The relationship between serum thyroid hormone levels, subclinical hypothyroidism, and coronary collateral circulation in patients with stable coronary artery disease

Kararlı koroner arter hastalarında koroner kollateral dolaşımı ile subklinik hipotiroidizm ve serum tiroid hormonu düzeyleri arasındaki ilişki

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ABSTRACT

Objective: Thyroid disease is a common endocrine disease with important effects on the cardiovascular system. As an adaptive response to myocardial ischemia, coronary collateral circulation (CCC) plays an important role in obstructive coronary artery disease (CAD). The association between serum thyroid hormone levels and development of CCC was investigated in the present study.

Methods: In total, 430 consecutive patients who underwent coronary angiography procedure and had documented total occlusion in at least 1 major coronary artery were investigated retrospectively. Degree of CCC was classified according to Cohen-Rentrop method. Serum free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were assessed by the chemiluminescence immunoassay technique.

Results: In spite of diabetes mellitus (p=0.019), smoking (p<0.001), and TSH (p<0.001), FT3 (p<0.001), FT4 (p=0.015), and subclinical hypothyroidism (SCH) (p<0.001) ratios were significantly different between groups. In regression analysis, SCH (p=0.024), DM (p=0.021), smoking (p<0.001), and heart failure (p=0.029) were independent predictors of poor CCC development in multivariate model 1. When regression analyses were performed based on multivariate model 2, TSH (p<0.001), FT3 (p<0.001), heart failure (p=0.022), smoking (p<0.001), and hyperlipidemia (HPL) (p=0.046) were independent predictors of poor CCC development.

Conclusion: In addition to traditional risk factors, SCH, higher serum TSH, and lower FT3 levels were associated with development of poor CCC in patients with obstructive CAD.

ÖZET

Amaç: Tiroid hastalıkları kardiyovasküler sistem üzerine kayda değer etkileri olan yaygın bir endokrin hastalıktır. Miyokart iskemisine bir uyum cevabı olan koroner kollateral dolaşımı, tıkayıcı koroner arter hastalıklarında önemli bir rol üstlenmektedir. Bu çalışmada, serum tiroid hormonu seviyeleri ile koroner kollateral dolaşımı arasındaki ilişki araştırıldı.

Yöntemler: Çalışmamızda koroner anjiyografi uygulanan ve en az bir epikardiyal koroner arterde tıkayıcı darlık saptanan 430 ardışık hastanın verileri geriye dönük olarak incelendi. Koroner kollateral derecelendirilmesi Cohen-Rentrop metoduna göre yapıldı. Serum serbest triiyodotironin (ST3), serbest tiroksin (ST4) ve tiroid uyarıcı hormon seviyeleri kemilüminesans immünoassay tekniği ile değerlendirildi.

Bulgular: Çalışmamızda diabetes mellitus (DM) (p=0.019), sigara (p<0.001), TSH (p<0.001), FT3 (p<0.001), FT4 (p=0.015) ve SH (p<0.001) oranları gruplar arasında farklılık göstermesine rağmen diğer parametreler benzerdi. Regresyon analizinde (model 1), subklinik hipotiroidizm (SH) (p=0.024), DM (p=0.021), sigara (p<0.001) ve kalp yetersizliği (p=0.029) kötü koroner kollateral dolaşımının bağımsız öngördürücüleri olarak saptandı. Tiroid uyarıcı hormon seviyesi (p<0.001), serbest T3 seviyesi (p<0.001), kalp yetersizliği (p=0.022), sigara (p<0.001) ve hiperlipidemi (p=0.046) model 2'de kötü koroner kollateral dolaşımı gelişimini bağımsız olarak öngördürmektedir.

Sonuç: Geleneksel risk faktörlerine ilave olarak SH, serum yüksek tiroid uyarıcı hormon seviyeleri ve düşük serbest T3 seviyeleri tıkayıcı koroner arter hastalığı olanlarda kötü koroner kollateral gelişimi ile ilişkilidir.

