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Is thyroid-stimulating hormone a predictor of severity of carotid artery disease?

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Abstract. – OBJECTIVE: The relationship between thyroid function and carotid artery stenosis in euthyroid patients is controversial. Therefore, we aimed at evaluating the relationship between the severity of carotid artery disease (CAD) and thyroid-stimulating hormone (TSH) levels in euthyroid patients.

PATIENTS AND METHODS: A total of 90 euthyroid patients with CAD were trichotomized into three groups based on CAD severity. Group 1 comprised patients who had one internal carotid artery with total stenosis and the other with more than 50% stenosis. In Group 2, patients had one internal carotid artery with total stenosis and the other with less than 50% stenosis. Group 3 comprised patients with less than 50% stenosis in both internal carotid arteries. Demographic data, complete blood count, biochemical parameters, and thyroid function parameters were compared between the groups.

RESULTS: No significant relationship was noted between the severity of CAD and demographic data and comorbidity rates. A comparison of the biochemical parameters revealed that TSH levels were significantly different between the groups. Post-hoc analysis showed that Group 1 and Group 3 differed significantly with respect to TSH levels (0.75 ± 0.37 IU/mL *vs.* 1.39 ± 1.00 IU/mL, *p*=0.002). A cut-off value of 0.65 yielded 46.67% sensitivity and 81.67% specificity, whereas a cut-off value of 0.70 yielded 53.33% sensitivity and 75.00% specificity. The area under the curve was 0.691 (95% CI, 0.576-0.806) (*p*=0.003).

CONCLUSIONS: TSH can be demonstrated to predict severe carotid artery disease. Therefore, the severity of CAD can be assessed using TSH levels.

Key Words:
Carotid artery stenosis, Atherosclerosis, Biomarkers.

Introduction

The anterior pituitary gland receives its blood supply from the superior hypophyseal artery, which is a branch of the internal carotid artery; in contrast, the posterior pituitary gland receives its blood supply from both the internal carotid and posterior communicating arteries. The hypothalamic-pituitary hormones are controlled by the upper central region of the brain, which regulates the body's hormone balance through various axes. One of these is the hypothalamic-pituitary-thyroid axis. Thyroid-stimulating hormone (TSH) is secreted from cells in the anterior pituitary gland. Few studies[1,2] have demonstrated a relationship between carotid artery stenosis and the levels of TSH in euthyroid patients, but no significant relationship has been established between carotid artery stenosis and TSH levels in euthyroid patients. In addition, increased TSH levels have been reported following revascularization for carotid artery stenosis in euthyroid patients[3]. It has been previously shown that carotid artery aneurysm, carotid cavernous fistula and internal carotid agenesis reduce TSH secretion[4-7]. Endovascular therapy has been shown to improve TSH and T4 levels in patients with pituitary dysfunction secondary to an unruptured internal carotid artery aneurysm[4-5]. Therefore, we think that decreased TSH levels can be observed with reduced pituitary perfusion, that is, with the increasing severity of carotid artery disease (CAD). The present study aimed at investigating the relationship between the severity of CAD and TSH in euthyroid patients.

Patients and Methods

This study included patients who had undergone carotid angiography between September 2010 and March 2019. The study patients were divided into three groups based on their CAD severity, as determined by the angiography results. Group 1 included patients who had one internal carotid artery with total stenosis and those whose

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other artery had more than 50% stenosis. Group 2 was composed by patients with one of their internal carotid arteries having total stenosis and the other artery having less than 50% stenosis. Group 3 comprised patients who had less than 50% stenosis in both internal carotid arteries. Of the 52 patients in the first group, 22 were excluded because they did not meet the inclusion criteria. The second and third groups included 30 patients each with demographic characteristics that were similar to those in the first group. All three groups of patients had less than 30% stenosis in both bilateral external carotid arteries.

