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Higher Serum Free Thyroxine Levels Are Associated with Coronary Artery Disease

CHAN-HEE JUNG, EUN-JUNG RHEE, HUN-SUB SHIN*, SOOK-KYOUNG JO, JONG-CHUL WON, CHEOL-YOUNG PARK, BYUNG-JIN KIM*, KI-CHUL SUNG*, BUM-SOO KIM*, WON-YOUNG LEE, KI-WON OH, JIN-HO KANG*, SUNG-WOO PARK, MAN-HO LEE* AND SUN-WOO KIM

Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, 110746, South Korea

**Department of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, 110746, South Korea*

Abstract. Thyroid hormone has many effects on the heart and cardiovascular system. Thyrotoxicosis is associated with increased cardiovascular morbidity and mortality, primarily due to heart failure and thromboembolism. However, the relationship between thyroid hormone excess and the cardiac complications of angina pectoris and myocardial infarction remains largely speculative. Moreover, few studies have been reported on the effect of thyroid hormone levels within normal range on coronary artery disease (CAD). Therefore we examined the association of thyroid function with coronary artery diseases in euthyroid angina patients. Total 192 subjects (mean age; 60.8 yrs) were enrolled in which coronary angiograms were performed due to chest pain. We measured free thyroxine (FT_4), thyroid stimulating hormone (TSH), serum lipid levels and high-sensitivity C-reactive protein (hsCRP) levels and analyzed their association with the presence of CAD. Serum FT_4 levels were higher in patients with CAD compared with the patients without CAD (1.31 ± 0.30 vs 1.20 ± 0.23, $p = 0.006$), and high FT_4 level was associated with the presence of multi-vessel disease. Multivariate analysis showed that age (odds ratio (OR) 1.04; 95% confidence interval (CI) 1.01–1.07, $p = 0.007$), hypertension (OR 2.04; 95% CI 1.06–3.90, $p = 0.036$) and FT_4 (OR 4.23; 95% CI 1.12–15.99, $p = 0.033$), were the determinants for CAD. The relative risk (RR) for CAD in highest tertile of FT_4 showed increased risk compared with the lowest tertile (RR 1.98; 95% CI 0.98–3.99, $p<0.001$). Our study showed that FT_4 levels were associated with the presence and the severity of CAD. Also, this study suggests that elevated serum FT_4 levels even within normal range could be a risk factor for CAD. Further studies will be necessary to confirm the relationship of thyroid function and CAD.

Key words: Thyroid function, Free thyroxine, Coronary artery disease

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THYROID hormone has many effects on the heart and cardiovascular system [1, 2]. High prevalence of coronary artery diseases (CAD) in overt hypothyroidism has been reported widely, and recent data provide evidences that subclinical hypothyroidism may be associated with atherosclerosis and myocardial infarction [3–6]. The association of thyroid disease with atherosclerotic cardiovascular disease may partly be explained by the role of thyroid hormone in the regulation of lipid metabolism and in its effect on blood pressure [7–9].

Likewise, hyperthyroid state is associated with an increased risk for cardiovascular events [10–12]. Data from a previously reported cohort study, elderly subjects with lower serum TSH levels showed increased cardiovascular mortality compared with the general population [13]. Recently, Dorr *et al.* reported an association of thyroid function with left ventricular hypertrophy and intima media thickness [14]. They also reported that decreased serum TSH level is an independent risk factor for elevated plasma fibrinogen

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Correspondence to: Eun Jung RHEE, M.D., Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, #108 Pyung-Dong, Jongro-Ku, Seoul 110-746, Korea

levels as a possible explanation for the high cardiovascular mortality among the affected subjects [15].

Although many reports demonstrated an association of thyroid function and atherosclerosis, most studies have been made with patients with thyroid dysfunction. But most subjects at risk for cardiovascular disease in actual clinical situation are euthyroid. Moreover, few studies have been made on the effect of thyroid hormone according to the presence or severity of CAD documented by coronary angiogram in angina patients [16, 17]. Therefore, we aimed to investigate the relationship between thyroid hormone and CAD in euthyroid angina patients.

