

# The Association of Thyroid Hormones with Coronary Atherosclerotic Severity in Euthyroid Patients

## Authors

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## ABSTRACT

The aim of the work was to explore the correlation between thyroid hormones and coronary atherosclerotic severity. This cross-sectional study included 340 euthyroid patients who underwent diagnostic coronary artery angiography (CAG). Gensini Score (GS) was applied to assess the severity of coronary atherosclerosis. Thyroid hormones and routine biochemical parameters were measured. The associations between thyroid hormones and coronary atherosclerosis severity were analyzed. Thyroid hormones levels or parameters were taken as both continuous variables and tertiles into analysis, and the lowest tertile was usually used as the reference (OR = 1) for medium and highest tertiles. Free triiodothyronine (FT3) level was associated with  $GS \geq 22$  (Median GS) in Model I adjusted for age and sex [Continuous: OR = 0.46, 95% CI (0.23, 0.92),  $p = 0.029$ ; Tertile 3: OR = 0.54, 95% CI (0.30, 0.97),  $p = 0.038$ ], and Model II adjusted for all known risk factors of coronary artery disease (CAD) [Continuous: OR = 0.44, 95% CI (0.20, 0.95),  $p = 0.036$ ; Tertile 3: OR = 0.49, 95% CI (0.25, 0.96),  $p = 0.039$ ]. Subjects with highest tertile of FT3 to free thyroxine (FT4) ratio (FT3/FT4 ratio) appeared to have the remarkably decreased risk of CAD in both Non-adjusted Model [OR = 0.49, 95% CI (0.24, 0.98),  $p = 0.044$ ] and Model I [OR = 0.45, 95% CI (0.22, 0.93),  $p = 0.031$ ]. Higher FT3 level within normal range was independently and negatively associated with severity of coronary atherosclerosis. Besides, FT3/FT4 ratio was remarkably correlated with the prevalence of CAD in euthyroid population.

## Introduction

Despite increasing advances in the prevention and treatment of coronary artery disease (CAD), it has remained globally the single largest cause of mortality [1]. The inexorable progress of CAD, in spite of optimal guideline-based primary and secondary prevention, indicates the multifactorial etiology of the disease and the pressing need to explore other underlying mechanisms that may cause or exacerbate coronary atherosclerosis.

Thyroid hormones exert multiple effects on the cardiovascular system. Thyroid dysfunction leads to changes in endothelial function, systemic vascular resistance, blood pressure, cardiac contractility, cardiac output, and myocardial oxygen consumption [2]. The relationship between CAD and hyperthyroidism or hypothyroidism have been widely established for a long time [3, 4]. Nevertheless, relatively less studies have focused on population with euthyroid status. For example, Steinberger et al. have reported free triiodothyronine (FT3) and free thyroxine (FT4) were positively associated with resting heart rate [5]. In addition, several observational studies demonstrated FT3 level was inversely associated with the presence of CAD or the severity of coronary atherosclerosis in euthyroid subjects [6–8], however, FT4, FT3 to FT4 ratio (FT3/FT4 ratio) and thyroid stimulating hormone (TSH) were not investigated in those studies. With regards to the relation between FT4 or TSH and CAD, the results of current research were conflicting [9–13]. Besides, the exploration of underlying confounders between thyroid hormones and CAD is insufficient.

Therefore, this study aimed to investigate the association between thyroid hormones levels or parameters (including FT3, FT4, FT3/FT4 ratio, and TSH) and the presence of CAD as well as severity of coronary atherosclerosis assessed by GS in euthyroid adults. We are also committed to explore potential confounding factor in the association.