Hypertension was defined as having persistently elevated blood pressure higher than 140/90 mmHg or using antihypertensive medication; diabetes mellitus was defined as either having a fasting blood glucose level of 126 mg/dL as reflected by at least two measurements or using antidiabetic medication; and hyperlipidaemia was defined as either having total serum cholesterol >200 mg/dL or using lipid-lowering drugs. The following exclusions were applied: patients with TSH, free thyroxine (fT4) and free tri-iodothyronin (fT3) levels outside the normal reference range; patients who had received treatment for a thyroid disorder; patients with bilateral internal carotid occlusion, stenosis of a major intracranial artery, carotid-cavernous fistulas or carotid artery aneurysms; patients with insufficient test results; patients with a history of thyroid or pituitary surgery; patients with chronic liver or kidney disease; patients with a malignancy.

Blood samples for the biochemical analyses were drawn after 12 h of fasting from the antecubital vein into test tubes without anticoagulant; samples were centrifuged for 10-15 min at 2,500-3,000 rpm, and the serum was separated by decantation. Serum thyroid hormone levels (fT3, fT4 and TSH) were measured with a chemiluminescence immunoassay using the Architect system (Abbott, Wiesbaden, Germany), according to the manufacturer's instructions. The following measurements were accepted as normal values in the laboratory: fT4 8.1-19.1 pg/mL, fT3 1.57-4.71 pg/mL and TSH 0.35-4.94 μIU/mL. Euthyroidism was defined as having serum TSH, fT4 and fT3 levels within the normal reference range. Patients with increased TSH levels combined with fT4 and fT3 levels within the normal range were considered to have subclinical hypothyroidism. Patients with TSH levels below the normal range combined with fT4 and fT3 levels within the normal range were considered to have subclinical hyperthyroidism. A decrease in fT4 and fT3 below the assay reference range, in addition to increased TSH in patients with clinical symptoms, was considered overt hypothyroidism. An increase in fT4 and fT3 above the assay reference range accompanied by suppressed TSH in patients with clinical symptoms was considered overt hyperthyroidism.

Statistical Analysis

The statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY, USA). Initially, the continuous variables (quantitative) were recorded with the mean ± SD values, and the categorical variables (qualitative) were recorded as percentages (%). The normal distribution of the variables was verified with the Kolmogorov-Smirnov's test. The associations between the non-normally distributed variables, the correlation coefficients and their significances were calculated using the Spearman's test. Comparisons between the groups were performed using ANOVA when the distribution was normal or with the Kruskal-Wallis' test and the Mann-Whitney U test when the distribution was not normal. Post-hoc analysis was performed using Tukey's HSD and Dunn's tests. Then, receiver operations characteristic (ROC) curves were created to identify and graphically display the cut-off values for the predictive role of TSH. The results were presented as the area under the curve (AUC), and the best cut-off values were assigned to points of higher sensitivity and specificity (according to Youden's index). A p-value lower than 0.05 was considered statistically significant.

Results

The present study included 90 patients, 70 males and 20 females. The mean age of the patients was 70.90 ± 9.18 years in Group 1, 67.27 ± 8.66 years in Group 2 and 70.43 ± 10.4 years in Group 3 (p=0.176). There were 30 patients in each study group (designated Group 1, Group 2 or Group 3). The study included 67 patients with hypertension, 27 patients with diabetes mellitus, 21 patients with hyperlipidaemia, 34 patients with CAD and 10 patients with peripheral artery disease. Eight of the patients were smokers. No significant relationships were noted between CAD severity and demographic data or comorbidity rates (Table I).

Table I. Demographic data and comorbidity rates based on the severity of carotid artery disease.