Materials and Methods

Subjects and Measurements

We retrospectively reviewed 204 patients in which coronary angiograms were performed due to chest pain in the department of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, from November, 2005 to February, 2006. The patients with known thyroid diseases and those taking anti-thyroid medication were excluded from the study (n = 3). In addition, those who were prescribed to amiodarone, which might affect thyroid function, were also excluded (n = 1). Those who had acute infectious diseases, chronic kidney disease (creatinine ≤2.0 mg/dL) and malignant tumor were excluded from the study population (n = 8). Finally, a total of 192 patients (104 males, 88 females, mean age 60.85 ± 11.24 years) were enrolled. We assessed the presence of the diabetes mellitus, hypertension and smoking. The medical history of diabetes mellitus and hypertension was obtained from a previous medical diagnosis or from the medical record for oral hypoglycemic agents, insulin or antihypertensive drugs, and blood pressure ≤140/90 mmHg or fasting blood glucose levels ≤126 mg/dL in previously untreated patients.

Height, weight, systolic and diastolic blood pressures were measured in duplicate and the results were averaged. Weight and height were measured in Kg and cm, respectively, down to two decimal points. The body mass index (BMI) was calculated by dividing the weight (Kg) with the square of height (m^2).

After 12 hours of fasting, blood sampling was done. Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were measured from the samples and hexokinase method was used to measure blood glucose levels and enzymatic colorimetric test was used to measure the total cholesterol and triglyceride levels. Selective inhibition method was used to measure the serum level of HDL-C and the homogeneous enzymatic colorimetric test was used to measure the serum level of LDL-C (Bayer Health Care, ADVIA 1650, USA). Lipoprotein (a) and high-sensitivity C-reactive protein (hs-CRP) were measured by immunonephelometry (Dade Behring Co., Marburg, Germany) and apolipoprotein A (ApoA) and apolipoprotein B (ApoB) by rate nephelometry (Beckman Instruments, Fullerton. CA, USA). The intra-assay coefficient of variation (CV) and inter-assay CV for hs-CRP was 2.3–4.4% and 2.1–5.7% and intra-assay CV and inter-assay for Lp(a) was 1.8–4.1% and 2.8–5.3%. The intra-assay and inter-assay CV for Apo A are 2.2% and 5.7% and for Apo B are 1.9% and 2.4%.

Serum FT_4 and TSH levels were measured by immunoradiometric assay (IRMA) using a commercial kit (RIA-gnost® hTSH, FT_4, Schering-Cis Bio International, Gif-sur-Yvette, France) and their normal ranges were 0.7–2.0 ng/dL (FT_4) and 0.25–5 μIU/ml (TSH). The intra-assay CV and inter-assay CV for FT_4 were 2.3–4.4% and 2.1–5.7%. We divided the patients into three group according to the FT_4 tertile.

Coronary artery angiogram was performed in all patients. Significant stenosis was defined as the internal diameter decreased by more than 50%. Patients were grouped according to the number of significantly stenotic vessels into normal, 1-vessel, 2-vessel and 3-vessel diseased groups.

Statistical method

Statistical analysis was performed using the SPSS for windows version 11.0. The statistic results were presented as mean ± standard deviation (SD) or median and ranges. The comparison of the mean values between subjects with and without CAD, was analyzed by Student's *t*-test. The chi-square test was used for categorical variables. Because FT_4 and TSH didn't fit for normal distribution, log transformations were applied to the values. After log transformation of FT_4, Kruscal-Wallis test was used to analyze differences of FT_4 levels according to the number of vessels with

stenosis. Serum FT_4 levels were divided into tertiles and cluster analysis was used to evaluate the relative risk for each tertiles of FT_4 for its association with CAD. Multiple logistic regression analysis was done to assess the determinants for CAD. The relationship of the number of stenosis with FT_4 level was analyzed with chi-square test and linear-by linear association analysis. A 95% confidence interval (CI) was used for each risk. $P<0.05$ was considered as statistically significant.

Results

The general characteristics of the subjects

The general characteristics of the study subjects are presented in Table 1. In 55 cases (52.9%) out of total 104 cases of males and 36 cases (40.9%) out of 88 female cases, significant stenosis was detected by coronary artery angiogram, which didn't show significant difference in prevalence of coronary artery stenosis ($p = 0.098$).