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Coronary collateral circulation (CCC) plays an important role in obstructive coronary artery disease (CAD), as an adaptive response to myocardial ischemia.[1] Although angiographically invisible coronary collateral connections may be present in patients without obstructive CAD, these connections become apparent in patients with obstructive CAD.[2] Many factors that may affect CCC development have been evaluated thus far. In spite of increased awareness regarding the development of CCC, thyroid hormone levels and subclinical thyroid disease have not been clearly evaluated.[3,4]

Thyroid disease is a common endocrine disease with important effects on the cardiovascular system, as changes in thyroid function result in significant alterations in cardiac hemodynamics, even if subclinical.[5–8] Because vascular smooth muscle cells are an important target of thyroid-stimulating hormone (TSH), TSH may impair endothelial function and inhibit vascular smooth cell migration.[9,10] Previous studies have shown that subclinical hypothyroidism (SCH) is associated with atherosclerosis, increased carotid intima-media thickness, carotid plaques, and increased prevalence and severity of cardiovascular disease.[6–8] Furthermore, an experimental study showed that serum free triiodothyronine (FT3) may be related to increased capillary density and angiogenesis.[11] Although many factors related to the development of CCC have been investigated, it is unclear whether serum thyroid hormone levels and SCH may be a risk factor for the development of poor CCC. Therefore, we investigated the association between serum thyroid hormone levels, SCH, and the development of CCC in patients with obstructive CAD.

METHODS

Between November 2012 and October 2014, due to abnormal noninvasive test results, 430 consecutive patients who had undergone coronary angiography and had documented total occlusion in at least one major coronary artery were enrolled in our study retrospectively. Patients with a history of myocardial infarction or severe epicardial coronary stenosis (>70% stenosis in any major epicardial coronary artery), malignancy, decompensated or severe heart failure (left ventricular ejection fraction <30%), or severe hepatic or chronic kidney disease (serum creatinine levels >1.5 mg/dL) were excluded from our study, as were patients with coronary artery bypass grafting and severe valvular heart disease.

Abbreviations:

CAD	*Coronary artery disease*
CCC	*Coronary collateral circulation*
CI	*Confidence interval*
DM	*Diabetes mellitus*
FT3	*Serum free triiodothyronine*
FT4	*Free thyroxine*
HPL	*Hyperlipidemia*
OR	*Odds ratio*
SCH	*Subclinical hypothyroidism*
TSH	*Thyroid-stimulating hormone*

Patients who used any medication that could affect thyroid hormone levels, such as levothyroxine sodium, propylthiouracil, amiodarone, estrogens, lithium, or corticosteroids, and patients with clinical thyroid diseases, such as overt hypothyroidism, overt or subclinical hyperthyroidism, or sub-acute thyroiditis, were also excluded.[12–15] Study protocol was approved by the local ethics committee, and informed consent was obtained from all participants.

Baseline clinical and demographic data, and medical histories were recorded using information on file. Hypertension was defined as blood pressure ≥140/90 mmHg or treatment with an antihypertensive medication. Diabetes mellitus (DM) was defined as fasting glucose level ≥126 mg/dL, or treatment with an oral anti-diabetic drug or insulin. Hyperlipidemia (HPL) was defined according to current guidelines.[16] Smokers were defined as current cigarette smokers or patients who had quit smoking within 1 month of procedure. Transthoracic echocardiography was performed prior to percutaneous coronary intervention, and data was recorded in patient files. Severe heart failure was defined as left ventricular ejection fraction <30%, calculated using modified Simpson's method.

Blood sampling and laboratory assays

In addition to routine biochemical and hematological parameters, serum TSH, FT3, and free thyroxine (FT4) levels had also been measured routinely prior to percutaneous coronary intervention. Blood samples had been obtained from a peripheral vein between 8:00 and 10:00, after an 8-hour fast, before coronary angiography procedure. Hematological parameters had been measured using an XT-2000i analyzer (Sysmex America Inc., Mundelein, IL, USA). Serum urea, creatinine, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, and glucose levels were measured using routine laboratory techniques. FT3, FT4, and TSH levels were evaluated by chemiluminescence immunoassay method using E170

(Elecsys module) immunoassay analyzers (Roche Diagnostics, Mannheim, Germany). Reference intervals for FT3, FT4, and TSH were 1.71–3.71 pg/dL, 0.70–1.48 ng/dL, and 0.35–4.94 IU/mL, respectively.

