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The Association between Thyroid Hormone Levels, and Coronary Slow Flow Phenomenon and Coronary Artery Disease in Euthyroid Patients

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ABSTRACT

Background: Thyroid hormones are well-known for their various effects on the cardiovascular system. However, contradictory results have been obtained regarding the association between thyroid hormones within the Reference Range (RR) and Coronary Artery Disease (CAD). Moreover, scarce evidence is available regarding the association between thyroid hormones and Coronary Slow Flow Phenomenon (CSFP).

Objective: This study aimed to investigate the relationship between thyroid hormones in the RR, and CSFP and CAD.

Methods: A total of 1033 euthyroid patients who underwent coronary angiography were enrolled and divided into four groups based on their coronary angiography and Thrombolysis in Myocardial Infarction (TIMI) flow grade: Normal Coronary Artery (NCA), CSFP, Non-obstructive CAD (N-CAD), and Obstructive CAD (O-CAD). Multivariate multinomial regression analysis was conducted to assess the association between thyroid hormone levels and CSFP as well as CAD. Thereafter, the prediction accuracy of Free Triiodothyronine (FT3) levels for the presence of CSFP and CAD was evaluated by the Receiver Operating Characteristic (ROC) curve analysis.

Results: FT3 serum level was significantly lower in the CSFP and both CAD groups compared to the NCA group ($P < 0.001$). FT3 level was inversely correlated to the presence of CSFP and CAD (both N-CAD and O-CAD) only in young females. Moreover, TSH was found to be an independent predictor of O-CAD in young individuals, regardless of their gender. Furthermore, FT3 levels ≤ 2.56 pg/mL predicted the presence of CSFP (78% sensitivity and 62% specificity) and FT3 levels ≤ 2.38 pg/mL predicted the presence of CAD (64% sensitivity and 75% specificity) in young females.

Conclusion: FT3 level was negatively associated with CSFP and CAD in young females. In addition, high levels of TSH were associated with O-CAD only in young patients. Further studies are required to shed more light upon the regarded associations.

1. Background

The functions of the cardiovascular system and the thyroid hormones are closely connected (1). A body of evidence suggested an increase in the risk of cardiovascular disorders in the patients affected by subclinical thyrotoxicosis or subclinical hypothyroidism (2, 3). While most studies have focused on the correlation between thyroid hormones and the cardiovascular system in the populations with impaired thyroid function, several recent studies have delved into the correlation between thyroid hormone levels in the Reference Range (RR) and cardiovascular diseases.

Coronary Slow Flow Phenomenon (CSFP) is a clinically significant angiographic finding defined by delayed opacification of vessels in a normal coronary angiogram (4). Although CSFP is a well-known occurrence to interventional cardiologists pertaining direct clinical application, information concerning the etiopathogenesis of CSFP remains vague. Furthermore, a limited number

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of studies have focused on the association between thyroid hormones and CSFP (5).

Up to now, contradictory findings have been obtained regarding the association between thyroid hormones in RR and the presence of Coronary Artery Disease (CAD). Although a few studies have reported a correlation between free thyroxine (FT4) level and CAD (6), others have indicated the respected association with free triiodothyronine (FT3) level (7, 8). Moreover, Yang et al. (9) concluded that higher Thyrotropin (TSH) levels were associated with the presence of CAD in the individuals aged ≤ 65 years. However, a considerable number of studies have failed to find any associations between TSH and the presence of CAD (8, 10).

2. Objectives

This study aims to determine the correlation between thyroid hormones in the RR and CSFP as well as CAD among the euthyroid patients having undergone coronary angiography.

3. Patients and Methods

3.1. Study Population

A total of 1033 euthyroid patients were enrolled into this study from October 2017 to May 2019. The study design was approved by the Institutional Ethics Committee of Shahid Rajaie Cardiovascular Medical and Research Center. Written informed consents were also obtained from all enrolled patients. Patients with a positive history of percutaneous Coronary Angiography (CAG) due to angina-like chest pain and normal thyroid hormone values at the time of intervention were eligible for enrollment. The normal ranges of FT3, FT4, and TSH were 1.71 - 3.71 pg/mL, 0.7 - 1.48 ng/dL, and 0.35 - 4.99 mU/L, respectively. Patients with a history of thyroid impairment, acute myocardial infarction, coronary artery revascularization, heart failure, ectatic epicardial coronary arteries, severe hepatic or renal dysfunction, systemic inflammatory diseases, cancer, and any other chronic disease as well as those who were under treatment with thyroid regulating medications were excluded.