The comparisons of the variables according to the CAD severity

Coronary angiographic findings showed normal findings in 101, one-vessel disease in 51, two-vessel disease in 25, and triple-vessel disease in 15 patients. Subjects with coronary artery disease were significantly older than those with normal coronary artery (63.6 ± 9.8 vs 58.4 ± 11.9, $p = 0.001$), and fasting blood glucose levels were significantly higher in subjects with coronary artery stenosis than those with normal coronary artery (122.5 ± 50.6 vs 105.6 ± 24.7, $p = 0.005$). FT_4 levels were significantly higher in subjects with coronary artery stenosis than those with normal coronary artery (1.23 vs 1.18, $p = 0.006$).

In regard to TSH, TC, LDL-C, TG, BMI, HDL-C, hs-CRP, Lp(a), apoA and apoB, any significant differences were not detected between the two groups. In the entire study population, patients with diabetes mellitus (DM) were 46 cases out of 192 cases (24%). Among the subjects with DM, 31 subjects showed significant coronary artery stenosis and the remaining 15 subjects showed normal coronary angiogram findings, and a statistically significant difference was observed between the two groups (34.1% vs 14.9%, $p = 0.002$). In the entire study population, patients

Table 1. General characteristics of CAD cases and control patients

	Total	CAD	Control	P
Age (years)	60.85 ± 11.24	63.63 ± 9.75	58.35 ± 11.94	0.001
Gender, M/F	104/88	55/36	49/52	0.065
BMI (kg/m^2)	25.46 ± 3.23	25.15 ± 3.09	25.69 ± 3.33	0.324
DM	46 (24.0%)	31 (16.1%)	15 (7.8%)	0.002
HTN	93 (48.4%)	55 (28.6%)	38 (19.8%)	0.001
Smoking	43 (22.8%)	20 (10.6%)	23 (12.2%)	0.535
FPG (mg/dL)	113.59 ± 39.98	122.46 ± 50.61	105.60 ± 24.71	0.005
T-chol (mg/dL)	168.34 ± 40.52	167.14 ± 40.01	169.43 ± 41.15	0.698
TG (mg/dL)	133.88 ± 81.92	141.77 ± 79.14	126.49 ± 84.19	0.209
HDL-chol (mg/dL)	43.53 ± 10.49	42.18 ± 10.42	44.83 ± 10.44	0.091
LDL-chol (mg/dL)	98.59 ± 33.42	97.97 ± 33.44	99.14 ± 33.56	0.811
FreeT_4	1.21 (1.10~1.34)	1.23 (1.13~1.35)	1.18 (1.09~1.30)	0.006
TSH	1.65 (1.09~2.39)	1.59 (1.04~2.37)	1.76 (1.16~2.47)	0.333
HsCRP	0.79 ± 1.98	0.84 ± 2.05	0.73 ± 1.91	0.747
Apo A	126.16 ± 22.02	123.67 ± 23.01	127.94 ± 21.30	0.335
Apo B	93.77 ± 26.88	94.14 ± 23.35	93.50 ± 29.33	0.904
Atrial fibrillation	7 (3.6%)	2 (1.04%)	5 (2.6%)	0.310

Data except FT_4 and TSH are presented as means ± SD. FT_4 and TSH values are expressed by median and range. BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; FPG, fasting plasma glucose; T-chol, total cholesterol; TG, triglyceride; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; hsCRP, high-sensitivity c-reactive protein; Apo A, apolipoprotein A; Apo B, apolipoprotein B

Table 2. Relationship between the levels of thyroid hormone and biochemical variables

	LnFreeT$_4$		LnTSH	
	r	*p*	*r*	*p*
Age (years)	0.049	0.501	0.121	0.094
BMI (kg/m^2)	–0.169*	0.043	0.197*	0.018
FPG (mg/dL)	0.041	0.568	0.008	0.913
T-chol (mg/dL)	0.032	0.660	0.173*	0.017
TG (mg/dL)	–0.059	0.429	0.080	0.284
HDL-chol (mg/dL)	0.031	0.675	0.086	0.252
LDL-chol (mg/dL)	0.087	0.234	0.134	0.065
hsCRP	0.195*	0.019	–0.066	0.434
Apo A	–0.036	0.716	0.012	0.901
Apo B	–0.011	0.912	0.239*	0.015
FreeT$_4$	–	–	–0.256*	<0.001
TSH	–0.256*	<0.001	–	–