Coronary angiography and CCC scoring

Coronary angiography procedures had been performed using femoral or radial artery approach. Coronary angiograms and degree of CCC were evaluated by 2 experienced cardiologists who were blinded to study design and laboratory results. CCC degree was classified according to Cohen-Rentrop method: grade 0, no filling of any collateral artery; grade 1, filling of side branches of artery to be perfused by collateral vessels without visualization of epicardial segment; grade 2, partial filling of epicardial artery by collateral vessels; grade 3, complete filling of epicardial artery by collateral vessels.[17] Patients with grades 0 or 1 were defined as having "poor CCC," and grades 2 or 3 defined as "good CCC." Collateral grading was evaluated according to the better vessel when CCC was observed in more than one vessel.

Statistical analysis

All analyses were performed using SPSS (version 19.0 for Windows; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate whether distribution of continuous variables was normal or not. Continuous data are presented as mean±SD and/or median (minimum to maximum) based on normality of variables. Mean differences among groups were compared by Student's t-test, and Mann-Whitney U test was applied to compare median values. Categorical variables were summarized as percentages and compared with chi-square test.

To evaluate effects of various factors on poor CCC development, multivariate logistic regression analyses were performed using backward LR method. Variables for which the p value was <0.25 in univariate analysis were identified as potential risk markers and included in full multivariate model as covariates. As SCH is determined on the basis of serum thyroid hormone levels, they were not entered into the same multivariate model, and 2 multivariate models were used. Model 1 included SCH, DM, beta-blocker usage, HPL, smoking, heart failure, statin usage, angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker usage, and platelet count. Model 2 included serum thyroid hormone levels, DM, beta-blocker usage, HPL, smoking, heart failure, statin usage, angiotensin-converting-enzyme inhibitor / angiotensin-receptor blocker usage, and platelet count. Coefficients with 95% confidence interval (CI) are presented. A p value <0.05 was considered significant.

RESULTS

The 430 patients evaluated were divided into 2 groups based on CCC development: poor CCC (group 1) and good CCC (group 2). Clinical, hematological, and angiographic characteristics of the study population are shown in Table 1. In spite of DM (p=0.019), smoking (p<0.001), and TSH (p<0.001), FT3 (p<0.001), FT4 (p=0.015) and SCH (p<0.001) ratios were significantly different between groups, while other variables were similar.

Multivariate logistic regression analyses are presented in Table 2. Results of the present study demonstrate that SCH (odds ratio [OR], 2.502; 95% CI, 1.130–5.539; p=0.024), DM (OR, 1.771; 95% CI, 1.089–2.878; p=0.021), smoking (OR, 2.164; 95% CI, 1.387–3.375; p<0.001), and heart failure (OR, 0.180; 95% CI, 0.039–0.836; p=0.029) were independent predictors of poor CCC development, based on model 1. When regression analyses were performed based on model 2 (thyroid hormones and CCC development), TSH (OR, 2.684; 95% CI, 1.969–3.659; p<0.001), FT3 (OR, 0.159; 95% CI, 0.052–0.489; p<0.001), heart failure (OR, 0.158; 95% CI, 0.033–0.765; p=0.022), smoking (OR, 2.587; 95% CI, 1.458–4.520; p<0.001), and HPL (OR, 1.807; 95% CI, 1.010–3.231; p=0.046) were also found to be independent predictors of poor CCC development in patients with stable CAD.

DISCUSSION

The present study demonstrated that SCH, DM, smoking, heart failure, and HPL were independent risk factors for poor CCC development. Results also demonstrated that serum TSH and FT3 levels predicted poor CCC development independently, while FT4 did not.