3.2. Data Collection

Information regarding the previous treatments and risk factors for CAD (smoking, hypertension, diabetes mellitus, dyslipidemia, and family history of CAD) was obtained from the patients' medical records. Additionally, anthropometric measurements were made with bare feet and lightweight clothing. Besides, Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Patients with BMI ≥ 30 kg/m2 were considered to be obese.

A fasting (12-14 hours) blood sample was obtained from all participants between 6:00 and 8:00 A.M. before percutaneous CAG. Creatinine and lipid profile including Total Cholesterol (TC), Triglyceride (TG), High Density Lipoprotein Cholesterol (HDL-C), and Low Density Lipoprotein Cholesterol (LDL-C) were assayed by the relevant kits (Pars Azmoun, Tehran, Iran) using an automatic biochemistry analyzer (Hitachi 917, Japan). Serum thyroid hormone levels were also determined via chemiluminescence immunoassay using Abbott diagnostic kits on an Abbott ARCHITECTTM i2000 SR immunoassay analyzer (Chicago, Illinois, USA).

All patients were assessed through both standard left and right coronary angiographies carried out using a Judkins catheter via the femoral or radial approach. Right and left coronary angiographies were performed in multiple projections using standard techniques for the evaluation of coronary artery stenosis and Thrombolysis in Myocardial Infarction (TIMI) flow grade.

3.3. Definitions

Based on their coronary artery angiography reports and TIMI flow grades, the participants were classified into four groups as follows:

1. Normal Coronary Artery (NCA): no coronary artery stenosis and normal TIMI flow grade 4.

2. CSFP: CSFP was considered only in patients with angiographically normal (smooth) coronary arteries and was defined as TIMI-2 flow grade (i.e., requiring ≥ 3 beats to visualize the distal vasculature of at least one of the three major epicardial coronary vessels) (11-13).

3. Non-obstructive CAD (N-CAD): N-CAD was defined as a coronary artery stenosis of 20%-49% in the left main coronary artery or a stenosis of 20%-69% in any other epicardial coronary artery as recorded by the clinician in the catheterization report (14, 15).

4. Obstructive CAD (O-CAD): O-CAD was defined as any stenosis ≥ 50% in the left main coronary artery or ≥ 70% stenosis in any other coronary artery (14).

3.4. Statistical Analysis

Baseline data have been expressed as mean ± SD (for normally distributed data) or median with interquartile range (for abnormally distributed data) for continuous variables and as percentages for categorical variables. In order to compare the study subgroups regarding different variables, one-way ANOVA or Kruskal-Wallis test (for abnormally distributed data) were employed for continuous variables and chi-square test for categorical variables. In order to investigate the correlation between FT3 and TSH levels and the presence of CSFP and CAD, univariate and multivariate multinomial logistic regression analyses were conducted. The same analyses were performed after categorization based on gender and age groups. Multivariate multinomial logistic regression analyses were performed after adjusting for potential confounders, including age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, family history of CAD, obesity, and creatinine. Based on a previous meta-analysis, the age cut-off for stratification was determined as 65 years (16). The cut-off value of FT3 for predicting the presence of CSFP and CAD with the corresponding sensitivity and specificity was estimated through the Receiver Operating Characteristic (ROC) curve analysis. All statistical analyses were performed using the SPSS 20 software (SPSS, Chicago, IL, USA) and MedCalc 15.8 software (MedCalc Software, Ostend, Belgium). Two-tailed P-values < 0.05 were considered to be statistically significant.