BMI, body mass index; FPG, fasting plasma glucose; T-chol, total cholesterol; TG, triglyceride; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; hsCRP, high-sensitivity c-reactive protein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; Ln, log transformed

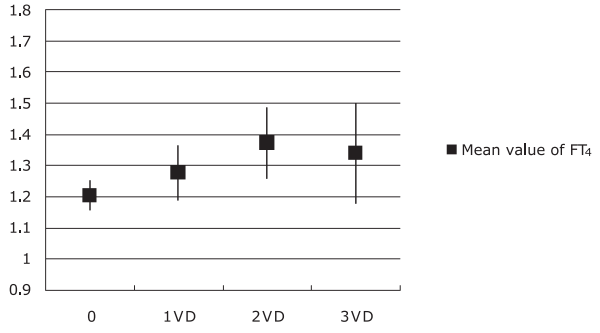

Fig. 1. Mean concentration of FT$_4$ according to the severity of CAD

with hypertension were 93 cases out of 192 cases (48.4%), among them, 55 subjects showed significant coronary artery stenosis and 38 subjects showed normal coronary artery angiogram findings, and a statistically significant difference was observed between the two groups (60.4% vs 37.6%, $p = 0.001$).

The patients were divided into four groups according to the number of vessels with stenosis. The mean concentrations of FT$_4$ showed steadily increasing tendency (1.20, 1.28, 1.37 and 1.34, $p = 0.042$) according to the severity of CAD (Fig. 1).

We found that 7 patients showed atrial fibrillation (Af) on electrocardiogram (ECG) and among the subjects with Af, only two patients had CAD. Frequency of Af was not significantly different between the two groups ($p = 0.310$).

Table 3. Multivariate logistic regression for the risk of the coronary artery disease

	Odds Ratio	95% confidence interval	P value
Age	1.04	1.012~1.077	0.007
HTN	2.04	1.064~3.897	0.032
DM	2.05	0.955~4.397	0.065
Smoking	1.45	0.664~3.183	0.349
FT$_4$	4.23	1.121~15.985	0.033
TSH	0.91	0.737~1.132	0.408

The relation of the thyroid function and biochemical parameters

Significant negative correlations were identified between serum FT$_4$ levels, and BMI and TSH (r = –0.169, $p = 0.043$, r = –0.256; $p < 0.001$). FT$_4$ levels showed significantly positive correlation with serum hs-CRP levels (r = 0.195, $p = 0.019$)(Table 2). TSH levels showed significantly positive correlation with BMI and Apo B levels (r = 0.197, $p = 0.018$, r = 0.239; $p = 0.015$) (Table 2).

The relation of the thyroid function with the presence of coronary artery diseases

The multivariate logistic regression analysis revealed an adjusted OR of 4.2 (95% CI, 1.121–15.985; $p = 0.033$) for the occurrence of CAD in the presence of elevated serum FT$_4$ level. Significant additional risk factors for the presence of CAD, were age (OR 1.04;

Table 4. OR (95% CI) for the risk of the coronary artery disease in tertiles of free thyroxine

	Odds ratio	95% confidence interval	P value
FT_4 1st tertile	1	—	—
FT_4 2nd tertile	1.64	0.811~3.315	0.168
FT_4 3rd tertile	1.98	0.983~3.985	0.056

Table 5. The frequency (number) of multi-vessel disease according to the tertiles of free thyroxine

	FT_4 1st tertile	FT_4 2nd tertile	FT_4 3rd tertile
Normal	41	31	29
One vessel disease	17	18	16
Two vessel disease	4	9	12
Three vessel disease	4	4	7

95% CI 1.012–1.077; $p = 0.007$) and hypertension (OR 2.04; 95% CI 1.064–3.897; $p = 0.032$). The inverse correlation observed between serum TSH level and the presence of CAD failed to reach statistical significance (OR 0.91; 95% CI 0.738–1.131; $p = 0.406$) (Table 3). Other risk factors such as DM and smoking status were not significantly related to the presence of CAD.

We classified the patients according to the tertiles of their FT_4 levels. The cutoff values for the tertile groups were as follows: 1) ≤1.13; 2) 1.14–1.28; 3) 1.29–2.0 ng/dL. The ORs for CAD according to the tertiles of serum FT_4 levels are shown in Table 4. The relative risks of CAD in the highest quartile of the FT_4 levels were 1.98 (95% CI, 0.983–3.985) as compared to the subjects in the lowest tertile of the FT_4 levels, but showed statistically borderline significant ($p < 0.001$).