	Carotid artery disease			
	Group 1	Group 2	Group 3	*p*-value
Gender (male) n %	23 (76.67)	25 (83.33)	22 (73.33)	0.638
Age (years)	70.90 ± 9.18	67.27 ± 8.66	70.43 ± 10.4	0.176
Hypertansion n (%)	26 (86.67)	20 (66.67)	21 (70.00)	0.164
Diabetes mellitus n (%)	12 (40.00)	7 (23.33)	8 (26.67)	0.329
Hyperlipidemia n (%)	6 (20.00)	10 (33.33)	5 (16.67)	0.271
Smoking n (%)	5 (16.67)	3 (10.00)	0 (0.00)	0.074
Coronary artery disease n (%)	10 (33.33)	13 (43.33)	11 (36.67)	0.718
Peripheral vascular disease n (%)	4 (13.33)	4 (13.33)	2 (6.67)	0.638

Values are mean ± SD.

The measured hematologic, biochemical and hormone levels were compared to CAD severity (Table II). A comparison of the biochemical parameters revealed that TSH levels were significantly different between the groups (Table II, Figure 1). Post-hoc analysis showed that Group 1 and Group 3 differed from each other significantly with respect to TSH levels (0.75 ± 0.37 IU/mL *vs.* 1.39 ± 1.00 IU/mL, $p = 0.002$), while comparison of Group 2 and Group 3 (0.96 ± 0.46 IU/mL *vs.* 1.39 ± 1.00 IU/mL, $p = 0.259$) and comparison of Group 1 and Group 2 (0.75 ± 0.37 IU/mL *vs.* 0.96 ± 0.46 IU/mL, $p = 0.272$) were not significantly different with respect to TSH levels.

The significant cut-off values for the TSH levels were analyzed to determine whether they could be used to identify CAD severity. A cut-off value of 0.65 yielded 46.67% sensitivity and 81.67% specificity, whereas a cut-off value of 0.70 yielded 53.33% sensitivity and 75.00% specificity. The area under the curve (AUC) was 0.691 (95% CI, 0.576-0.806) ($p = 0.003$) (Figure 2).

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between thyroid-stimulating hormones and the severity of

Table II. Comparison of the measured hematologic, biochemical and hormone values with respect to the severity of carotid artery disease.

	Carotid artery disease			
	Group 1	Group 2	Group 3	*p*-value
Glucose (mg/dL)	124.23 ± 61.41	129.20 ± 45.06	117.70 ± 53.58	0.400
Creatinine (mg/dL)	0.93 ± 0.19	0.86 ± 0.15	0.87 ± 0.16	0.249
Sodium (mEq/L)	139.13 ± 2.75	139.60 ± 2.06	139.07 ± 2.53	0.611
Potassium (mEq/L)	4.31 ± 0.35	4.35 ± 0.40	4.50 ± 0.40	0.203
Albumin (g/dL)	3.83 ± 0.39	4.03 ± 0.38	3.98 ± 0.39	0.238
TSH (IU/mL)	0.75 ± 0.37	0.96 ± 0.46	1.39 ± 1.00	**0.003**
Free T4 (ng/dL)	14.07 ± 2.49	13.97 ± 2.11	13.10 ± 2.00	0.155
Free T3 (ng/dL)	3.92 ± 0.99	3.88 ± 0.78	3.78 ± 0.74	0.852
Hemoglobin (g/dL)	13.72 ± 1.14	14.00 ± 1.18	13.48 ± 1.07	0.205
Hematocrit (%)	40.84 ± 3.40	42.39 ± 3.38	40.79 ± 3.67	0.097
WBC (10^3/µl)	8.13 ± 1.94	7.61 ± 1.80	7.14 ± 1.53	0.100
Platelet (10^3/µL)	249.10 ± 94.74	254.83 ± 67.00	229.10 ± 69.21	0.240
TC (mg/dL)	184.17 ± 43.61	198.20 ± 47.69	201.93 ± 54.55	0.336
LDL-C (mg/dL)	122.73 ± 37.44	140.37 ± 39.22	135.03 ± 39.50	0.201
Triglyceride (mg/dL)	148.43 ± 80.56	136.73 ± 68.62	152.53 ± 95.03	0.949
HDL-C (mg/dL)	39.47 ± 11.66	40.93 ± 8.32	44.99 ± 14.66	0.372

TC: Total plasma cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White Blood Cell, TSH: Thyroid stimulating hormone, Free T3: Free triiodothyronine, FreeT4: Free thyroxine, p: Pearson correlation. Values are mean ± SD.