4. Results

The patients' baseline characteristics have been summarized in Table 1. The mean age of the patients was 59.4 ± 10.6 years and 67% of the participants aged ≤ 65 years. Additionally, the majority of the patients (58.7%) were female. The prevalence of dyslipidemia, hypertension, and diabetes mellitus was 75.9%, 45.3%, and 39.7%, respectively. Besides, 22.6% of the participants had a positive family history of CAD and 19.9% of them were smokers. The mean serum levels of FT3 and TSH were 2.3 ± 0.4 pg/mL and 1.8 ± 0.9 mU/mL, respectively.

The baseline characteristics of each group of patients have been presented in Table 2. Among the 1033 patients, the frequency of NCA, CSFP, N-CAD, and O-CAD was 219 (21.3%), 151 (14.7%), 236 (22.9%), and 424 (41.2%), respectively. The patients in the NCA group had the lowest mean age (55 ± 11 years), while those in the O-CAD group had the highest mean age (61 ± 9 years). Moreover, the prevalence of diabetes mellitus, hypertension, and dyslipidemia was higher among the O-CAD patients. Indeed, the mean FT3 serum level was significantly lower in the CSFP (2.32 ± 0.3 pg/mL), N-CAD (2.29 ± 0.3 pg/mL), and O-CAD (2.21 ± 0.4 pg/mL) groups compared to the NCA group (2.55 ± 0.4 pg/mL) (P < 0.001). The mean serum TSH level was also higher in the O-CAD group compared to the NCA group (1.5 ± 0.9 vs. 2.0 ± 1.0 mU/mL, P < 0.001).

The mean FT3 serum values for both sexes have been illustrated in Figure 1. Among females, the mean serum FT3 level was significantly lower in the CSFP (2.40 ± 0.3 pg/mL), N-CAD (2.37 ± 0.4 pg/mL), and O-CAD (2.25 ± 0.3 pg/mL) groups compared to the NCA group (2.6 ± 0.4 pg/mL) (P < 0.001). Additionally, the mean FT3 serum level was significantly lower among the O-CAD individuals compared to the N-CAD group (2.37 ± 0.4 vs. 2.25 ± 0.3 pg/mL, P = 0.038). Among the male participants, no significant difference was observed between the NCA group and CSFP (2.23 ± 0.3 pg/mL) and N-CAD (2.37 ± 0.4 pg/mL) groups regarding the FT3 serum level. However, the mean FT3

Table 1. Baseline Characteristics of The 1033 Euthyroid Study Participants

Variables	Number (%) or Mean (SD) or Mean (Interquartile Range 25 - 75)
Age	59.4±10.6
Age ≤ 65 years	692 (67.0)
Age > 65 years	341 (33.0)
Female	606 (58.7)
Obesity [a]	460 (44.5)
Diabetes mellitus	413 (39.7)
Hypertension	468 (45.3)
Smoking	206 (19.9)
Dyslipidemia	770 (75.9)
Family history of CAD	235 (22.6)
Total cholesterol, mg/dL	148.6 ± 38.3
HDL-cholesterol, mg/dL	39.3 ± 8.9
LDL-cholesterol, mg/dL	84.3 ± 29.7
Triglyceride, mg/dL	140 (89-170)
Ejection fraction	47.1 ± 8.4
Creatinine, mg/dL	0.93 ± 0.43
FT3, pg/mL	2.3 ± 0.4
TSH, mU/mL	1.8 ± 0.9
FT4, ng/dL	1.1 ± 0.1

Abbreviations: SD, standard deviation; obesity [a], body mass index ≥ 30 kg/m2; CAD, coronary artery disease; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; FT3, free triiodothyronine; TSH, thyroid stimulating hormone; FT4, free thyroxine.

Table 2. The Characteristics of Euthyroid Patients Regarding Coronary Angiography