62.1% of the subjects in the lowest tertile of serum FT_4 level (≤1.13 ng/dL) did not show any significant coronary artery stenosis, and 25.8% of the subjects had one-vessel disease and 12.1% had multi-vessel disease (≥2 two-vessel disease). Among the subjects in the second tertile group (1.14≤FT_4 level≤1.28 ng/dL), 50% didn't have any significant stenosis, 29.0% had one-vessel disease and 21% had multi-vessel disease, and for the subjects in the highest tertile (≥1.29 ng/dL), the frequencies were 45.3%, 25% and 29.7%, respectively (Table 5, Fig. 2).

Regarding the frequency of multi-vessel disease according to the level of FT_4, the subjects in the highest tertile FT_4 showed the highest frequency for the multi-vessel disease ($p = 0.014$).

Discussion

In this study, we found that mean FT_4 levels were higher in subjects with CAD compared with the subjects without CAD. Furthermore, high serum FT_4 level was associated with the presence and with the increased risk for CAD, even in patients with normal thyroid function.

The hypothesis that the variation of thyroid hormone concentrations even within the statistically normal

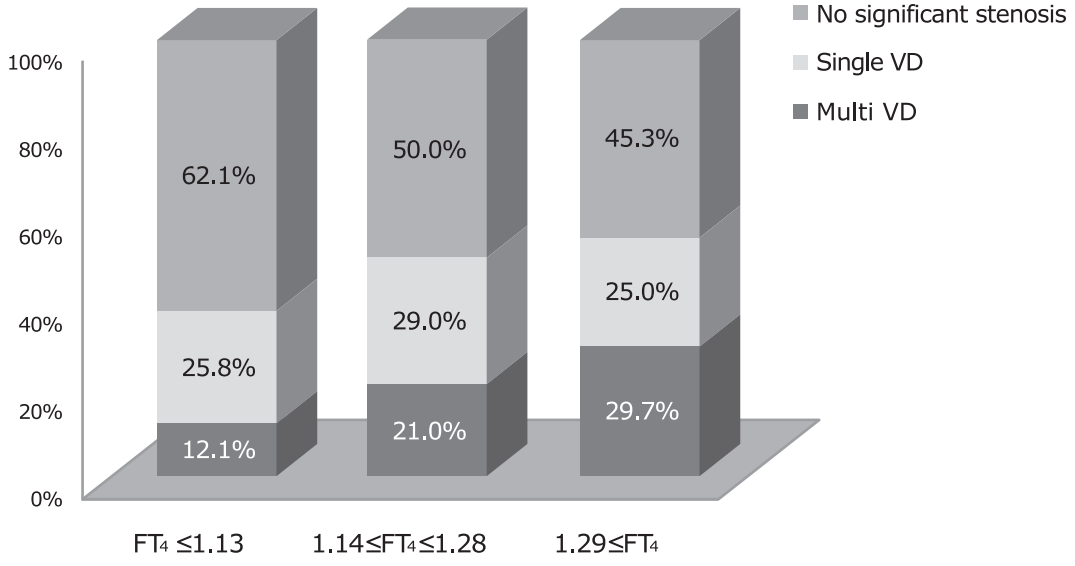

Fig. 2. The frequency (%) of multi-vessel disease according to the tertiles of free thyroxine

range, might influence the development and the outcome of CAD, is not entirely new, although the results failed to show consistent results. Our study findings are in contrast to the findings reported by Auer *et al.* and Yun *et al.* [16, 17]. Auer *et al.* [16] studied a total of 100 consecutive men and women who underwent coronary artery angiogram [16]. They reported that higher levels of serum FT_4 concentrations were associated with the decreased severity of coronary atherosclerosis and higher levels of serum thyrotropin levels were associated with increased severity of coronary atherosclerosis. Very recently, Yun *et al.* [17] studied 344 patients with angina who underwent elective coronary artery angiogram [17]. They reported that although it was not an independent predictor for CAD in patients with normal thyroid function, high serum TSH level was associated with multi-vessel disease. In contrast, in the study by Peters *et al.* [18], they examined thyroid function in a total of 1049 patients, immediately on emergency medical admission. They concluded that an elevation of serum free T_3 levels at the time of hospital admission was associated with a 2.6-fold greater likelihood of the presence of a coronary event. Moreover, an initially elevated free T_3 level is associated with a 3-fold higher risk of developing a subsequent coronary event during the next 3 years. Our present study revealed that elevated serum FT_4 levels was associated with increased OR of 4.4 for the presence of CAD after adjustment for other risk factors. Furthermore, the presence of hypertension was shown to be a risk factor for the CAD with an OR of 1.99, respectively. But present study did not find any significant differences in the levels of serum TSH, TC, LDL-C, TG, BMI, HDL-C, hsCRP, Lp(a), apo A and apo B with respect to the presence of CAD.