## Subjects and Methods

### Study Population

There were overall 595 patients from North China with circulating thyroid function measurement results who underwent coronary

artery angiography (CAG) at the Peking Union Medical College Hospital (PUMCH) between January 2013 and April 2016 for chest pain and precordial discomfort on basis of positive noninvasive test results (i. e., electrocardiogram suggestive of ischemia, suspicious coronary computed tomography angiography, positive exercise tolerance test, and so on). Out of the above participants, 147 patients were excluded with prior history of percutaneous transluminal coronary intervention (PCI) or coronary artery bypass grafting (CABG). Also 108 patients were excluded because of abnormal levels of thyroid hormones, medical history of hyperthyroidism or hypothyroidism. Finally, 340 euthyroid patients were studied, including 267 cases with CAD defined by diameter stenosis at  $\geq 50\%$  in at least one main branch of coronary artery, and 73 participants with all coronary artery stenosis  $< 50\%$  as non-CAD (► Fig. 1).

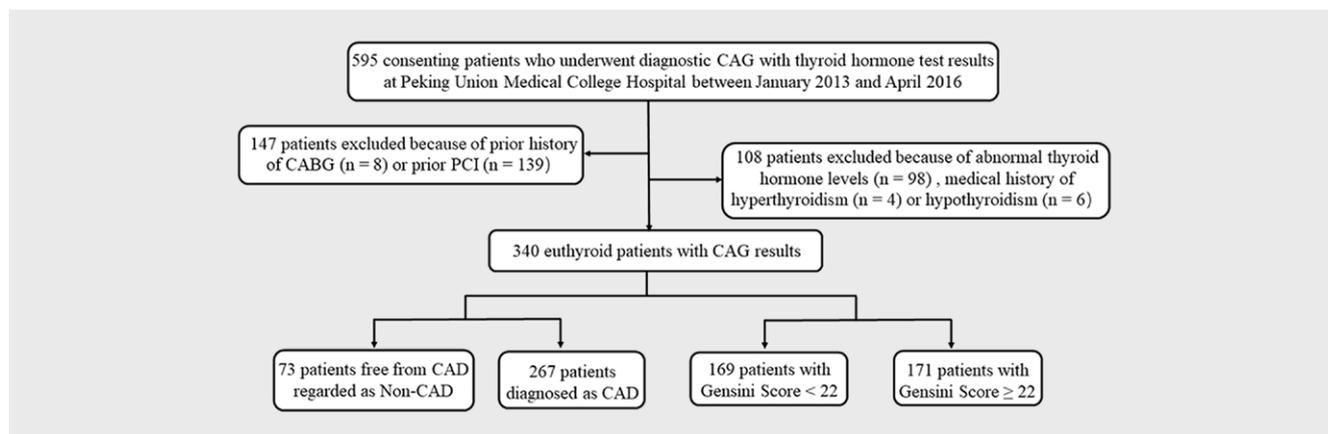
### Ethics Approval

Consent has been obtained from each patient after full explanation of the purpose and nature of all procedures. The protocol and the process of the study were approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1580). The entire study was conducted in consistent with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

### Collection of blood samples and determination of variables

Following an overnight fast for at least 8 hours, blood samples were collected from all patients and the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and hemoglobin A1c (HbA1c) were determined by conventional automated laboratory methods in the clinical laboratory of PUMCH.

The thyroid hormones including FT3, FT4, and TSH were tested by direct chemiluminescence method (ADVIA Centaur, Siemens, USA). The reference intervals of the laboratory in PUMCH were listed as follows: FT3, 1.80–4.10 pg/ml; FT4, 0.81–1.89 ng/dl; TSH, 0.38–4.34  $\mu$ U/ml. The subjects with circulating levels of thyroid hormones within the above reference range were taken as euthyroid patients. Patients with thyroid hormone levels out of the ref-



► Fig. 1 Flowchart of coronary atherosclerosis screening and quantification in patients. CAG: Coronary arteriography; CABG: Coronary artery bypass grafting; PCI: Percutaneous transluminal coronary intervention; CAD: Coronary artery disease.

erence range (98 patients) and prior or current thyroid disease, including those taking thyroid medications (10 patients) were excluded (► Fig. 1).