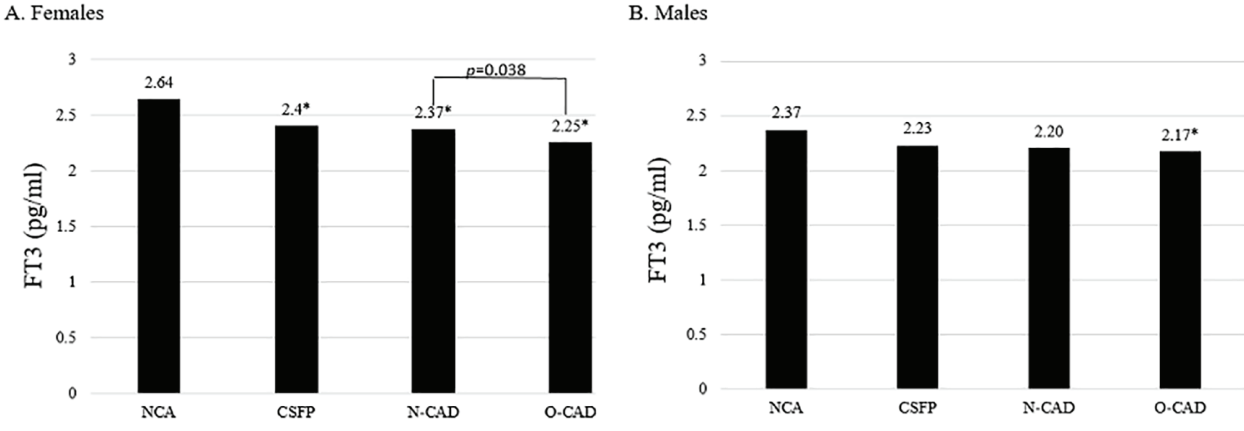
Variables	NCA, n = 219	CSFP, n = 151	N-CAD, n = 236	O-CAD, n = 424	P value
Age	55 ± 10	59 ± 10	58 ± 10	61 ± 9	< 0.001
Age groups					< 0.001
Age ≤ 65 years	180 (82.2)	104 (68.9)	159 (67.4)	248 (58.5)	-
Age > 65 years	39 (17.8)	47 (31.1)	77 (32.6)	176 (41.5)	-
Female	146 (77)	83 (55)	145 (61)	229 (50)	< 0.001
Obesity [a]	86 (39.3)	68 (45.0)	105 (44.5)	201 (47.4)	0.275
Diabetes mellitus	40 (18.3)	54 (35.8)	100 (42.4)	218 (51.4)	< 0.001
Hypertension	45 (20.5)	47 (31.1)	121 (51.3)	254 (59.9)	< 0.001
Smoking	22 (10.0)	23 (14.6)	50 (21.2)	112 (26.4)	< 0.001
Dyslipidemia	101 (47.36)	112 (77.8)	189 (80.4.)	365 (86.7)	< 0.001
Family history of CAD	40 (18.3)	29 (19.2)	55 (23.3)	111 (26.2)	0.092
Total cholesterol, mg/dL	142 ± 41	146 ± 39	149 ± 36	151 ± 38	0.041
HDL-cholesterol, mg/dL	41.9 ± 8.8	39.1 ± 9.8	39.4 ± 8.7	38.4 ± 8.2	< 0.001
LDL-cholesterol, mg/dL	79.7 ± 26	82.6 ± 30	85.5 ± 31	89.2 ± 31	0.002
Triglyceride, mg/dL	134 (90 - 156)	137 (87 - 113)	143 (89 - 184)	147 (99 - 174)	0.008
Ejection fraction	48.5 ± 7.2	48.3 ± 7.6	46.4 ± 8.8	46.0 ± 8.6	0.043
Creatinine, mg/dL	0.89 ± 0.67	0.89 ± 0.27	0.95 ± 0.50	0.97 ± 0.49	0.001
FT3, pg/mL	2.55 ± 0.4	2.32 ± 0.3*	2.29 ± 0.3*	2.21 ± 0.4*	< 0.001
TSH, mU/mL	1.52 ± 0.9	1.72 ± 0.7	1.74 ± 1.0	2.0 ± 1.0*	< 0.001
FT4, ng/dL	1.15 ± 0.1	1.13 ± 0.15	1.12 ± 0.16	1.11 ± 0.16	0.014

Abbreviations: NCA, normal coronary artery; CSFP, coronary slow flow phenomenon; N-CAD, non-obstructive coronary artery disease; O-CAD, obstructive coronary artery disease; Obesity [a], body mass index ≥ 30 kg/m2; CAD, coronary artery disease; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; FT3, free triiodothyronine; TSH, thyroid stimulating hormone; FT4, free thyroxine.