Several mechanisms explain the causal relations between thyroid hormone excess and cardiovascular disease including Af, cardiovascular hypertrophy and inflammation [7, 14, 15, 19–22]. Likewise, the hyperthyroid state is associated with an increased risk of thromboembolic events. By Dorr *et al.* demonstrated an association of thyroid hormone excess with left ventricular hypertrophy, intima-media thickness, fibrinolytic activity and coagulation activity [14, 15]. In this study, we found that only 7 patients had Af on ECG and two subjects among them had CAD. It is unlikely that relationship between elevated thyroid hormone and CAD was mediated by Af in our study.

The relationship between thyroid hormone excess and the cardiac complications of angina pectoris and myocardial infarction remains largely speculative yet [16, 18, 23]. Very recently, Volzke *et al.* [24] systematically reviewed the studies on the relation between thyroid dysfunction and cardiovascular mortality and all-cause mortality. Most studies on the relationship of both subclinical and overt hyperthyroidism with mortality, are limited by not considering the major confounders and the selection bias. They conclude that there is insufficient data to draw final conclusions on the causal relationship between thyroid dysfunction and cardiovascular and all-cause mortality.

The reason for the discrepancies between the previously reported studies on the relationships of thyroid function with cardiovascular disease is not clear, but there are a few possible explanations. First, considering the narrow reference range of normal serum thyroxine levels, the numbers of subjects enrolled in the previous studies were too small to detect a subtle change in the thyroid function in relation with CAD. In fact, the numbers of the subjects enrolled were in the range of 100–300, except for the study by Peters *et al.* [18]. Second, study subjects were too heterogenous. A few of the previously reported studies [18, 19] and our study included angina and acute myocardial infarction (MI) subjects but the study by Yun *et al.* [19] included only subjects with angina pectoris, excluding acute MI [16–18]. It is possible that different relationships between thyroid function and acute MI or angina pectoris could exist. In the study by Friberg *et al.* [25], thyroid function, especially triiodothyronine (T_3) was rapidly down-regulated in the subjects with acute MI. This could be explained by the protective mechanism of the thyroid function axis to down-regulate the energy demand and protect the ischemic heart from being exposed to too much loading. However, their results showed that patients with a history of angina pectoris had higher serum FT_4 levels and the highest serum levels of FT_4 were found in patients with unstable angina pectoris [25]. There is, at least in the euthyroid range, a discrepancy between the effects that thyroid hormone has on acute MI or angina. Therefore, to clarify the differences, more specifically designed studies are required.

Our study has several limitations. First, since it is a cross-sectional study, the causality cannot be established between the thyroid function and CAD; it can only suggest an association. Well designed prospective research will be necessary to clarify the role of

thyroid hormone within normal range in the development of CAD. Second, we could not assess the complete thyroid functional status, since we didn't measure serum total T_3 levels, the active form of thyroid hormones in the tissue level. T_3 has been known to have profound effects on the cardiovascular system [26, 27]. The lack of serum T_3 measurement in our study, might potentially have potentially biased the study results. However, as FT_4 and TSH are the main forms measured in the clinical setting to assess thyroid function, it might not have biased that much. Third, as mentioned above, the heterogeneity of the study subjects with respect to angina and acute MI could be considered as a limitation. Fourth, the power of the study could have been stronger if the number of the study subjects were larger.

In conclusion, this study suggests that even within normal range, a small increase of the serum FT_4 level is associated with the presence and the severity of CAD in Korean population. Further studies are warranted in the future, with larger study population in various ethnic groups to clarify the discrepancies.

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