Free triiodothyronine in relation to coronary severity at different ages: Gensini score assessment in 4206 euthyroid patients

Bing-Yang ZHOU, Yuan-Lin GUO, Na-Qiong WU, Cheng-Gang ZHU, Ying GAO, Ping QING, Xiao-Lin LI, Yao WANG, Geng LIU, Qian DONG, Jian-Jun LI
Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract

Objective To study whether free triiodothyronine (FT3) within normal range has effects on the presence and severity of coronary artery disease (CAD) in different gender and age groups. Methods A total of 4206 euthyroid patients were consecutively enrolled and divided into CAD group (n = 3306) and non-CAD group (n = 900). All patients underwent coronary angiography (CAG). Gensini score (GS) was used to determine the severity of coronary artery stenosis. Severe CAD was defined as GS > 32 and mild CAD was defined as GS ≤ 32. Logistic regression analysis and linear regression analysis were conducted to determine the association of FT3 with CAD in patients with different gender and ages. Results Concentration of FT3 was lower in patients with CAD than that in angiography-normal control group (P < 0.05). In addition, concentration of FT3 was lower in severe CAD than that in mild CAD. After adjusting for traditional cardiovascular risk factors and potential confounders, FT3 was negatively correlated with the presence of CAD, but not in the old patients (> 65 years old). Multivariable linear regression analysis showed that FT3 was negatively associated with GS in male and young patients with stable CAD, but not in the old patients. Conclusions Low FT3 within normal range was negatively associated with the presence and severity of CAD in young patients, but not in the old ones. Further studies are needed to confirm our findings.

1 Introduction

Thyroid disease is quite common and thyroid hormone exerts numerous effects on cardiovascular system. Free triiodothyronine (FT3), the biologically active form of thyroid hormone, has been demonstrated to be associated with cardiovascular risk factor, myocardial injury indicator and mortality in acute myocardial infarct (AMI) patient. In fact, most of previous studies focused on the correlation of thyroid hormone with cardiovascular system in patients with damaged thyroid function. In addition, studies with regards to the relationship between thyroid hormone within normal range and coronary artery disease (CAD) indicated that FT3 is negatively correlated with CAD, free thyroxine (FT4) is either non-correlated or positively associated with CAD. Furthermore, few studies conducted the severity of CAD with a Gensini score (GS) assessment. More important, these studies were limited by small sample sizes.

To our knowledge, no study has studied the relation of FT3 within normal range to CAD in different gender and age groups. Therefore, in the present study, we consecutively enrolled 4206 euthyroid patients who underwent percutaneous coronary angiography (CAG), and aimed to examine the correlation of FT3 within normal levels with the presence and severity of CAD in different gender and age groups. The severity of CAD was calculated by GS system.

2 Methods

2.1 Study population

In the present study, a total of 4206 Chinese euthyroid patients were consecutively enrolled from March 2011 to April 2015. The study was in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Board of the Fuwai Hospital (Beijing, China).
formed consent was obtained from all enrolled patients. All patients underwent percutaneous CAG due to angina-like chest pain. Euthyroidism was defined as all thyroid hormone fractions within normal range. The normal range of FT3 was between 1.79 pg/mL and 4.09 pg/mL. CAD includes stable CAD and AMI. Stable CAD was diagnosed as old myocardial infarction or the presence of coronary lesions ≥ 50% in at least one major epicardial artery segment by CAG analysis. Non-CAD was defined as the presence of stenosis less than 50% without unstable plaques (such as coronary artery dissection and ulcer, etc) or those without any signs of coronary artery atherosclerosis by CAG analysis. Severe CAD was defined as GS > 32 and mild CAD was defined as GS ≤ 32. The diagnosis of AMI was according to “Third Universal Definition of Myocardial Infarction”. Hypertension (HTN) was defined as repeated systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or taking anti-hypertensive drugs. Diabetes mellitus (DM) was defined as fasting serum glucose ≥ 7.0 mmol/L or random serum glucose ≥ 11.0 mmol/L or the 2-hour serum glucose of the oral glucose tolerance test ≥ 11.0 mmol/L or using hypoglycemic medications currently. Hyperlipidemia was defined as total cholesterol ≥ 5.1 mmol/L or triglyceride ≥ 1.7 mmol/L or using lipid-lowering medications. Body mass index (BMI) was calculated by square of weight divided by height. Exclusion criteria were thyroid dysfunction, low T3 syndrome, thyroid autoimmunity, history of levothyroxine replacement therapy and amiodarone, heart failure, severe liver and renal insufficiency, infectious or systemic inflammatory diseases and chronic diseases.