### Assessment of coronary atherosclerotic severity

Diagnostic CAG of each patient was performed with an angiography unit by an experienced cardiologist (Integris H; Philips Medical Systems, Amsterdam, the Netherlands). The imaging of coronary artery stenosis was completed from multiple projections. Based on the CAG results, CAD was diagnosed in cases for the presence of  $\geq 50\%$  stenosis in at least one main branch of coronary, while non-CAD were defined as  $< 50\%$  stenosis in all coronary arteries. Furthermore, Gensini Score (GS) was calculated to quantify the coronary atherosclerotic severity by assigning a stenosis severity score to each coronary segment according to the degree of luminal narrowing and the detailed localization [14], the results of which were double checked by two separate researchers. The included participants were divided into the group of  $GS \geq 22$  (171 patients) and the group of  $GS < 22$  (169 patients) with the median GS of them (22 scores) (► Fig. 1).

### Statistical analysis

The continuous variables were expressed as mean  $\pm$  standard deviation or median with inter-quartile ranges if necessary. The categorical variables were represented as count and percentage. The Kruskal–Wallis test was performed for the comparison of continuous variables among tertile groups of FT3. And categorical variables were compared by Fisher exact test. Univariable and multivariate logistic regression analysis was applied to determine the independent association between thyroid hormone levels (including FT3, FT3/FT4 ratio, FT4 and TSH) and CAD or  $GS \geq 22$ . Additional stratified analysis and test for interaction of the association between FT3 and  $GS \geq 22$  were conducted according to the following variables: age ( $< 65$  years vs.  $\geq 65$  years), sex (male vs. female), active smoking (yes vs. no) and body mass index (BMI) ( $< 24$  kg/m<sup>2</sup> vs.  $\geq 24$  kg/m<sup>2</sup>). Multiple imputation, based on 5 replications and a chained equation approach method in the R MI procedure, was performed to account for missing data (including BMI, blood lipid levels and HbA1c) as sensitivity analysis. A two-tailed  $p < 0.05$  was considered as statistically significant in all analyses. All the statistical analysis was performed using the Empower Stats (www.empowerstats.com, X & Y solutions, Inc. Boston, MA, USA) and R software version 3.6.1 (http://www.R-project.org). The forest plot was drawn with RStudio program, version 4.0.2 (http://www.R-project.org).

## Results

### Study participants and baseline characteristics

A total of 340 patients were included in the final analysis (► Fig. 1). Participants were divided according to tertiles of FT3 levels and general characteristics of the study population, including demographics, clinical characteristics, laboratory indexes, and coronary atherosclerotic burden, are presented in ► Table 1. Compared to subjects with lower tertiles of FT3, those with the highest circulating FT3 levels showed a higher prevalence in women or smokers,

and lower age and HbA1c while higher FT4. BMI, history of chronic disease (such as hypertension, hyperlipidemia and diabetes), lipids profiles (including TC, HDL-C, LDL-C and TG), TSH, presence of CAD and GS did not differ statistically among three groups.

### Association between thyroid hormones and coronary atherosclerosis

Multifactorial logistic regression analysis was performed to evaluate the relationship between thyroid hormones levels and atherosclerosis. FT3 level, taken as continuous variable or categorical variable in tertiles, was not statistically associated with the presence of CAD in non-adjusted Model and two adjusted models ( $p > 0.05$ ). The lowest tertile of thyroid hormones levels or indexes was usually used as the reference (OR = 1) for medium and highest tertiles. The GS high than or equal to median value of included patients ( $GS \geq 22$ ) was used to represent severe coronary lesion. No significant association was observed between continuous FT3 and  $GS \geq 22$  [OR = 0.66, 95% CI (0.35, 1.24),  $p = 0.197$ ], neither was that between highest tertile of FT3 and  $GS \geq 22$  compared to the lowest tertile [OR = 0.75, 95% CI (0.45, 1.27),  $p = 0.285$ ]. However, the association between FT3 and  $GS \geq 22$  became significant after the adjustment for several factors in two adjusted models (Model I and Model II). Specifically, in Model I, age and sex were adjusted for [Continuous FT3: OR = 0.46, 95% CI (0.23, 0.92),  $p = 0.029$ ; Tertile 3 of FT3: OR = 0.54, 95% CI (0.30, 0.97),  $p = 0.038$ ]. Based on Model I, Model II was further adjusted for the following variables, including BMI, active smoking, hypertension, diabetes, HbA1c, LDL-C, HDL-C, and TG [Continuous FT3: OR = 0.44, 95% CI (0.20, 0.95),  $p = 0.036$ ; Tertile 3 of FT3: OR = 0.49, 95% CI (0.25, 0.96),  $p = 0.039$ ] (► Table 2). By contrast, subjects with the highest tertile of FT3/FT4 ratio seemed to have the remarkably decreased risk of CAD in both non-adjusted Model [OR = 0.49, 95% CI (0.24, 0.98),  $p = 0.044$ ] and Model I [OR = 0.45, 95% CI (0.22, 0.93),  $p = 0.031$ ]. However, the reduced risk of CAD became insignificant in Model 2, the fully adjusted model. No significant association between FT3/FT4 ratio and  $GS \geq 22$  was found (► Table 3).

