflammatory condition, familial hypercholesterolemia, as well as the absence of information about conventional risk factors for CAD and the thyroid function status. Baseline characteristics, laboratory findings, and diagnostic ICA features were collected using a designed sheet. The study was approved by the local ethics committee of our institution.

Diagnostic ICA and SS assessments

All diagnostic ICAs were done according to the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) guidelines (17). All procedures were performed via femoral or radial artery using Judkins' method. The detection of CAD was confirmed when the lumen of coronary arteries decreased by 50-70% or >70% by the luminal plaque. Subsequently, the number of coronary arteries by decreased lumen was confirmed. Patients were categorized as normal coronary arteries or minimal involvement, single vessel disease, or two/three vessels disease (multivessel disease).

Moreover, we quantitatively calculated the SS for patients to measure the severity of CAD. The SS was calculated for coronary artery stenosis >50% of diameter, and vessels with diameter greater than 1.5 mm, by the implementation of the SS criteria (18). The calculation of the SS was performed using a calculator in a webpage (http://www.syntaxscore.com). We divided our patients into high and low SS using the median value of SS among the study population. The SS was evaluated visually by experienced interventional cardiologists blinded to the thyroid function test and baseline characteristics.

Laboratories and examinations

The past clinical conditions were gathered using the physical examination and medical charts. The diagnosis of hypertension was made as systolic and diastolic blood pressures above 130 and 80 mm Hg, respectively, and/or consuming drugs for controlling hypertension (19). Given our institution protocols, the blood samples for laboratory measurements were obtained about 6 hours before undergoing diagnostic ICA. The serum levels of TSH and drugs for thyroid diseases were obtained at baseline. TSH categories were identified as euthyroid (0.3 to 5.0 μU/L), hyperthyroid (<0.3 μU/L), or hypothyroid (>5.0 μU/L). Patients were categorized into three groups: 1) euthyroid in cases with TSH values in 0.3 to 5.0 μU/L and not taking drugs for thyroid diseases; 2) hypothyroid in cases taking drugs for thyroid diseases or with an increased TSH level; and 3) hyperthyroid in cases with TSH values less than 0.3 μU/ml and not taking drugs for thyroid diseases. In addition to TSH values, the serum levels of free triiodothyronine and free thyroxine were also measured.

Follow-up outcome

All patients were followed up for 3-month duration after diagnostic ICA. The development of ischemic events and any other cardiovascular events and mortality were assessed. Hospitalization due to ischemic events was defined as those with chest pain associated with elevations in cardiac enzymes who hospitalized for therapeutic interventions, drug-based or intervention modalities.

Statistical analysis

Continuous data were reported as mean±standard deviation or median (interquartile range [IQR], 25^{th} and 75^{th} percentiles). Given the distribution normality of variables, continuous data were compared using t-test, Mann Whitney U test, or Kruskal-Wallis test as appropriate. Categorical variables were compared between groups by applying the chi-squared test. Bivariate correlations were calculated using the Spearman's correlation coefficients (i.e. ρ values) between thyroid hormones and the SS. To evaluate the

predictors of CAD severity measured by diagnostic ICA and the SS, we implemented binary regression and multinomial regression analyses, respectively. In the binary regression analysis, the SS, was defined as a categorical dependent variable (<8 versus ≥8 score using the median value of SS among the study population). In the multinomial logistic regression analysis, the severity of CAD, as a dependent variable, was categorized as normal/minimal CAD, single vessel CAD, and two/three vessels CAD. Moreover, another binary logistic regression analysis was also applied to evaluate the predictors of outcome during follow-up period, as a dependent variable. In regression models, covariates consisted of age, sex, diabetes mellitus, hypertension, thyroid hormones, and body mass index. When the event during follow-up was the dependent variable, we entered the SS as a covariate too. Consequently, 95% confidence intervals (CI) and odds ratios (OR) were reported. The significance of the goodness-of-fit analysis was also reported. Two-tailed p-values were reported for analyses. All analyses were performed using the STATA software (StataCorp, TX, USA).