CCC primarily develops in response to myocardial ischemia, which cannot be completed because CCC, as an arterio-arterial anastomotic connection, plays an important role in preventing ischemic damage.[1] Billinger et al. showed that patients with poor CCC experience higher incidence of acute coronary

Table 1. Baseline clinical, laboratory, and angiographic findings according to CCC development

Variables	Poor CCC (n=117)	Good CCC (n=313)	*p*
Age (year)	63.5±8.8	62.4±10.1	0.312
Sex male, n (%)	72 (61.5)	199 (63.0)	0.697
Diabetes Mellitus, n (%)	40 (34.2)	72 (23.0)	**0.019**
Hypertension, n (%)	59 (50.4)	142 (45.4)	0.349
Hyperlipidemia, n (%)	63 (53.8)	149 (47.6)	0.249
Smoking, n (%)	63 (54.7)	117 (37.4)	**<0.001**
Heart failure, n (%)	2 (1.7)	20 (6.4)	0.050
LVEF (%), median (min-max)*	45.0 (30.0–63.0)	47.0 (30.0–66.0)	0.157
Statin, n (%)	60 (51.3)	141 (45.0)	0.249
Acetylsalicylic acid, n (%)	74 (63.2)	187 (59.7)	0.508
Beta-blocker, n (%)	49 (41.9)	164 (52.4)	0.052
ACEI-ARB, n (%)	39 (33.3)	85 (27.2)	0.208
Calcium-channel-blocker, n (%)	15 (12.8)	32 (10.2)	0.442
Oral anti-diabetic drug, n (%)	24 (20.5)	64 (20.4)	0.988
Insulin, n (%)	14 (12.0)	24 (7.7)	0.162
Glucose (mg/dL), median (min-max)*	109.0 (58.0–359.0)	104.0 (55.0–587.0)	0.855
HDL (mg/dL)	40.20±10.38	38.87±13.58	0.339
LDL (mg/dL), median (min-max)*	100.0 (43.0–248.0)	94.0 (25.0–221.0)	0.332
Triglyceride (mg/dL), median (min-max)*	98.0 (43.0–415.0)	99.0 (28.0–570.0)	0.450
Creatinine (mg/dL), median (min-max)*	0.9 (0.3–2.0)	0.9 (0.3–2.6)	0.899
White blood cell (x10^3/mm^3)	8.71±1.81	8.85±1.83	0.459
Hemoglobin (g/dL)	12.90±2.16	13.09±1.96	0.387
Platelet count (x10^3/mm^3), median (min-max)*	228.0 (107.0–430.0)	238.0 (107.0–458.0)	**0.084**
TSH (IU/mL), median (min-max)*	4.3 (3.0–11.0)	2.8 (0.3–7.0)	**<0.001**
FT3 (pg/dL), median (min-max)*	1.8 (1.7–3.0)	2.1 (1.7–3.7)	**<0.001**
FT4 (ng/dL), median (min-max)*	0.9 (0.7–1.2)	1.0 (0.7–1.4)	**0.015**
Blood urea nitrogen, median (min-max)*	32.0 (13.0–191.0)	34.0 (13.0–191.0)	0.348
1-vessel disease, n (%)	33 (28.2)	73 (23.3)	0.296
2-vessel disease, n (%)	58 (49.6)	168 (53.7)	0.448
3-vessel disease, n (%)	26 (22.2)	72 (23.0)	0.864
Subclinical hypothyroidism, n (%)	14 (12.0)	17 (5.4)	**0.020**

* Mann-Whitney U test was used.
LVEF: Left ventricular ejection fraction; ACEI/ARB: Angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; CCC: Coronary collateral circulation.

syndrome than those with good CCC.[18] A number of studies have shown that myocardial perfusion and left ventricular function may be maintained in patients with good CCC.[19–21] Pressure gradient caused by obstructive CAD and myocardial ischemia are primary triggering factors for development of CCC.[22] In addition to microcirculatory failure and atherosclerotic lesions, many factors (diabetes, hypertension, endothelial dysfunction, drugs, genetics, and smoking) can negatively affect the development of CCC.[23] The present study determined that DM did not affect poor CCC development in model 2. However, given the retrospective design of the study, we did not have access to certain data including DM duration and glyce-