Similar analysis was conducted to evaluate the relation between two other thyroid related hormones (including FT4 and TSH) and the presence of CAD or  $GS \geq 22$ , afterwards, the correlations were not demonstrated ( $p > 0.05$ ) (Tables S1, S2).

### Stratified analysis and test for interaction

The stratified and interaction analysis were performed according to several potential confounders (including age, sex, smoking and BMI) and the results are illustrated in ► Fig. 2. Each stratification was adjusted for all of variables (including age, sex, BMI, active smoking, hypertension, diabetes, HbA1c, LDL-C, HDL-C, and TG), except for the stratification factor itself. For example, circulating FT3 was noticeably associated with  $GS \geq 22$  in men [OR = 0.39, 95% CI (0.16, 0.99),  $p = 0.048$ ], smokers [OR = 0.34, 95% CI (0.12, 0.99),  $p = 0.047$ ] and subjects with age  $< 65$  years [OR = 0.33, 95% CI (0.13, 0.84),  $p = 0.019$ ]. No significant effect modifiers were found among these stratification factors ( $p$  for interaction  $> 0.05$ ). As is presented in Table S3, logistic regression analysis was conducted to estimate the association between the above three significant confounders (age, sex and active smoking) and FT3 levels or  $GS \geq 22$ .

► **Table 1** Baseline characteristics of the study participants according to tertiles of FT3.

Characteristics	Tertiles of FT3				p-value
	All n = 340	T1 n = 110	T2 n = 112	T3 n = 118	
<b>Demographics</b>					
Age (years)	59.6 ± 11.7	63.2 ± 11.5	61.2 ± 10.1	54.6 ± 11.7	<0.001
Sex, male (n)	231 (67.9%)	60 (54.5%)	32 (28.6%)	17 (14.4%)	<0.001
BMI (kg/m <sup>2</sup> )	25.6 ± 3.3	25.1 ± 3.6	25.8 ± 3.1	25.9 ± 3.2	0.065
Active smoking (n)	172 (50.6%)	43 (39.1%)	53 (47.3%)	76 (64.4%)	<0.001
<b>Clinical characteristics</b>					
Hypertension (n)	233 (68.5%)	80 (72.7%)	75 (67.0%)	78 (66.1%)	0.510
Hyperlipidemia (n)	209 (61.5%)	75 (68.2%)	61 (54.5%)	73 (61.9%)	0.110
Diabetes (n)	126 (37.1%)	48 (43.6%)	43 (38.4%)	35 (29.7%)	0.087
<b>Metabolic indicators</b>					
Total cholesterol (mmol/l)	4.19 ± 1.03	4.19 ± 1.08	4.22 ± 1.04	4.18 ± 0.99	0.915
LDL cholesterol (mmol/l)	2.52 ± 0.91	2.50 ± 0.94	2.50 ± 0.92	2.56 ± 0.87	0.675
HDL cholesterol (mmol/l)	1.02 ± 0.26	1.03 ± 0.27	1.04 ± 0.26	0.99 ± 0.26	0.217
Triglyceride (mmol/l)	1.64 ± 1.15	1.71 ± 1.28	1.60 ± 1.16	1.62 ± 1.01	0.940
HbA1c (mmol/mol)	46.30 ± 14.78	49.76 ± 17.71	45.94 ± 13.51	43.26 ± 11.95	0.009
<b>Thyroid hormones</b>					
FT3 (pg/ml)	2.99 ± 0.34	2.62 ± 0.17	2.97 ± 0.09	3.36 ± 0.20	<0.001
FT4 (ng/dl)	1.21 ± 0.16	1.14 ± 0.15	1.22 ± 0.17	1.25 ± 1.14	<0.001
TSH (μU/ml)	1.97 ± 0.93	2.00 ± 0.94	1.96 ± 0.93	1.95 ± 0.92	0.919
<b>Coronary atherosclerotic burden</b>					
CAD (n)	267 (78.5%)	88 (80.0%)	85 (75.9%)	94 (79.7%)	0.707
Gensini Score	22 [8,44]	24 [10,58]	20 [8,40]	19 [5,40]	0.177