Results

Baseline characteristics

A total of 150 participants who underwent ICA were evaluated in this prospective study. The patients' mean age was 60±11 years, and 35.3% of them were female. Female patients were older (65.5±8.6 versus 55.9±9.9; P<0.001), were more obese (38.6% versus 11.8%; P=0.001) and had a higher rate of hypertension than males (68.4% versus 45.2%; P=0.006). On the other hand, male patients had a higher rate of prior history of myocardial infarction (25.8% versus 12.3%; P=0.047) compared to females. The severity of CAD by the ICA and the SS (6 [0, 14] versus 8 [2, 16] in females and males, respectively; P=0.103) was comparable between both sexes. All characteristics are gathered in Table 1.

Female patients had higher rates of hypothyroidism (22.8% versus 4.3%; P=0.002) and hyperthyroidism (3.5% versus 2.2%; P=0.002) compared to male patients. The TSH level was higher in females than that in males (3.1 [1.7, 5] versus 1.8 [1, 3.3] mU/L; P=0.002). Thyroid function categorization based on the TSH level and the use drugs for thyroid diseases (hypothyroid, euthyroid, and hyperthyroid) demonstrated that female patients had a higher rate of hypothyroidism than males (26.3% versus 8.6%; P=0.014). The serum levels of free triiodothyronine and free thyroxine were found to be comparable between both sexes (Table 1).

CAD and thyroid function

The correlations between the SS and free triiodothyronine and free thyroxine were comparable. However, there was significant correlation between TSH values and the SS (ρ=0.202, P=0.013; Figure 1). These correlations were comparable among males and females (all had P>0.05), while the TSH level was only correlated with the SS among females (ρ=0.477, P<0.001; Figure 2).

When we compared the serum levels of thyroid hormones among groups by the numbers of coronary artery involvements (defined as three groups: normal/minimal, single vessel disease, and multivessel disease), TSH level was different among groups (P=0.012), while other hormone levels were comparable. Of pairwise comparisons, TSH was higher in the group of multivessel diseases compared to the first and second groups (P=0.006 and P=0.039, respectively). Moreover, free triiodothyronine was higher in the second group compared to third group (P=0.027). Based on sex group comparisons, TSH was significantly higher in the multivessel disease group compared to other groups among females, but not males. Of pairwise comparisons, TSH was also higher in the multivessel disease group compared to both of first and second groups (P<0.001). Moreover, free triiodothyronine was significantly higher in the second group compared to third group among male patients (P=0.022; Table 2).

Follow-up outcomes and thyroid function

After 3 months follow-up, death due to cardiovascular etiologies or any other causes as well as thromboembolic events were not developed. A total of 25 (16.7%) patients were hospitalized due to ischemic event during follow-up period. The serum levels of thyroid hormones were comparable between groups by the development of ischemic events (all have P>0.05). However, participant with follow-up events had a higher rate of multivessel disease (P=0.007) and a higher level of SS (P=0.004) compared to those without events at follow-up period.

The number of individuals with events at follow-up period was comparable between both sexes (19.3% in females versus 15.1% in males; P=0.498). Among females, the severity of CAD and the SS were comparable. Among males, thyroid hormones were comparable between those with or without events. However, patients with events at follow-up period were more diagnosed with multivessel disease (P=0.036) and

had a higher level of SS (*P*=0.014).

Predictors of CAD severity and follow-up outcomes

The main predictors of the SS≥8 included age (OR 1.060, 95% CI 1.018-1.104; *P*=0.005) and female (OR 2.941, 95% CI 1.198-7.218; *P*=0.019). According to the multinomial logistic regression analysis, only female sex was significantly predicted the presence of single vessel disease (OR 3.208, 95% CI 1.005-10.243; *P*=0.049). On the other hand, the main predictors of multivessel disease included age (OR 1.077, 95% CI 1.026-1.132, *P*=0.003), female sex (OR 5.853, 95% CI 1.880-18.222, *P*=0.002), free thyroxin (OR 0.733, 95% CI 0.547-0.981, *P*=0.037), and thyrotropin (OR 1.333, 95% CI 1.079-1.647, *P*=0.008). Other values are also summarized in Table 3. Moreover, the only predictor of follow-up events was the elevated SS values ≥8 (OR 6.913, 95% CI 2.133-22.406, *P*=0.001). The goodness-of-fits for all regression models were statistically non-significant (*P*>0.05).

