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Original Article

Evaluation of the association between thyroid hormone levels and coronary slow flow in euthyroid patients: a retrospective study

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ABSTRACT

Aims: Coronary slow flow (CSF) is an angiographic phenomenon characterized by delayed distal opacification of coronary arteries despite the absence of obstructive lesions. Although thyroid hormones are known to modulate cardiovascular hemodynamics, their potential association with CSF remains uncertain.

Methods: This retrospective, single-center, observational study included 170 patients (85 with angiographically confirmed CSF and 85 with normal coronary flow). Patients with overt thyroid dysfunction were excluded. Demographic, clinical, and biochemical characteristics were compared between the groups. Thyroid-related parameters (TSH, FT3, FT4, and FT4/FT3 ratio) were analyzed using receiver operating characteristic (ROC) curves and logistic regression to determine their discriminative and independent predictive value for CSF.

Results: Patients with CSF were significantly younger (49.3±10.0 vs. 54.8±11.1 years, p<0.001), predominantly male (72.9% vs. 47.1%, p=0.001), and more frequently smokers (59.0% vs. 36.9%, p=0.021) compared with controls. In multivariable logistic regression analysis, only age remained an independent predictor of CSF (OR 0.95, 95% CI 0.92-0.98, p=0.002). None of the thyroid parameters, including the FT4/FT3 ratio, demonstrated significant discriminative ability for CSF in ROC curve analysis (all AUC <0.60, p>0.05).

Conclusion: In euthyroid individuals, thyroid hormone levels and their ratios were not independently associated with coronary slow flow, whereas younger age and smoking emerged as stronger correlates. These findings suggest that routine thyroid hormone evaluation may not offer additional diagnostic or prognostic value in CSF.

Keywords: Coronary slow flow, thyroid hormones, euthyroid, microvascular dysfunction

INTRODUCTION

Coronary slow flow (CSF) is an angiographic phenomenon characterized by delayed opacification of the distal coronary arteries in the absence of obstructive epicardial stenosis and is most commonly quantified using the thrombolysis in myocardial infarction (TIMI) frame count method.[1] The prevalence of CSF has been reported in approximately 1-7% of patients undergoing diagnostic coronary angiography.[2] Although the exact pathophysiology remains uncertain, accumulating evidence suggests that endothelial dysfunction, microvascular abnormalities, diffuse atherosclerosis, and chronic low-grade inflammation are key contributors.[3,4] Clinically, CSF has been associated with recurrent angina, arrhythmias, myocardial ischemia, and even sudden cardiac death, emphasizing that it is far from a benign angiographic finding.[5,6]

Thyroid hormones exert multiple cardiovascular effects by modulating heart rate, myocardial contractility, systemic vascular resistance, endothelial function, and lipid metabolism.[7] Both overt and subclinical thyroid dysfunctions have been associated with a range of cardiovascular disorders, including coronary artery disease, arrhythmias, and heart failure.[8,9] Beyond these systemic effects, thyroid hormones may also influence coronary microvascular tone and flow regulation through mechanisms involving endothelial nitric oxide synthesis, vascular smooth muscle responsiveness, and tissue oxygen demand.[10,11]

Several studies have examined the potential relationship between thyroid function and coronary flow dynamics, yet the results have been inconsistent. Evrengül et al.[12] reported lower free triiodothyronine (FT3) levels in CSF patients compared with controls, whereas Chen et al.[13] suggested that free thyroxine (FT4) might be associated with CSF, particularly in women. Conversely, other investigations have failed to demonstrate any significant relationship between thyroid parameters and CSF.[14] These conflicting findings raise an important question: do thyroid hormones exert any measurable influence on coronary flow within the physiological (euthyroid) range, or are their vascular effects limited to states of overt dysfunction?

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Given the established cardiovascular actions of thyroid hormones and the lack of clarity regarding their potential influence under normal thyroid function, this study aimed to evaluate the association between thyroid hormone levels and coronary slow flow specifically in a euthyroid patient population. By restricting the analysis to individuals without thyroid dysfunction, we sought to determine whether minor hormonal variations within the normal physiological range hold any clinical or microvascular relevance for CSF.

METHODS

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Batman Training and and Research Hospital Scientific Researches Ethics Committee (Date: 24.06.2018, Decision No: 280118606,429). Given the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived by the ethics committee.