Table 2. Predictors of development of poor CCC in final steps of multivariate logistic regression analyses according to model 1 (Subclinical hypothyroidism and CCC)*

Variables	OR	95% CI	*p*
Subclinical hypothyroidism	2.502	1.130–5.539	**0.024**
Diabetes mellitus	1.771	1.089–2.878	**0.021**
Beta-blocker usage	0.664	0.425–1.038	0.072
Smoking	2.164	1.387–3.375	**<0.001**
Platelet counts	1.000	1.000–1.000	0.090
Heart failure	0.180	0.039–.836	**0.029**

*Subclinical hypothyroidism, Diabetes mellitus, beta-blocker usage, hyperlipidemia, smoking, heart failure, statin usage, angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker usage, and platelet count were included in the analysis as covariates. CCC: Coronary collateral circulation.

Table 3. Predictors of development of poor CCC in final steps of multivariate logistic regression analyses according to model 2 (thyroid hormones and CCC)*

Variables	OR	95% CI	*p*
Hyperlipidemia	1.807	1.010–3.231	**0.046**
Beta-blocker usage	0.606	0.343–1.071	0.085
Smoking	2.587	1.458–4.520	**<0.001**
Platelet counts	1.000	1.000–1.000	0.057
Heart failure	0.158	0.033–0.765	**0.022**
Thyroid stimulating hormone	2.684	1.969–3.659	**<0.001**
Free triiodothyronine	0.159	0.052–0.489	**<0.001**
Free thyroxine	5.171	0.730–36.642	0.100

*Thyroid stimulating hormone, free triiodothyronine, free thyroxine, Diabetes mellitus, beta-blocker usage, hyperlipidemia, smoking, heart failure, statin usage, angiotensin converting enzyme inhibitor/angiotensin receptor blocker usage, platelet count were included in the analysis as covariates. CCC: Coronary Collateral Circulation.

mic control status, which may be responsible for this conflicting result.[24–26]

SCH is a well-known risk factor for atherosclerosis, and high serum TSH and low serum FT3 levels are associated with CAD severity.[7,27] SCH is a common endocrine disease that affects approximately 4% of the general population and 10–15% of the elderly population.[28,29] A number of mechanisms have been proposed to explain the relationship between SCH and adverse cardiovascular effects. Endothelial cells play an important role in the collateral maturation process,[30] and vascular smooth muscle cells are also an important TSH target.[9] Yoneda et al. showed that injecting TSH in conduit arteries resulted in significant impairment of endothelial vasodilation.[10] Moreover, plasma platelet-activating factor acetylhydrolase activity and peripheral vascular resistance increase, which may contribute to poor CCC development in patients with SCH.[31,32]

Even in cases of asymptomatic SCH, patients have increased atherosclerotic burden and inflammatory status.[33,34] Studies have suggested that higher inflammatory status inhibits endothelial cell functions, such as migration and angiogenesis.[22,23] Our study showed that while SCH, TSH, and FT3 levels predicted poor CCC development, levels of FT4 did not have significant predictive value in the development of CCC. Similarly, previous studies have shown that FT4 is a prohormone that cannot be transported by myocytes, so the heart depends mainly on triiodothyronine, which affects cardiac function through genomic and non-genomic effects.[35,36]

The present study was the first to investigate the relationship between serum thyroid hormone levels,

SCH, and CCC development. There were a number of limitations, such as retrospective design and relatively small number of patients. Other limitations included a lack of information regarding duration of thyroid dysfunction, inflammatory markers, and serum thyroid antibody levels, as well as a lack of follow-up data.

Conclusion

SCH was associated with development of poor CCC in patients with obstructive CAD. Presence of good CCC is important in obstructive CAD cases, particularly in patients for whom coronary revascularization is unsuitable. Treating risk factors that predispose these patients to poor CCC is especially important. The present study suggests that SCH may be a risk factor, and should be monitored and treated.

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