Table 1. Baseline characteristics, features of coronary artery evaluation, and laboratories in groups by sex

		Female (n=57)	Male (n=93)	*P*
Age, year		65.5 ± 8.6	55.9 ± 9.9	<0.001
BMI, kg/m^2		28.2 ± 4.5	25.7 ± 3.6	<0.001
Weight status				0.001
Normal weight		17 (29.8%)	38 (40.9%)	
Overweight		18 (31.6%)	44 (47.3%)	
Obesity		22 (38.6%)	11 (11.8%)	
Diabetes mellitus		20 (35.1%)	30 (32.3%)	0.721
Hypertension		39 (68.4%)	42 (45.2%)	0.006
Prior history of IHD		26 (45.6%)	39 (41.9%)	0.659
Prior history of AMI		7 (12.3%)	24 (25.8%)	0.047
Prior history of CABG		1 (1.8%)	3 (3.2%)	0.587
Prior history of coronary artery stenting		10 (17.5%)	28 (30.1%)	0.086
Familial history of CAD		12 (21.1%)	26 (28%)	0.345
Cerebrovascular accidents		2 (3.5%)	4 (4.3%)	0.810
Prior history of thyroid disease				0.002
Hypothyroidism		13 (22.8%)	4 (4.3%)	
Hyperthyroidism		2 (3.5%)	2 (2.2%)	
ICA				0.205
Normal/Minimal involvement		26 (45.6%)	29 (31.1%)	
Single VD		12 (21.1%)	25 (26.9%)	
Multivessel disease		19 (33.3%)	39 (42%)	
SYNTAX Score		6 (0, 14)	8 (2, 16)	0.103
SYNTAX Score group				0.309
High ≥8		27 (47.4%)	52 (55.9%)	
Low <8		30 (52.6%)	41 (44.1%)	
Drug histories before ICA	**β-blockers**	39 (68.4%)	52 (55.9%)	0.128
	Statins	31 (54.4%)	46 (49.5%)	0.558
	ACE-I/ARB	7 (12.3%)	10 (10.8%)	0.774
	Clopidogrel	17 (29.8%)	23 (24.7%)	0.494
	Aspirin	32 (56.1%)	49 (52.7%)	0.681
	fT3, nmol/L	1.1 (0.9, 1.3)	1.1 (1, 1.3)	0.723
	fT4, µg/dL	8.1 (7.5, 9.2)	7.9 (7.4, 9.3)	0.576
	TSH, mU/L	3.1 (1.7, 5)	1.8 (1, 3.3)	0.002
	TSH status			0.014
	Hypothyroid	15 (26.3%)	8 (8.6%)	
	Euthyroid	40 (70.2%)	80 (86%)	
	Hyperthyroid	2 (3.5%)	5 (5.4%)	

All data are presented as number (%), mean±SD, or median (IQR, 25th-75th) ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; fT3, free triiodothyronine; fT4, free thyroxine; ICA, invasive coronary angiography; IHD, ischemic heart disease; TSH, thyroid stimulating hormone; VD, vessel disease

Table 2. Thyroid hormones in groups by the severity of coronary artery disease

		Normal/Minimal involvement	Single VD	Multivessel disease	*P*
fT3, nmol/L	**Total**	1.1 (0.9, 1.3)	1.2 (1.1, 1.3)	1.1 (0.9, 1.3) [b]	0.090
	Male	1.1 (0.9, 1.3)	1.2 (1.1, 1.3)	1 (1, 1.3) [b]	0.057
	Female	1.1 (0.9, 1.3)	1.1 (1, 1.3)	1.1 (0.9, 1.4)	0.728
fT4, µg/dL	**Total**	8.3 (7.5, 9.7)	8.1 (7.7, 9.3)	7.8 (7.2, 8.7)	0.113
	Male	8.2 (7.3, 9.3)	8.1 (7.5, 9.7)	7.8 (7.4, 8.7)	0.430
	Female	8.3 (7.5, 9.7)	8.2 (7.9, 9.1)	7.7 (6.7, 9.1)	0.390
TSH, mU/L	**Total**	1.8 (1, 3.1)	2.3 (1.2, 3.4)	3.1 (1.3, 5.1) [a, b]	0.012
	Male	1.6 (1, 2.3)	2.1 (1.1, 3.2)	2.3 (0.9, 3.8)	0.499
	Female	2.3 (1.1, 3.1)	2.3 (1.3, 3.6)	5.1 (3.5, 6.5) [a, b]	<0.001