Data have been presented as mean ± SD, mean (interquartile range), or number (%).

* Comparison to the NCA group, P < 0.05.

Figure 1. FT3 Levels in the Patients according to Coronary Angiography. A: Females, B: Males



Abbreviations: NCA, normal coronary artery; CSFP, coronary slow flow phenomenon; N-CAD, non-obstructive CAD; O-CAD, obstructive CAD; FT3, free triiodothyronine.
*Comparison to the NCA group, P < 0.05.

serum level was significantly lower in the O-CAD group compared to the NCA group (2.37 ± 0.4 vs. 2.17 ± 0.4 pg/mL, P = 0.015).

The associations between FT3 and TSH serum levels and the presence of CSFP and CAD have been presented in Tables 3 and 4, respectively. Accordingly, FT3 levels exhibited an inverse association with the presence of CSFP only among females (OR = 0.286 (0.0129 - 0.630), P = 0.002) and young patients (OR = 0.350 (0.176 - 0.698), P = 0.003). The results revealed that TSH was not a predictor for the presence of CSFP in either of the subgroups or the entirety of the study population (Table 3). The association between CAD (N-CAD and O-CAD) and FT3 level was only significant among females (P = 0.002 and P = 0.35) and young patients (P < 0.001 for both groups). Moreover, TSH was directly associated with the presence of O-CAD only in young patients, independent of gender (P < 0.001) (Table 4). Further analysis showed that in comparison to the N-CAD group, low levels of FT3 were the predictor of O-CAD (OR = 0.361, P = 0.015) only in young females (data not shown).

Based on the results of the ROC curve analysis, FT3 levels ≤ 2.56 pg/mL predicted the presence of CSFP with 78% sensitivity and 62% specificity in young females (95% CI (0.655 - 0.795), P < 0.001, Youden index J = 0.393). Moreover, FT3 levels ≤ 2.38 pg/mL predicted the presence of CAD with 64% sensitivity and 75% specificity (95% CI (0.739 - 0.829), P < 0.001, Youden index J = 0.3891) in young females (Figure 2).

Table 3. Multivariate Logistic Regression Analysis of the Correlation Between FT3 and TSH Levels and the Presence of CSFP in the Total Population and Each Study Subgroup

	FT3		TSH	
	Adjusted* OR (95% CI)	P value	Adjusted* OR (95% CI)	P value
Total population	0.415 (0.235 - 0.733)	0.002	1.154 (0.899 - 1.481)	0.260
Male	0.841 (0.342 - 2.071)	0.707	1.117 (0.763 - 1.636)	0.570
Female	0.286 (0.129 - 0.630)	0.002	1.159 (0.825 - 1.628)	0.395
Young age[a]	0.350 (0.176 - 0.698)	0.003	1.165 (0.871 - 1.557)	0.304
Old age	0.808 (0.222 - 2.945)	0.747	1.014 (0.587 - 1.752)	0.959

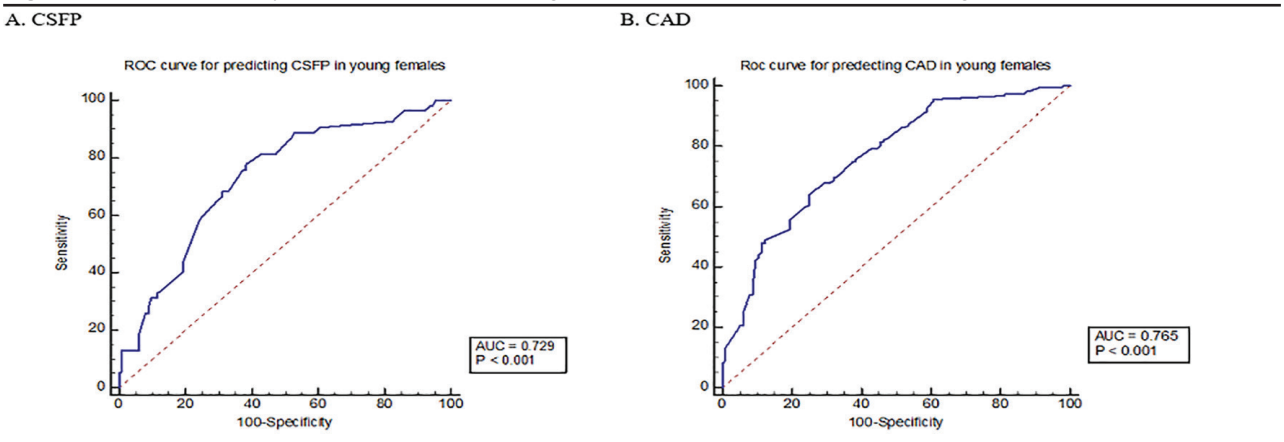
Abbreviations: CSFP, coronary slow flow phenomenon; FT3, free triiodothyronine; TSH, thyroid stimulating hormone; Young age[a], 65 years or younger.
*Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, family history of CAD, obesity, and creatinine.