2.2 Laboratory analysis

Blood samples of patients were collected into EDTA-containing tubes after at least 12-hour fasting in the morning before CAG. Concentrations of total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and lipoprotein (a) were measured by automatic biochemistry analyzer (Hitachi 7150, Japan). Serum FT3, FT4 and thyroid stimulating hormone (TSH) were measured using commercial kits by immulite 2000 chemiluminescent immunoassay (Diagnostic Products Corp, CA, USA).

2.3 GS calculation

CAG information was evaluated from catheter laboratory records by at least three interventional cardiologists. The severity of coronary artery stenosis was evaluated by the GS system, which was scored according to stenosis position and severity. The specific method has been shown in many previous studies. GS has been used to calculate the severity of coronary artery stenosis for a long time and is indicated to be superior and more effective to the method of using the number of diseased vessels. GS is also demonstrated to provide more valuable prognostic information on cardiovascular risk than the Leaman score and American College of Cardiology/American Heart Association (ACC/AHA) score in patients with acute coronary syndrome. Moreover, one study found that GS was not inferior to Synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) to assess the severity of coronary artery stenosis. Therefore, the GS was chosen in our study for the evaluation of coronary artery stenosis.

2.4 Statistical analysis

Baseline data was expressed as mean ± SD (normal distribution data) or median with quartile (abnormal distribution data) for continuous variables and n (%) for categorical variables. Continuous variables were analyzed by the Student t-test (normal distribution data) and Mann–Whitney U-test or Kruskal–Wallis test (abnormal distribution data) when appropriate. Categorical variables were analyzed by $X^2$ statistic test.

To investigate the correlation of FT3 with presence of CAD, binary univariate and multivariate logistic regression analyses were conducted. GS were transformed by log-normalization. Logistic models were adjusted for traditional cardiovascular risk factors (age, sex, HTN, DM, hyperlipidemia, obesity, current smoking). Multivariable linear regression analysis was performed to determine the relationship between FT3 and GS in stable CAD and AMI patients. The statistical analysis was performed with SPSS version 22.0 software (SPSS Inc., IL, USA), and two-tailed $P$ values < 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

Overall, we consecutively enrolled 4206 euthyroid patients who underwent CAG. The clinical and biochemical characteristics of patients were shown in Table 1. The mean age of the patients was 57.34 ± 9.69 years and 3048 (72.47%) participants were male. Patients were divided into CAD group (cases, $n = 3306$) and non-CAD group (controls, $n = 900$). The CAD patients are older and have higher percentage of hypertension, diabetes mellitus, current smoking ($P < 0.05$). FT3 is significantly lower in CAD group (2.95 ± 0.32 pg/mL, $P < 0.05$). Tertiles of GS: tertile 1 (0–10 scores), tertile 2 (11–32 scores), tertile 3 (> 32 scores).
Patients were classified into two groups according to tertiles of GS: severe-CAD group (GS > 32 scores) and mild CAD group (GS ≤ 32 scores). As shown in Figure 1, FT3 levels were lower in severe CAD group than that in mild CAD group.