All data are presented as median (IQR)
fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; VD, vessel disease
a There is a significant difference between group 3 and 1
b There is a significant difference between group 3 and 2

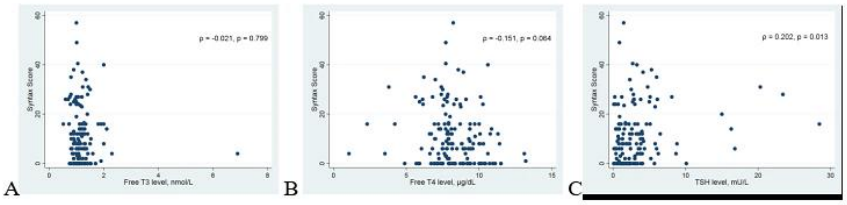

Figure 1. Correlations between the SS and the serum levels of (A) free triiodothyronine, (B) free thyroxine, and (C) thyrotropin

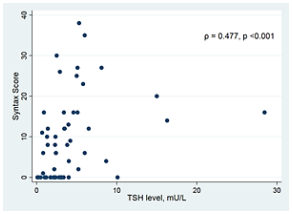

Figure 2. Correlations between the SS and the serum levels of TSH among females

Table 3. Predictors of the severity of coronary artery disease based on multivariable logistic regression analysis

Dependent variable	Covariates	OR (95% CI)	*P*
Model 1: SS group (<8 vs. ≥8)	Age	1.060 (1.018-1.104)	0.005
	Female	2.941 (1.198-7.218)	0.019
	Body mass index	1.001(0.915-1.096)	0.977
	Diabetes mellitus	0.683 (0.321-1.452)	0.322
	Hypertension	0.853 (0.409-1.780)	0.672
	fT3	0.648 (0.308-1.362)	0.252
	fT4	0.949 (0.766-1.175)	0.629
	TSH	1.148 (0.999-1.320)	0.052
Model 2: Single VD vs. Normal/Minimal involvement	Age	1.025 (0.975-1.078)	0.335
	Female	3.208 (1.005-10.243)	0.049
	Body mass index	1.074 (0.960-1.202)	0.212
	Diabetes mellitus	1.338 (0.512-3.498)	0.553
	Hypertension	1.038 (0.409-2.636)	0.937
	fT3	1.600 (0.427-5.996)	0.485
	fT4	0.887 (0.669-1.178)	0.408
	TSH	1.083 (0.855-1.372)	0.506
Model 3: Multivessel disease vs. Normal/Minimal involvement	Age	1.077 (1.026-1.132)	0.003
	Female	5.853 (1.880-18.222)	0.002
	Body mass index	0.990 (0.885-1.108)	0.862
	Diabetes mellitus	1.064 (0.426-2.660)	0.895
	Hypertension	1.228 (0.502-3.004)	0.653
	fT3	1.287 (0.351-4.721)	0.704
	fT4	0.733 (0.547-0.981)	0.037
	TSH	1.333 (1.079-1.647)	0.008

CAD, coronary artery disease; CI, confidence interval; fT3, free triiodothyronine; fT4, free thyroxine; OR, odds ratio; SS, SYNTAX score; TSH, thyroid stimulating hormone, VD, vessel disease

Discussion

In this investigation we found that there was a direct correlation between THS level and the SS, but it was only significant among females. In addition, the numbers of involved coronary arteries were significantly enhanced with increasing the TSH levels, only among females. The main predictors of increased SS included age and female. Moreover, the main predictors of multivessel disease included age, female, free thyroxin, and thyrotropin. When we evaluated outcomes during 3-month follow-up period, among both sexes, thyroid hormones were comparable between patients with or without events during follow-up. In addition, only increased SS was associated with the development of events. These findings underscore the significance of thyroid functions among patients with CAD and its association with sex and follow-up outcomes.