Continuous data are presented as means ± SD or medians (interquartile ranges), and categorical variables are presented as counts (%). BMI: Body mass index; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid-stimulating hormone; CAD: Coronary artery disease.

Age < 65 years was positively related to FT3 levels compared with age ≥ 65 years [ $\beta = 0.16$ , 95% CI (0.09, 0.24),  $p < 0.001$ ], so were sex (male) [ $\beta = 0.24$ , 95% CI (0.16, 0.31),  $p < 0.001$ ] and active smoking [ $\beta = 0.13$ , 95% CI (0.05, 0.20),  $p < 0.001$ ]. Age < 65 years was irrelevant to  $GS \geq 22$  [OR = 0.97, 95% CI (0.62, 1.51),  $p = 0.881$ ], however, sex (male) and active smoking were correlated with  $GS \geq 22$  [Sex: OR = 1.91, 95% CI (1.20, 3.03),  $p = 0.006$ ; Active smoking: OR = 1.90, 95% CI (1.23, 2.92),  $p = 0.004$ ].

### Sensitivity analysis

As a cross-sectional study, missing data of adjusted variables was inevitable, including BMI (n = 35), blood lipid levels (n = 1) and HbA1c (n = 24) in this study. Multiple imputation was used to evaluate the stability of critical results with missing data. As expected, both continuous FT3 levels and Tertile 3 of FT3 were stably associated with  $GS \geq 22$  after MI [Continuous: OR = 0.52, 95% CI (0.32, 0.84),  $p = 0.008$ ; Tertile 3: OR = 0.61, 95% CI (0.40, 0.93),  $p = 0.021$ ], which is presented in Table S4.

## Discussion

### The major findings

This cross-sectional study, performed in euthyroid Chinese patients who underwent the diagnostic CAG, explored the association between thyroid hormones levels or parameters (including FT3, FT4, FT3/FT4 ratio and TSH) and the presence of CAD or severe coronary atherosclerosis defined by  $GS \geq 22$ . The major finding was elevated FT3 level was significantly and inversely associated with higher  $GS \geq 22$ , independent of various traditional risk factors of CAD. This finding suggested low but clinically normal FT3 concentration might be potential risk factors for serious coronary atherosclerosis. An additional finding was the notable relation between FT3/FT4 ratio and the prevalence of CAD, following adjusted for age and sex. In comparison, neither FT4 nor TSH levels were established as significantly correlated factors for CAD or higher GS.

► **Table 2** Association between FT3 levels and severity of coronary atherosclerosis in multifactorial regression model.