Study Design and Population

This single-center, retrospective, observational study included a total of 170 patients who underwent diagnostic coronary angiography due to chest pain and suspected ischemic heart disease. Patients were divided into two equal groups: those with coronary slow flow (CSF, n=85) and those with normal coronary flow (n=85). CSF was defined as delayed distal vessel opacification in the absence of significant epicardial stenosis, confirmed by corrected TIMI frame count criteria.

To minimize endocrine and metabolic confounding, the study specifically included only euthyroid individuals. This approach allowed the evaluation of whether small variations in thyroid hormone levels within the physiological range have any measurable impact on coronary flow, independent of overt thyroid dysfunction.

Exclusion criteria were obstructive coronary artery disease, known thyroid dysfunction or use of thyroid-related medications, significant renal or hepatic impairment, active infection or inflammatory disease, and incomplete laboratory data.

Laboratory and Clinical Variables

Venous blood samples were collected after an overnight fast. Standard biochemical parameters including glucose, creatinine, lipid profile, and C-reactive protein were measured using automated analyzers. Thyroid hormones including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured by chemiluminescence immunoassay. Demographic and clinical characteristics (age, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking status) were obtained from medical records.

Statistical Analysis

Continuous variables were presented as mean±standard deviation or median (IQR) depending on distribution and compared with students T test or Mann-Whitney U test. Categorical variables were expressed as counts (percentages) and compared using the chi-square test. Receiver operating characteristic (ROC) analysis was performed for TSH, FT3, FT4, and the FT4/FT3 ratio. Logistic regression analysis was used to determine independent predictors of CSF, with results presented as odds ratios (OR) and 95% confidence intervals (CI).

Given the balanced design and sample size, the study was considered to have reasonable sensitivity to detect moderate associations; therefore, the absence of significant relationships is unlikely to reflect a major limitation of statistical power. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 170 patients were included in the final analysis, consisting of 85 patients with coronary slow flow (CSF) and 85 patients with normal coronary flow.

Demographic and Laboratory Characteristics

Baseline clinical and laboratory findings of the study groups are summarized in **Table 1**. Patients in the CSF group were significantly younger than those in the normal flow group (49.3±10.0 vs. 54.8±11.1 years, p<0.001). The proportion of male patients was higher in the CSF group (72.9% vs. 47.1%, p=0.001). The rate of smoking was also significantly higher among CSF patients (59.0% vs. 36.9%, p=0.021). There were no significant between-group differences with respect to diabetes mellitus or hyperlipidemia.

Table 1. Demographic and laboratory characteristics

Variable	Normal flow (n=85)	CSF (n=85)	p-value
Age (years)	54.78±11.12	49.28±9.96	<0.001
Male sex, n (%)	40 (47.1%)	62 (72.9%)	0.001
Hypertension, n (%)	24 (36.9%)	17 (20%)	0.047
Diabetes mellitus, n (%)	25 (30.1%)	16 (18.8%)	0.127
Hyperlipidemia, n (%)	34 (40.5%)	42 (50.6%)	0.247
Smoking, n (%)	24 (36.9%)	36 (59.0%)	0.021
Creatinine (mg/dl)	0.86±0.36	0.86±0.24	0.256
CRP (mg/L)	4.14±7.9	4.46±8.50	0.341
Total cholesterol (mg/dl)	185.49±38.35	179.05±40.15	0.114
LDL cholesterol (mg/dl)	103.11±33.19	98.47±31.50	0.359
Triglycerides (mg/dl)	129.31±57.22	156.26±65.56	0.0024
WBC (x10^3/µL)	7.89±2.32	8.15±2.29	0.364
Platelets (x10^3/µL)	259.80±74.04	244.18±70.84	0.468
TSH (µIU/ml)	1.83±1.69	1.86±1.94	0.971
FT3 (pg/ml)	3.30±0.57	3.41±0.67	0.485
FT4 (ng/dl)	1.38±0.35	1.36±0.40	0.575

CSF: Coronary slow flow, CRP: C-reactive protein, LDL: Low-density lipoprotein, WBC: White blood count, TSH: Thyroid-stimulating hormone, FT3: Free t3, FT4: Free t4

Among laboratory parameters, serum triglyceride levels were significantly higher in the CSF group compared with the normal flow group (156.3±65.6 mg/dl vs. 129.3±57.2 mg/dl, p=0.002), whereas other biochemical and hematologic indices-including glucose, creatinine, and CRP-showed no significant differences. Similarly, thyroid hormone levels (TSH, FT3, and FT4) were comparable between groups (all p>0.05).