Several studies demonstrated association between the severity of CAD and thyroid function and some of them showed no association (20,21). Auer *et al.*, (6) showed that higher values of free triiodothyronine and thyroxin were associated with a less severity of CAD. On the other hand, higher values of thyrotropin levels were associated with a greater severity of CAD. Ortolani *et al.*, (22) have also showed that higher levels of TSH in normal reference ranges were associated with the presence and CAD. Among 344 angina patients who underwent elective ICA, increased levels of TSH was associated with multivessel CAD and the higher values of Gensini score; however, it did not predict multivessel CAD in multivariable analysis (23). Moreover, among CAD patients underwent percutaneous coronary intervention along with rotational atherectomy, the higher values of SS was associated with more rates of thyroid diseases (24). In contrast, in a group of patients undergoing percutaneous coronary intervention, the SS values were comparable between free triiodothyronine tertiles (25). In our study we showed that the higher levels of TSH correlated with the higher SS values, and also it was associated with the increased number of coronary artery involvement.

The impacts of age and sex on the association between thyroid function have been found in patients with dyslipidemia (15) and hypertension (16). Yang *et al.*, (7) showed that the elevated TSH values was associated with CAD in patients undergoing ICA, but such an association was only observed among males under 65 years old. To the best of our knowledge no other studies explored the impacts of age and sex on association between the CAD severity and thyroid function. We showed for the first time that the correlations between elevated TSH levels and the increased SS values and the multivessel CAD were detected only among females not males. We also found that the main predictors of multivessel disease included age, female, free thyroxin, and thyrotropin. We think that such an association needs to be explored in large studies before implementation into the routine cardiometabolic practices. The impacts of age and sex on risk stratification of patients with concomitant cardiac and thyroid diseases are of great importance in our daily practice.

The prognosis of patients with cardiac diseases can also be influenced by thyroid function, even with small changes in hormone levels (26). Bai *et al*., (27) showed that hypothyroid disease had more severe CAD and worse prognosis during a mean duration of 15.3 months. Li and his colleagues (28) also found that among CAD patients with high TSH, there was a higher risk of cardiovascular events (hazard ratio 2.05, 95% CI 1.08-3.88). In addition, Ndrepepa *et al*., (8) found that the third tertile of TSH level was associated with 30-day mortality (hazard ratio 2.30, 95% CI 1.33-3.97 for each tertile increase) in patients undergoing percutaneous coronary artery intervention. Of note, the association between thyroid function and the outcomes of patients with CAD might be influenced by sex so that in a meta-analysis (29), there was a higher risk of cardiovascular events in patients with subclinical hypothyroidism, but only among males (risk ratio 1.17, 95% CI 1.03-1.34). In contrast, Brozaitiene and colleagues demonstrated that free thyroxin level predicted all-cause mortality (hazard ratio 1.15, 95% CI 1.04-1.27) and cardiac mortality (hazard ratio 1.15, 95% CI 1.02-1.29) in CAD patients, but it was not a sex-related difference (30). In our study, we also found in the multivariate analysis that the main predictors of multivessel disease included age (OR 1.077), female (OR 5.853), free thyroxin (OR 0.733), and thyrotropin (OR 1.333). On the other hand, only age (OR 1.060) and female (OR 2.941) predicted the higher SS values. In addition, only the increased SS value (OR 6.913) was associated with cardiovascular events during follow-up period. Based on our findings, the association between the severity of CAD quantifying by the SS values and thyroid hormones might be influenced by sex. Moreover, patients' prognosis cannot be predicted by thyroid hormones, instead it was associated with severe CAD involvement by angiographic measurements. Further large-scale studies

with long-term follow-up can provide us invaluable findings regarding the association between thyroid functions and CAD prognosis as well as factors affecting such association.

Study Limitations

Our study was a prospective cross-sectional study with short-term follow-up; however, it suffers from some limitations. Firstly, it included a small sample of patients who underwent ICA. Secondly, it has a short-term follow-up period which can impact on our findings. Finally, we have applied exclusion criteria for factors influencing thyroid hormones and also used multivariable analysis, but some unmeasured might change our findings that need to be investigated in future studies with large-scale population and long-term follow-up period.

Thyroid hormones are associated with the presence and the severity of CAD quantifying by the SS values and the number of involved coronary artery, but it might be sex related. However, thyroid hormones could not predict short-term outcomes of CAD patients.

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