Outcome		Non-adjusted Model		Model I		Model II	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
CAD	Continuous FT3 (pg/ml)	0.77 (0.36,1.64)	0.503	0.55 (0.24,1.28)	0.163	0.70 (0.27,1.84)	0.468
	Tertiles of FT3						
	Tertile 1	1.00		1.00		1.00	
	Tertile 2	0.79 (0.42,1.49)	0.461	0.60 (0.31,1.19)	0.142	0.84 (0.38,1.83)	0.656
	Tertile 3	0.98 (0.51,1.87)	0.949	0.73 (0.35,1.52)	0.405	0.91 (0.38,2.16)	0.830
Gensini Score $\geq 22$	Continuous FT3 (pg/ml)	0.66 (0.35,1.24)	0.197	0.46 (0.23,0.92)	0.029	0.44 (0.20,0.95)	0.036
	Tertiles of FT3						
	Tertile 1	1.00		1.00		1.00	
	Tertile 2	0.80 (0.47,1.36)	0.417	0.63 (0.36,1.11)	0.111	0.56 (0.29,1.06)	0.076
	Tertile 3	0.75 (0.45,1.27)	0.285	0.54 (0.30,0.97)	0.038	0.49 (0.25,0.96)	0.039

Model I: Adjusted for age and sex. Model II: Adjusted for all of these variables, including age, sex, BMI, active smoking, hypertension, diabetes, LDL-C, HDL-C and TG.

► **Table 3** Association between FT3/FT4 and severity of coronary atherosclerosis in multifactorial regression model.

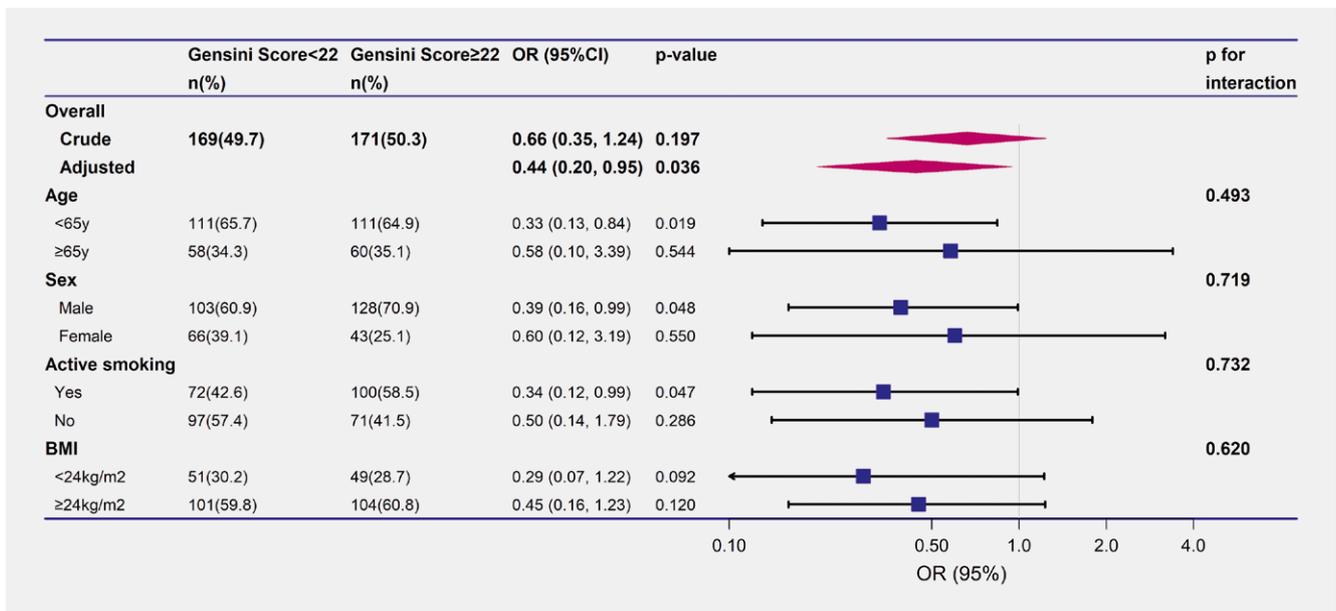
Outcome		Non-adjusted model		Model I		Model II	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
CAD	Tertiles of FT3/FT4						
	Tertile 1	1.00		1.00		1.00	
	Tertile 2	0.79 (0.39,1.63)	0.531	0.70 (0.33,1.46)	0.338	0.91 (0.37,2.26)	0.841
	Tertile 3	0.49 (0.24,0.98)	0.044	0.45 (0.22,0.93)	0.031	0.48 (0.20,1.11)	0.087
Gensini Score $\geq 22$	Tertiles of FT3/FT4						
	Tertile 1	1.00		1.00		1.00	
	Tertile 2	1.00 (0.58,1.72)	0.996	0.91 (0.53,1.59)	0.111	1.13 (0.59,2.16)	0.722
	Tertile 3	0.80 (0.46,1.39)	0.427	0.76 (0.43,1.33)	0.336	0.79 (0.41,1.51)	0.477