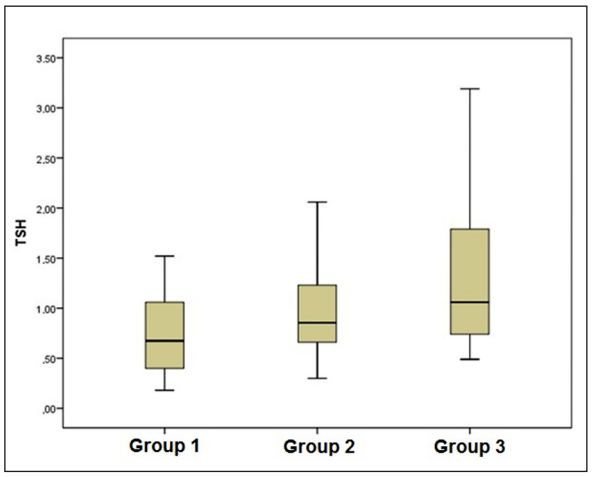

Figure 1. TSH levels according to the severity of carotid artery disease.

carotid artery disease. We observed that TSH levels decreased with increased CAD severity. In addition, fT4 and fT3 levels increased with increasing severity of CAD, but this result was not statistically significant.

The thyroid hormones controlled by the hypothalamic-pituitary-thyroid axis consist of T3 and T4. Studies[8] have shown that both hypothyroidism and hyperthyroidism are associated with an increased incidence of cardiovascular diseases. Hypothyroidism may lead to atherosclerotic vascular disease secondary to diastolic hypertension, cardiac dysfunction and hypercholesterolemia[9].

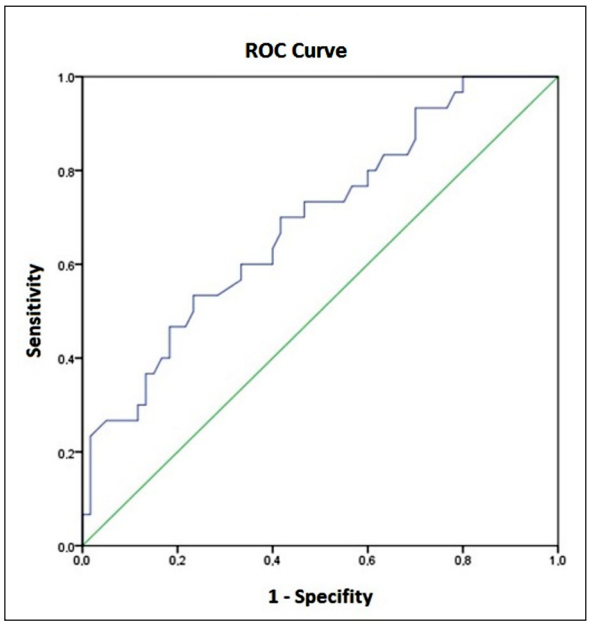

Figure 2. ROC curve demonstrating the cut-off value of TSH to predict severe carotid artery disease.

Moreover, euthyroidism has been found to be associated with carotid atherosclerosis and increased levels of inflammatory marker[10-12]. Studies[1,10-15] have shown relationships between normal thyroid hormone levels and inflammatory markers, mitral annular calcification, carotid intima-media thickness, and carotid artery stenosis. In addition, the presence of carotid atheromatous plaque has been found to be associated with low fT4 levels in euthyroid patients with ischaemic stroke[16]. Liu et al[16] showed the relationship between low-to-normal thyroid function and the presence of carotid atheromatous plaque. This relationship can be explained by several mechanisms. For instance, low fT4 levels may lead to atherosclerosis by causing impaired endothelial function, in addition to increasing lipid levels, insulin resistance and hypertension[17-20]. Similarly, a study by Jeong et al[1] showed the relationship between low-to-normal thyroid function and atherosclerotic conditions, such as carotid artery stenosis. In this study, we found that fT4 levels increased with increasing severity of CAD, irrespective of carotid artery stenosis, in euthyroid patients. We suggest that these patients may have increased heart rate, pulse, cardiac output, arterial stiffness and blood pressure due to increased fT4 levels, and this could increase the severity of atherosclerotic CAD.