### 3.2 Logistic regression analysis

To examine independent predictors for the presence of CAD, univariate and multivariate logistic regression analyses were performed. Table 2 showed that, after adjustment for traditional and potential confounders including age, gender, HTN, DM, hyperlipidemia, current smoking, obesity, FT3 was demonstrated to be significantly and negatively associated with the presence of CAD (odds ratio (OR): 0.591; 95% confidence interval (CI): 0.452–0.772; P < 0.001).

**Table 2. Logistic regression analysis of the correlation of FT3 with the presence of CAD.**

| Model | Unadjusted model | Adjusted model |
|-------|------------------|----------------|
|       | OR (95% CI)       | P value        | OR (95% CI)       | P value        |
| 1 (Total) | 0.788 (0.625 – 0.993) | 0.043          | 0.591 (0.452 – 0.772) | < 0.001        |
| 2 (Male)  | 0.518 (0.378 – 0.709) | < 0.001        | 0.663 (0.477 – 0.921) | 0.014          |
| 3 (Female) | 0.377 (0.244 – 0.583) | < 0.001        | 0.458 (0.287 – 0.730) | 0.001          |
| 4 (Young) | 0.897 (0.691 – 1.166) | 0.417          | 0.565 (0.420 – 0.761) | < 0.001        |
| 5 (Old)   | 0.780 (0.448 – 1.359) | 0.380          | 0.657 (0.354 – 1.211) | 0.184          |

### Figure 1. Levels of FT3 in severe CAD (GS >32) and mild CAD group (GS ≤ 32).

CAD: coronary artery disease; FT3: free triiodothyronine; GS: Gensini score.
0.001], male subgroup (OR: 0.663; 95% CI: 0.477–0.921; \( P = 0.014 \)), female subgroup (OR: 0.458; 95% CI: 0.287–0.730; \( P = 0.001 \)), young subgroup (OR: 0.565; 95% CI: 0.420–0.761; \( P < 0.001 \)). But, in the subgroup of old patients over 65 years old, no relationship was found between FT3 and the presence of CAD before and after further adjustment for potential confounders.

### 3.3 Linear regression analysis of FT3 with GS

As shown in Table 3, FT3 was negatively correlated with GS in stable CAD group and subgroup of male and young after adjustment for confounders including age, gender, HTN, DM, hyperlipidemia, current smoking, obesity. However, in AMI patients, no association of FT3 with GS was found (Table 4).

#### Table 3. Correlation analysis and linear regression analysis of the relation of FT3 to GS in stable CAD patients.

| Model | Gensini score | Unstandardized coefficients B | Standardized coefficients (Beta) | \( P \) value |
|-------|---------------|-------------------------------|----------------------------------|--------------|
| 1 (Total) | -0.043 | 0.018 | -0.080 | -0.066 | 0.001 |
| 2 (Male) | -0.083 | < 0.001 | -0.093 | -0.071 | 0.001 |
| 3 (Female) | -0.072 | 0.044 | -0.047 | -0.034 | 0.355 |
| 4 (Young) | -0.043 | 0.032 | -0.100 | -0.082 | 0.001 |
| 5 (Old) | -0.037 | 0.304 | - | - | - |

CAD: coronary artery disease; FT3: free triiodothyronine; GS: Gensini score.

#### Table 4. Correlation analysis and linear regression analysis of the relation of FT3 to GS in AMI subjects.

| Model | Gensini score | Unstandardized coefficients B | Standardized coefficients (Beta) | \( P \) value |
|-------|---------------|-------------------------------|----------------------------------|--------------|
| 1 (Total) | -0.131 | 0.038 | -0.070 | -0.073 | 0.282 |
| 2 (Male) | -0.143 | 0.033 | -0.093 | -0.092 | 0.191 |
| 3 (Female) | 0.006 | 0.976 | - | - | - |
| 4 (Young) | -0.140 | 0.041 | -0.117 | -0.117 | 0.107 |
| 5 (Old) | 0.183 | 0.285 | - | - | - |

AMI: acute myocardial infarction; FT3: free triiodothyronine; GS: Gensini score.