Model I: Adjusted for age and sex; Model II: Adjusted for all of these variables, including age, sex, BMI, active smoking, hypertension, diabetes, HbA1c, LDL-C, HDL-C, and TG.

## The interpretation of main findings

We found FT3 was independently and negatively associated with severe coronary atherosclerosis. An observational study by Ertas et al. [8] proved lower FT3 levels within the normal range are an independent predictor of CAD and severe atherosclerosis of coronary (GS > 20) in 119 euthyroid Turkish patients. In another study [7] including 100 euthyroid Indian patients with stable angina and quantifying the severity of coronary stenosis with GS system, it was established that FT3 was negatively correlated with severe CAD. Homogeneously, Zhou et al. [6], who enrolled 4206 euthyroid Chinese patients, indicated that as normal FT3 levels declined, the presence and severity of CAD decreased in young population, but not in the old ones over 65 years old. Our results cohered with the study by

Zhou et al. [6] and we further investigated the FT3/FT4 ratio, FT4 and TSH simultaneously. We found firstly FT3/FT4 ratio was related to the prevalence of CAD, independent of age and sex. Whereas, FT3/FT4 ratio was not significantly correlated with the prevalence of coronary atherosclerosis in another study conducted in euthyroid population with Type 2 Diabetes [15]. This disparity was probably due to the heterogeneities between included participants, especially the different glucose metabolism status which is related to both thyroid hormones and artery atherosclerosis. Among a prospective cohort of 2106 euthyroid patients with triple vessel coronary artery disease [16], lower FT3/FT4 ratio was in connection with increased risks of long-term cardiac deaths as well as major adverse cardiac and cerebrovascular events (MACCEs), such



**Fig. 2** Stratified analyses of the association between FT3 and Gensini Score according to various baseline characteristics. The analysis was adjusted for all of these variables, including age, sex, BMI, active smoking, hypertension, diabetes, HbA1c, LDL-C, HDL-C, and TG, except for the specific stratification variable of that analysis.

as all-cause death, myocardial infarction, and stroke with the median follow-up for 5.3 years, suggesting the potential correlation between FT3/FT4 ratio with CAD.

Age, sex, and smoking were important factors, which were relevant to either FT3 or GS ≥ 22 in this study. We found FT3 was independently associated with more severe coronary atherosclerosis in the subjects with age < 65 years but not in the older ones, consistent with previous studies [6, 17]. One of the possible reasons was depressed thyroid function, declined conversion of T4 to T3 and decreased sensitivity in organs to thyroid hormone with age [18]. Another possibility was the growing morbidity of glycemic and lipid metabolic problems, hypertension and other predictors of CAD in the aged, which may influence and interfere the impact of thyroid hormone on CAD. Similarly significant association between FT3 and GS ≥ 22 in the males and smokers. It is not difficult to understand that sex and smoking are closely correlated with atherosclerosis. With regards to the correlation between them and FT3, there were different reasons. Circulating FT3 in males was higher than that in females throughout life except in the very young and very old, due to the potentiation effect of testosterone on the liver type 1 iodothyronine deiodinase (ID1), which catalyzes the deiodination of T4 followed by the production of biologically active T3 [19, 20]. Cigarette smoking contributes to a rise of serum FT3 and FT4 induced by the activation of the sympathetic nervous system and abnormal immune profile in thyroid. All of those might be potential confounding factors between FT3 and CAD.