Logistic Regression Analysis

Results of the univariate and multivariate logistic regression analyses are presented in **Table 2**. In univariate analysis, younger age (OR 0.94, 95% CI 0.90-0.98, p=0.001), male sex (OR 2.92, 95% CI 1.36-6.26, p=0.006), and smoking (OR 2.51,

95% CI 1.20-5.25, p=0.015) were significantly associated with the presence of CSF.

Table 2. Logistic regression analysis of predictors of coronary slow flow

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age (years)	0.94 (0.90-0.98)	0.001	0.95 (0.91-0.99)	0.007
Male sex	2.80 (1.33-5.91)	0.007	2.20 (0.73-6.60)	0.160
Smoking	2.27 (1.10-4.67)	0.027	0.95 (0.32-2.80)	0.920
FT3 (pg/ml)	1.62 (0.87-3.01)	0.129	1.40 (0.69-2.85)	0.354
FT4 (ng/dl)	0.99 (0.38-2.56)	0.988	0.63 (0.19-2.08)	0.449
TSH (μIU/ml)	1.03 (0.54-1.96)	0.94	0.91 (0.47-1.74)	0.78

OR: Odds ratios, CI: Confidence intervals, FT3: Free t3, FT4: Free t4, TSH: Thyroid-stimulating hormone

Hypertension and triglyceride levels also showed significant associations in univariate analysis but did not remain independent predictors after multivariable adjustment. In the final multivariate model including age, sex, smoking, FT3, and FT4, only age remained an independent predictor of CSF (OR 0.96, 95% CI 0.92-0.99, p=0.030).

When TSH was additionally included in the multivariate model, it did not emerge as an independent predictor of CSF (OR 0.91, 95% CI 0.47-1.74, p=0.78).

ROC Curve Analysis

ROC curves of thyroid parameters are shown in **Figure**. The discriminatory power of thyroid hormones for predicting CSF was poor, with AUC values of 0.50 for TSH, 0.53 for FT3, 0.48 for FT4, and 0.46 for the FT4/FT3 ratio. No clinically relevant cut-off values with adequate sensitivity and specificity could be determined.

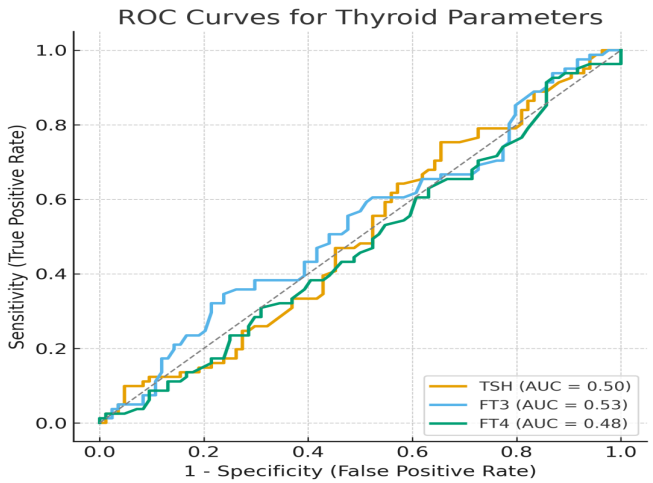

Figure. ROC curves of thyroid hormones (TSH, FT3, FT4, and FT4/FT3 ratio) for predicting coronary slow flow ROC curves are shown for serum thyroid hormone parameters in patients with CSF versus controls. The AUC was 0.50 for TSH, 0.53 for FT3, 0.48 for FT4, and 0.46 for the FT4/FT3 ratio, indicating no significant discriminatory power.

ROC: Receiver operating characteristic, TSH: Thyroid-stimulating hormone, FT3: Free t3, FT4: Free t4, CSF: Coronary slow flow, AUC: Area under the curve

DISCUSSION

In this study, we examined whether thyroid hormone levels are associated with CSF. Patients with CSF were younger, more often male, and more frequently smokers than controls; however, in multivariable analysis only age remained an independent determinant. Thyroid markers (TSH, FT3, FT4, FT4/FT3) did not discriminate CSF status in ROC analyses. In line with prior negative studies, our findings suggest that subtle variations in thyroid hormones within the euthyroid range are unlikely to play a dominant role in CSF pathogenesis.