### 4 Discussion

The current study with large sample size, performed in a Chinese population of euthyroid patients who underwent CAG, examined the correlation of FT3 with the presence and severity of CAD. In addition, we assessed the relationship between FT3 and GS in different gender and age subgroups. As a result, we found the low FT3 level was negatively associated with the presence and severity of CAD in the young patients. The result indicates that depressed thyroid function may be a risk factor for CAD, especially in young individuals. Our data may provide novel information with respect to the role of FT3 in the presence and severity of CAD at different ages.

The association of thyroid dysfunction with cardiovascular risk factors and CAD has recognized for a long time, but few studies have investigated the relationship between thyroid hormone within normal range and cardiovascular disease. One study from Daswani, et al.[5] enrolled 100 euthyroid patients with stable CAD and defined the severity of coronary artery stenosis by using GS system. They excluded patients with acute coronary syndrome. Average age of all the subjects enrolled was under 65 years old. Finally, they found that FT3 was significantly and negatively correlated with severe CAD. Coceni, et al.[18] who examined 1047 patients with suspected CAD and normal levels of FT4 as well as TSH, indicated that low FT3 could be an independent risk factor for CAD. Moreover, they revealed that low FT3 syndrome exerted adverse influence on total and cardiac mortality with a follow-up of 31 months. Cappolla, et al.[19] enrolled 2843 euthyroid patients and revealed that FT4 within normal range was positively associated with atrial fibrillation, heart failure, composite cardiovascular outcomes and total mortality. In contrast, several studies did not find any correlation of FT4 with CAD. One study enrolled 1589 patients with normal thyroid function and found no relation of normal FT4 levels to the presence and severity of CAD.[20] Another study indicated that FT3 levels were statistically lower in severer CAD group than that in less severe CAD group, while FT4 levels were not statistically different in the two groups.[6] Our study was consistent with the result that FT3 levels were significantly lower in CAD group while FT4 levels were similar in CAD group and control group. Additionally, we found that lower FT3 level was negatively associated with the presence as well as the severity of CAD. This disparity might be due to the different ethnic backgrounds and sample sizes.

Previous studies have demonstrated that hypothyroidism is associated with atherosclerosis, endothelial vascular dysfunction, dyslipidemia, atrial fibrillation and main adverse cardiovascular and cerebrovascular events.[21–24] And studies also suggested that subclinical hypothyroidism is associated with increased risk of cardiovascular disease and higher CAD mortality.[25,26] These data indicated that depressed thyroid function increased the risk of CAD. FT3 is biologically active form of thyroid hormone and an isolated decrease of it may increase the risk of CAD in a similar fashion to overt or subclinical hypothyroidism. With regard to the exact mechanisms underlying the impact of lower levels
of thyroid hormone on CAD, it is still not comprehensively understood. Thyroid hormone has been demonstrated to be correlated with LDL-C, blood pressure, C-reactive protein, endothelial dysfunction, homeostasis model assessment for insulin resistance and coronary artery calcium scores, which are all indicated to be risk factors of cardiovascular disease. These risk factors may mediate the influence of low FT3 level on CAD. The expression of LDL-C receptor mRNA was decreased in hypothyroid rats by 50%, resulting in lowered degradation of LDL-C. Additionally, LDL-C in patients with low FT3 level was more susceptible to be oxidized and then triggered the process of atherosclerosis.

Patients with low FT3 level had higher prevalence peripheral vascular resistance and arterial stiffness which resulted in hypertension. It is suggested that thyroid hormone is an important regulator of endothelial nitric oxide (NO) production and endothelial vasodilatation is impaired in patients with depressed thyroid function.