In our study, neither FT4 nor TSH levels were significantly correlated with prevalent CAD or higher GS over median value. Actually, FT4 and TSH within the normal reference range have been investigated in several studies and the conclusions have not been unified so far. For example, in a study [9] of 2045 consecutive adults no less than 30 years old, neither FT4 nor TSH were indicated to be associated with CAD. There were also hints that lower FT4 was in-

versely related to coronary artery calcification and carotid intima media thickness (CIMT), the correlative risk factors of coronary atherosclerosis in euthyroid population [10, 11]. Boggio et al. [12] revealed TSH levels in the upper limits of normal range was correlated with the less favorable cardiometabolic status and consequently with the increased risk of developing cardiovascular diseases, in euthyroid 744 Italian women. According to the research focused on older adults in the United States, increased TSH and decreased FT4 within normal limits were associated with reduced risk of multiple adverse events, including heart failure, atrial fibrillation, composite cardiovascular outcomes, and mortality [13]. Those studies led us to a novel comprehensive view that FT4 or TSH were mainly proved to be related to several risk factors or surrogate indicators of CAD, instead of CAD itself diagnosed with gold standard like CAG. However, the genesis and development of CAD might be influenced by multitudinous factors. Moreover, the discrepancy may derive from heterogeneities of participants in race, age and comorbidities to some extent. In this study, we explored the association between thyroid hormone and coronary atherosclerosis, which was quantified through CAG instead of surrogate indicators or risk factors in a Chinese population.

### The mechanism of effects of thyroid hormones on coronary atherosclerosis

Thyroid hormones have been currently connected to endothelial function, blood pressure, lipids, insulin sensitivity, homocysteine, C-reactive protein, procoagulant state and so forth [2, 21–23], which may be mediating factors between FT3, the biologically active form of thyroid hormones, and coronary atherosclerosis. The production of nitric oxide (NO), which was revealed to mediate the rapid and direct vasodilatory effects of thyroid hormone at the level of isolated arteries [24, 25], was declined in patients with overt or subclinical hypothyroidism and improved by thyroid hormone re-

placement therapy [26–28]. Thyroxine (T4) tend to be converted to triiodothyronine (T3), the active form, under the action of deiodinase 2 (Dio2). Both long-term genomic and rapid non-genomic action of thyroid hormones occur upon binding T3 to thyroid hormone receptor- $\alpha$ , causing the generation of NO ultimately [29]. Whereas, T4 only plays a role in non-genomic action by binding itself to integrin receptors before the NO is generated [29]. That might explain that FT3, the free form of T3, were more correlated with severe coronary atherosclerosis compared with FT4, the free form of T4. As a marker indicating the conversion rate from T4 to T3, FT3/FT4 ratio was observed to negatively related to CAD, which could verify the speculation that T3 exerts more protective effects in the occurrence and aggravation of CAD.

### The strengths and limitations of the study

The strengths of this study are that all of our patients underwent standard CAG, the gold standard way of diagnosing CAD, to quantify the coronary atherosclerotic lesion, and that all of our patients were free from thyroid related history or drugs, which minimized underlying hybrid effects to a large degree. The limitations of study were unavoidable. First, this is a single-center study with limited sample size. Thus, our results need to be verified in multi-center study with larger sample size. Second, as a cross-sectional study, causal relationship could not be determined. Further prospective study is warranted. Last but not least, missing data of adjusted variables existed. However, we conducted sensitivity analysis through multiple imputation and confirmed the robustness of the results. Due to lack of data, the positive association between thyroid hormones and resting heart rate under euthyroid condition, which has been revealed by Steinberger et al. [5], was not explored further in this study.

### Conclusion

In this study, we found even in euthyroid population, higher FT3 level may be significantly and inversely associated with severity of coronary atherosclerosis, independent of traditional risk factors of CAD. FT3/FT4 ratio may be remarkably correlated with the prevalence of CAD, following adjustment for age and sex. Our findings offered some enlightenments to importance of screening of thyroid function and appropriate levels of thyroid hormone. Further studies are warranted to verify the results and explore the underlying mechanisms.

### Conflicts of Interest

The authors declare that they have no conflict of interest.

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