Table 4. Multivariate Logistic Regression Analysis of the Correlation Between FT3 and TSH Levels and the Presence of CAD in the Total Population and Each Study Subgroup

	N-CAD				O-CAD			
	FT3		TSH		FT3		TSH	
	Adjusted* OR (95% CI)	P value	Adjusted* OR (95% CI)	P value	Adjusted* OR (95% CI)	P value	Adjusted* OR (95% CI)	P value
Total population	0.396 (0.225 - 0.635)	< 0.001	1.139 (0.905 - 1.433)	0.268	0.262 (0.158 - 0.435)	< 0.001	1.483 (1.196 - 1.839)	< 0.001
Male	0.544 (0.236 - 1.256)	0.154	1.211 (0.833 - 1.759)	0.316	0.682 (0.308 - 1.510)	0.682	1.604 (1.136 - 2.264)	0.007
Female	0.343 (0.173 - 0.679)	0.002	1.098 (0.810 - 1.488)	0.548	0.130 (0.064 - 0.264)	< 0.001	1.364 (1.022 - 1.820)	0.035
Young age [a]	0.324 (0.175 - 0.599)	< 0.001	1.152 (0.884 - 1.503)	0.296	0.182 (0.098 - 0.341)	< 0.001	1.630 (1.267 - 2.097)	< 0.001
Old age	0.716 (0.204 - 2.515)	0.602	1.039 (0.608 - 1.774)	0.890	0.756 (0.229 - 2.498)	0.646	1.088 (0.661 - 1.793)	0.740

Abbreviations: N-CAD, non-obstructive coronary artery disease; O-CAD, obstructive coronary artery disease; FT3, free triiodothyronine; TSH, thyroid stimulating hormone; Young age[a], 65 years or younger.
* Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, family history of CAD, obesity, and creatinine.

Figure 2. ROC Curve Analysis of FT3 Levels Predicting the Presence of CSFP and CAD in Young Females. A: CSFP, B: CAD.



CSFP, coronary slow flow phenomenon; CAD, coronary artery disease; FT3, free triiodothyronine.

5. Discussion

The current study assessed the correlation between thyroid hormone levels and the presence of CSFP and CAD in euthyroid patients. This association was also evaluated between gender and age sub-groups. The results indicated that decreased serum levels of FT3 were associated with the presence of both CSFP and CAD only in young females. Furthermore, higher TSH levels were found to be an independent predictor of O-CAD solely in young individuals.

As the most active form of thyroid hormones, FT3 regulates an array of functions within the body. It appears that FT3 is capable of improving the cardiovascular system function by relaxation of smooth muscle cells, inhibition of collagen-induced platelet aggregation, improving endothelial function, and preventing hyper-coagulation (17). Moreover, a recent study pointed out that decreased FT3 levels in middle-aged and elderly people were directly associated with an increased risk of atherosclerosis, which plays an important role in the pathogenesis of both CSFP and CAD (18).