Previous investigations have reported conflicting results. Evrengül et al.[12] demonstrated lower FT3 levels in CSF patients, while Chen et al.[13] found reduced FT4, particularly in women. In contrast, Madak et al.[14] observed no significant differences in thyroid hormone levels between CSF and control groups. These inconsistencies may stem from population heterogeneity, sex distribution, sample size, or methodological differences.

Importantly, our findings emphasize that in a well-defined euthyroid population, thyroid hormones alone are unlikely to serve as independent predictors of CSF. This is clinically relevant because it highlights that routine thyroid hormone testing may not add diagnostic or prognostic value in daily practice. Instead, traditional cardiovascular risk factors such as younger age, male sex, and smoking remain the major determinants of CSF.

Beyond thyroid hormones, additional mechanisms have been implicated in CSF. Clinical data suggest that CSF is related to microvascular dysfunction, endothelial impairment, and inflammation.[15,16] Furthermore, Razvi et al.[17] emphasized that thyroid hormones can modulate cardiovascular performance through multiple pathways, including vascular tone and myocardial contractility. Vargas-Uricoechea et al.[20] also reviewed the complex effects of thyroid hormones on vascular physiology, noting potential interactions with small-vessel function.[18] Taken together, although thyroid hormones exert significant cardiovascular effects, our results suggest that these influences may not be strong enough to independently determine coronary flow in otherwise euthyroid individuals.

Another key message of our study is that negative results may still have positive implications. By demonstrating the limited role of thyroid hormones, we provide evidence that future research should focus more on the interplay between inflammation, microvascular dysfunction, and novel immunoinflammatory markers. Recently, indices such as the pan-immune-inflammation value (PIV) have shown stronger predictive value for CSF compared with conventional markers.[19,20] Furthermore, retinal and choroidal microvascular alterations in CSF patients, demonstrated by optical coherence tomography angiography, support the concept of generalized microvascular dysfunction.[21] These findings suggest that the contribution of thyroid hormones may be indirect, potentially acting as modulators rather than primary drivers of CSF pathogenesis.

At the experimental level, TSH has been shown to impair endothelial function by altering nitric oxide synthase and vasoactive mediator expression.[22] Although we did not find a direct clinical effect of thyroid hormones, this mechanistic evidence justifies further prospective studies, particularly in populations with subclinical thyroid dysfunction or in those with higher systemic inflammatory burden.

Furthermore, retinal and choroidal microvascular alterations in CSF patients, demonstrated by optical coherence tomography angiography, support the concept of generalized microvascular dysfunction.[23] These findings suggest that the contribution of thyroid hormones may be indirect, potentially acting as modulators rather than primary drivers of CSF pathogenesis. At the experimental level, TSH has been

shown to impair endothelial function by altering nitric oxide synthase and vasoactive mediator expression.[24] Although we did not find a direct clinical effect of thyroid hormones, this mechanistic evidence justifies further prospective studies, particularly in populations with subclinical thyroid dysfunction or in those with higher systemic inflammatory burden.

Limitations

This study has several limitations. First, it was a single-center, retrospective design, which may limit the generalizability of the findings. Second, coronary flow was assessed solely using the TIMI frame count; more sensitive measures of microvascular resistance or endothelial reactivity were not available. Third, only baseline thyroid hormone levels were analyzed, and dynamic variations over time could not be evaluated. Fourth, although patients with overt thyroid disease were excluded, the presence of unrecognized subclinical thyroid dysfunction cannot be completely ruled out. Finally, inflammatory and oxidative stress markers beyond conventional CRP were not assessed, which may have provided additional insight into the link between endocrine and microvascular processes.

CONCLUSION

As a result, our study demonstrates that thyroid hormone levels are not independently associated with coronary slow flow in euthyroid patients. While triglyceride levels were modestly higher among CSF patients, this relationship was not independent after multivariable adjustment. Conventional risk factors such as younger age and smoking remained the dominant determinants of CSF. These results indicate that, within the physiological range, thyroid hormone fluctuations have limited impact on coronary flow, and routine thyroid testing provides minimal additional diagnostic value. Future large-scale, prospective studies should further explore the interaction between thyroid physiology, lipid metabolism, inflammation, and microvascular function to better clarify their collective roles in the pathogenesis of coronary slow flow.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Batman Training and and Research Hospital Scientific Researches Ethics Committee (Date: 24.06.2018, Decision No: 280118606,429).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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