Whether symptomatic or not, carotid artery stenosis may affect the cerebrovascular system[21]. Instead of increasing carotid intima-media thickness, carotid artery stenosis is an indicator of advanced atherosclerosis. Severe carotid artery stenosis may lead to impaired cognitive functions[22]. Ischaemia and neurocognitive functions can be improved in patients who undergo carotid artery stenting with severe internal carotid artery stenosis[23-25]. Although Liu et al[16] found that patients with intracranial artery stenosis had increased fT4 levels and decreased TSH levels, they did not observe a significant relationship between T4 and TSH levels and intracranial artery stenosis; we think this may be due to decreased intracranial blood flow and pituitary perfusion, which supports our hypothesis. Our patient group was composed by patients with internal CAD, and the physiopathology of intracranial artery stenosis may be different.

TSH levels increase with advancing age. While thyroid functions tend to decrease with age, researchers[26,27] have shown that TSH levels exhibit a mean increase of 13% in patients older than 13 years, particularly in females. Although there

is a positive correlation between mortality and serum thyroxin levels in the elderly, increased TSH levels are associated with low mortality[28]. If there is endocrine dysfunction due to an insufficient supply to the pituitary gland, endocrine functions can be improved following revascularisation. In a study by Yeh et al[3], it was observed that TSH levels increased following revascularisation. Reportedly, pituitary perfusion could be reduced due to vascular pressure in carotid artery aneurysms, leading to decreased secretion of TSH and other pituitary hormones. It has also been shown that TSH and T4 levels improve with endovascular treatment in patients with pituitary dysfunction secondary to an internal carotid artery aneurysm that had not previously ruptured[4,5]. A carotid cavernous fistula may lead to hypoperfusion of the pituitary gland, resulting in decreased TSH and T4 levels[6]. Moreover, pituitary failure has reportedly been observed due to hypoperfusion in internal carotid agenesis[7]. In this study, we showed that TSH levels exhibited a statistically significant decrease stemming from reduced pituitary perfusion due to increased CAD severity.

Limitations

The limitations of our study were as follows: the study was designed to be retrospective with a small number of patients, and it was based on records from a single hospital. Thyroid antibody levels were not measured. All measurements were performed once, which may have led to misdiagnosing some patients with thyroid disease and a variance in fT4 levels. The pituitary-gonadal axis, pituitary-adrenal axis, growth hormone, prolactin, antidiuretic hormone and oxytocin hormones were not measured.

Conclusions

Consequently, TSH levels decreased with the increasing severity of CAD in euthyroid patients. TSH was demonstrated to predict severe carotid artery disease; therefore, the severity of CAD can be assessed using TSH levels. These results should be supported by randomized controlled studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Review Committees of the Sakarya University.

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Informed Consent

The patients were informed, and consent was obtained.

Availability of Data and Materials

The data and materials generated/analyzed in the present study are available from the corresponding author upon request.

Authors' Contribution

Conception and design: Y. Can, I. Kocayigit and N. Can; Acquisition of data: Y. Can, I. Kocayigit and N. Can; Analysis and interpretation of data: Y. Can, N. Can, I. Kocayigit and H. Kılıc; Drafting the article: Y. Can, H. Kılıc and R. Akdemir; Supervision: H. Kılıc and R. Akdemir; Validation and final approval: All authors.

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