CSFP is a clinical angiographic finding, which has been defined as a delay in the progression of the contrast dye injected directly into the coronary arteries during coronary angiography. Amongst the many suggested proposed pathophysiologies for CSFP, integrity of the coronary endothelium is the most important one (4). In addition, raised levels of homocysteine, which can be the consequence of decreased FT3 levels, pertains unfavorable effects on the function of coronary endothelium. Evrengul et al. (5) assessed the relationship between CSFP and thyroid hormones and reported significantly decreased FT3 levels in CSFP patients. Consistently, the current study findings demonstrated that FT3 level was an independent predictor of CSFP, albeit exclusively in young females.

In the current study, low levels of FT3 were found to be associated with the presence of both N-CAD and O-CAD. Nevertheless, the aforementioned association was observed only in young female individuals. Consistently, Zhou et al. (10) reported an inverse correlation between serum FT3 level and the presence of CAD among 4206 euthyroid patients. Furthermore, Coceani et al. (19) observed in 1047 euthyroid patients that low FT3 levels were accompanied with a higher risk of CAD and poorer outcomes. Incongruent findings have also been reported through the course of years (6, 20). As an instance, Jung et al. (6) showed that the presence and severity of CAD were solely related to FT4 levels. However, FT3 was not measured in that study. Ling et al. (20) also failed to determine a relationship between the FT4 and TSH serum levels and the presence of CAD in a population of euthyroid patients. Such discrepancies may arise from the heterogeneity of the study participants regarding age and sex distribution as well as differences in sample size, ethnicity, and characteristics of the selected euthyroid patients. Furthermore, an increased prevalence of cardiovascular risk factors was observed among the euthyroid population in the study by Ling et al. (20). Therefore, the influence of minimal fluctuation in thyroid hormone levels, remaining within the RR, on CAD could not be assessed.

The present study results indicated that higher TSH levels could be associated with O-CAD among young individuals. In the same line, Yun et al. (21) reported that higher TSH serum levels within the RR were only correlated to multi-vessel CAD. Additionally, Yang et al. (9) found that higher TSH levels within the RR were independently associated with the presence of CAD. Similar to the current study findings, the aforementioned association in the latter study was found only in the individuals who aged 65 years or less.

The current study results disclosed that females were more prone to the influence of variations in thyroid hormone levels. In a recent 10-year cohort of euthyroid females, thyroid hormone levels exhibited a direct association with the concentration of sexual hormones, such as estrogen and progesterone, during the menstrual period (22). Furthermore, evidence has suggested that estrogen not only retained protective cardiovascular effects, but also improved the function of vascular endothelium and smooth muscle contraction (23). Therefore, it can be hypothesized that low levels of thyroid hormones can be a cause of low estrogen and, subsequently, diminishes the cardiovascular protective attributes. Moreover, the results of a cross-sectional study in Germany revealed lower levels of FT3 in the women using oral hormonal contraceptives (OCP)

in the pre-menopausal period compared to the controls as well as men. Therefore, lower FT3 levels, which have been previously determined as a risk factor for CAD, could result from the administration of OCP, especially during the pre-menopausal period (24).

To the best of our knowledge, this study was the first to assess the association between thyroid hormones and the presence of CSFP and CAD in an Iranian population with a significant number of participants. The study measured the relationship between thyroid hormones and CSFP based on age and sex subgroups, which was not previously evaluated. However, the study had several limitations. Primarily, due to the single-centered setting and retrospective nature of the study, no causality could be proposed and only associations could be suggested. Unfortunately, the history of Hormone Replacement Therapy (HRT) and OCP use was not available in the present investigation. Therefore, adjustment of the confounding effects of HRT and OCP use was not possible.

5.1. Conclusion

The present study demonstrated that FT3 serum concentration in the RR was inversely correlated to the presence of CSFP and CAD only in young female patients. Moreover, higher levels of TSH were an independent predictor of O-CAD in young euthyroid patients. Further prospective and randomized-controlled studies are needed to confirm the findings.

5.2. Ethical Approval

This study was approved by the Ethics Committee of Shahid Rajaie Cardiovascular Medical and Research Center.

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Authors' Contribution

ET: data collection; ET, MG, and AK: statistical analysis; ET and MG: study design; AZ, RA, MG, and ZG: quality assessment; all authors: final revision and grammar editing.

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There is no financial disclosure.

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