In our study, we did not find the correlation of thyroid hormone with the presence and severity of CAD in old patients, consistent with previous studies. One of the possible reasons was the down-regulated sensitivity to thyroid hormone in older subjects. Furthermore, aging is correlated with adverse changes in body composition. Studies revealed that with aging, the release of free fatty acids from adipocytes increased and metabolically active tissues decreased. The excess free fatty acids increased insulin resistance, dyslipidemia, and then increased hypertension, diabetes mellitus, which were independent cardiovascular risk factors. The effects of these risk factors may overpass and confound the effect of normal levels of FT3 on cardiovascular system in the old.

We also examined the correlation of FT3 within normal levels with GS in patients with AMI. However, multivariable liner regression analysis showed no relationship between FT3 and GS in AMI patients. The AMI patients enrolled in our study were not hospitalized in the earliest time after occurrence of chest pain. The average time from chest pain to hospitalize were 14.26 ± 6.43 days in the present study. One study enrolled 47 euthyroid patients with AMI and found that maximal changes of thyroid hormone were found in two to three days after onset of symptoms. The study indicated that thyroid hormone was transiently down regulated during the acute phase of myocardial infarction in patients with normal thyroid function. Therefore, the effects of thyroid hormone on patients with AMI enrolled in the present study may disappear for the long interval period.

There were several limitations in this study. Firstly, it was a single-center and retrospective study. And it was a cross-sectional study and unable to determine whether low FT3 within normal range was a risk factor for CAD. Prospective and randomized controlled studies are needed to confirm it. Secondly, there was no follow-up data to examine the cardiac mortality and major adverse cardiovascular events.

In conclusion, the current study indicated that lower FT3 within normal range was negatively associated the presence and severity of CAD in young patients, but not in the old ones. More studies are needed to confirm our findings.

Acknowledgments

This study was partly supported by National Natural Scientific Foundation (81241121), Capital Special Foundation of Clinical Application Research (Z121107001012015), Capital Health Development Fund (2011400302, 2016-1-4035), and Beijing Natural Scientific Foundation (7131014) awarded to Dr. LJ JJ. The authors declare that they have no conflict of interest.

References

1. Canaris GJ, Manowitz NR, Mayor G, et al. The colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526–534.
2. Roef GL, Rietzschel ER, Van Daele CM, et al. Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects. Thyroid 2014; 24: 223–231.
3. Wang WY, Tang YD, Yang M, et al. Free triiodothyronine level indicates the degree of myocardial injury in patients with acute st-elevation myocardial infarction. Chin Med J (Engl) 2013; 126: 3926–3929.
4. Lymvaios I, Mourouzis I, Cokkinos DV, et al. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: A strong association? Eur J Endocrinol 2011; 165: 107–114.
5. Daswani R, Jayaprakash B, Shetty R, et al. Association of thyroid function with severity of coronary artery disease in euthyroid patients. J Clin Diag Res 2015; 9: 10–13.
6. Auer J, Berent R, Weber T, et al. Thyroid function is associated with presence and severity of coronary atherosclerosis. Clin Cardiol 2003; 26: 569–573.
7. Jung CH, Rhee EJ, Shin HS, et al. Higher serum free thyroxine levels are associated with coronary artery disease. Endocr J 2008; 55: 819–826.
8. Genders TSS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: Validation, updating, and extension. Eur Heart J 2011; 32: 1316–1330.
9. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal
definition of myocardial infarction. Nat Rev Cardiol 2012; 9: 2173–2195.

9 Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606.

10 Gong P, Luo SH, Li XL, et al. Relation of abo blood groups to the severity of coronary atherosclerosis: An gensini score assessment. Atherosclerosis 2014; 237: 748–753.

11 Chen J, Chen MH, Guo YL, et al. Plasma big endothelin-1 level and the severity of new-onset stable coronary artery disease. J Atherosclerosis Thromb 2014; 22: 126–135.

12 Juan C, Man-Hua C, Sha L, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: a gensini score assessment. J Atherosclerosis Thromb 2014; 21: 1271–1282.

13 Zhu BY, et al. Free triiodothyronine and CAD severity 983

14 Zencirci AE, Zencirci E, Degirmencioglu A, et al. The relationship between gensini score and st-segment resolution in patients with acute st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Kardiol Pol 2014; 72: 494–503.

15 Xu R-X, Li S, Li X-L, et al. High-density lipoprotein subfractions in relation with the severity of coronary artery disease: A gensini score assessment. J Clin Lipidol 2015; 9: 26–34.

16 Huang G, Zhao JL, Du H, et al. Coronary score adds prognostic information for patients with acute coronary syndrome. Circulation 2010; 74: 490–495.

17 Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of syntax and gensini application. Clin res in cardiol 2013; 102: 495–503.

18 Coccoani M, Iervasi G, Pingitore A, et al. Thyroid hormone and coronary artery disease: From clinical correlations to prognostic implications. Clin Cardiol 2009; 32:3 80–385.

19 Cappola AR, Arnold AM, Wulczyn K, et al. Thyroid function in the euthyroid range and adverse outcomes in older adults. J Clin Endocrinol Metab 2015; 100: 1088–1096.

20 Ling Y, Jiang J, Guo M, et al. Thyroid function, prevalent coronary heart disease, and severity of coronary atherosclerosis in patients undergoing coronary angiography. Int J Endocrinol 2015; 2015: 708272.

21 Napoli R, Guardasole V, Zarra E, et al. Impaired endothelial- and nonendothelial-mediated vasodilation in patients with acute or chronic hypothyroidism. Clinical Endocrinol 2010; 72: 107–111.

22 Pearce EN, Wilson PW, Yang Q, et al. Thyroid function and lipid subparticle sizes in patients with short-term hypothyroidism and a population-based cohort. J Clin Endocrinol Metab 2008; 93: 888–894.

23 Worku B, Tortolani AJ, Gulkarov I, et al. Preoperative hypothyroidism is a risk factor for postoperative atrial fibrillation in cardiac surgical patients. J Card Surg 2015; 30: 307–312.

24 Zhang M, Sara JD, Matsuzawa Y, et al. Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention. Eur Heart J 2016

25 Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. Jama 2010; 304: 1365–1374.

26 Ochs N, Auer R, Bauer DC, et al. Meta-analysis: Subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008; 148: 832–845.

27 Kim ES, Shin JA, Shin JY, et al. Association between low serum free thyroxine concentrations and coronary artery calcification in healthy euthyroid subjects. Thyroid 2012; 22: 870–876.

28 Staels B, Van TA, Chan L, et al. Alterations in thyroid status modulate apolipoprotein, hepatic triglyceride lipase, and low density lipoprotein receptor in rats. Endocrinol 1990; 127: 1144–1152.

29 Sundaram V, Hanna AN, Koneru L, et al. Both hypothyroidism and hyperthyroidism enhance low density lipoprotein oxidation. Journal of Clinical Endocrinology & Metabolism 1997; 82: 3421–3424.

30 Obuobie K, Smith J, Evans LM, et al. Increased central arterial stiffness in hypothyroidism. J Clin Endocrinol Metab 2002; 87: 4662–4666.

31 Lekakis J, Papamichael C, Alevizaki M, et al. Flow-mediated, endothelium-dependent vasodilatation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (tsh) values. Thyroid 1997; 7: 411–414.

32 Hyland KA, Arnold AM, Lee JS, et al. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: The cardiovascular health study. J Clin Endocrinol Metab 2013; 98: 533–540.

33 Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. Jama 2006; 295: 1033–1041.

34 Shanmugasundaram M, Rough SJ, Alpert JS. Dyslipidemia in the elderly: Should it be treated? Clin Cardiol 2010; 33: 4–9.

35 Friberg L, Werner S, Eggertsen G, et al. Rapid down-regulation of thyroid hormones in acute myocardial infarction: Is it cardioprotective in patients with angina? Arch Intern Med 2002; 162: 1388–1394.