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fT3 index/TSH index ratio and free thyroid hormone index in the differential diagnosis of thyrotoxicosis

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ABSTRACT

Aim: Common causes of thyrotoxicosis are hyperthyroidism and destructive thyroiditis. Hyperthyroidism is a condition characterized by high serum thyroid hormone levels as a result of over-synthesis of thyroid hormones, the most common causes of which are Graves' disease (GD) and toxic nodular goiter (TNG). Subacute thyroiditis (SAT) causes thyrotoxicosis due to the circulating thyroid hormones of destructive thyroiditis. Differential diagnosis is important because GD, TNG and SAT treatment approaches are different. The aim of this study was to analyze whether it is possible to make a differential diagnosis for these conditions by examining free thyroid hormones, fT3/fT4 ratio, fT3 index/TSH index (fT3I/TSHI) ratio and Free Thyroid Hormone Index (FTHI).

Material and Method: This retrospective study included 150 patients who were diagnosed with GD, TNG and SAT. The fT3 index (fT3I) was calculated as the ratio between the fT3 value and the fT3 upper limit of normal value (fT3I=fT3/4 pg/ml). The fT4 index (fT4I) was calculated as the ratio between the fT4 value and the fT4 upper limit of normal value (fT4I=fT4/1.23 mg/dl). The TSH index (TSHI) was calculated as the ratio between TSH value and the TSH lower limit of normal limit (TSHI=TSH/0.38 mIU/L). The FTHI index was calculated using the formula of (fT3 level/fT3 upper limit of normal) / (fT4 level/fT4 upper limit of normal).

Results: The fT3, fT3/fT4 ratio and FTHI were found to be higher in hyperthyroid patients compared to subacute thyroiditis patients. fT4 and fT3I/TSHI levels were similar in hyperthyroid patients and SAT patients (p=0.49, p=0.11, respectively). The cut-off level of FTHI for hyperthyroidism was determined as 0.97 with sensitivity of 75% and specificity of 76.3% (AUC=0.833, p< 0.001). When hyperthyroidic patients were divided into two groups as GD and TNG, no significant difference was found in fT3/fT4 ratio (p:0.99). The fT3 (p<0.001) and fT4 (p<0.001) values were found to be higher, and TSH values were found to be lower (p=0.001) in GD. The fT3I/TSHI ratio was found to be higher in Graves' patients (p<0.001). The cut off level for Graves' disease was determined as sT3I/TSHI>324.58.

Conclusion: FTHI is useful in differentiating hyperthyroid conditions such as GD and TNG from SAT. FTHI is insufficient in the differential diagnosis of Graves disease and TNG. The fT3I/TSHI ratio is higher in Graves' disease than in TNG and SAT. The combination of FTHI and sT3I/TSHI methods can increase diagnostic accuracy.

Keywords: Hyperthyroidism, free T4, T3/T4 ratio, graves disease, toxic nodular guatr, subacute thyroiditis

INTRODUCTION

Thyrotoxicosis is a condition characterized by an excess of thyroid hormones in the serum (1). There are two main mechanisms for the formation of thyrotoxicosis. The first is the mechanism called hyperthyroidism, characterized by increased thyroid hormone synthesis and secretion from the thyroid gland. The second type of thyrotoxicosis occurs as a result of destructive thyroiditis without an increase in hormone synthesis from the thyroid gland. In destructive thyroiditis, synthesized thyroid hormones enter the circulation and cause symptoms. The main causes of hyperthyroidism are Graves' Disease (GD) and toxic nodular goiter (TNG) (2). Subacute thyroiditis (SAT) is one of the causes of destructive thyroiditis (3,4). Differential diagnosis is essential since the treatment and follow-up of GD, TNG and destructive thyroiditis differ (5).

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Even if thyroid nodules are seen in ultrasonographic evaluation, differential diagnosis of thyrotoxicosis is difficult without scintigraphy. However, scintigraphic methods are contraindicated in cases such as pregnancy and breastfeeding (6). In addition, scintigraphic methods are not always accessible due to both the high cost and lack of availability in every center. Occasionally, radioactive iodine uptake is found to be low in hyperthyroid patients due to iodine contamination before the scintigraphic procedure. Radioactive iodine uptake may be high in the healing phase of destructive thyroiditis (7). In such scintigraphic limitations, TSH receptor antibodies are helpful in distinguishing GD from other conditions. However, there may be false-negative and false-positive results (8,9).

A total T3/total T4 ratio of <20 ng/mcg in thyrotoxic patients is considered an indicator of destructive thyrotoxicosis (7). Instead of total form, free T3 (fT3) and free T4 (fT4) measurements are more widely used because they are less affected by thyroid hormone binding proteins and are more accessible. The fT3/fT4 ratio has been reported as a useful indicator in differentiating subacute thyroiditis from Graves' disease (10,11). However, due to the limited number of studies and the heterogeneity of the studies, a clear recommendation cannot be made (12–18). Therefore, the aim of this study was to evaluate fT3 and fT4 ratios and levels in patients with Graves' disease, toxic nodular goiter and subacute thyroiditis.

MATERIAL AND METHOD

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision no:109/39). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

This retrospective study included thyrotoxicosis patients aged >18 years who presented at the endocrinology and metabolic diseases polyclinics of a tertiary hospital between 2018 and 2020. All persons included in the study signed the informed consent form. Patients with GD, TNG and SAT were included in the study. Patients with breastfeeding, pregnancy, kidney and hepatic failure, cancer or infection, and those using drugs that affect thyroid functions were excluded from the study. The diagnoses of Graves' disease, toxic nodular goiter, and subacute thyroiditis were made according to the criteria in **Table 1**. The patients were first evaluated in two groups; GD and TNG patients were evaluated as the hyperthyroidism group and SAT patients were evaluated as the destructive thyroiditis group. Then the GD, TNG and SAT patients were evaluated separately.

Laboratory Analysis

Beckman Coulter chemiluminescent immunoassay device was used to measure thyroid function tests (CA, USA). Reference ranges were defined as TSH: 0.38-5.33 mIU/L, fT4: 0.60-1.25 ng/dl, fT3: 2.28- 4 pg/ml. The fT3 index (fT3I) was calculated as the ratio between the fT3 value and the upper limit of fT3 normal value (fT3I=fT3/4 pg/ml). The fT4 index (fT4I) was calculated as the ratio between the fT4 value and the upper limit of fT4 normal value (fT4I=fT4/1.23 mg/dl). The TSH index (TSHI) was calculated as the ratio between TSH value and the lower limit of TSH normal limit (TSHI=TSH/0.38 mIU/L). The Free Thyroid hormone index (FTHI) was calculated as fT3I/fT4I ratio. fT3/fT4, fT3I/TSH and sT3I/TSHI were calculated by dividing the parameters by each other.

Statistical Analysis

Shapiro Wilk test was used to evaluate the parametric distribution. Non-parametric variables were expressed as median (range) values. In comparison of non-parametric multiple groups the Kruskal–Wallis test, and in comparison of non-parametric two groups Mann–Whitney U test were used. Tamhane tests were used in multiple group post hoc analyses. Categorical variables relationships were examined via Chi-Square test. For differential diagnosis, a cut-off value was determined using ROC curve. A value of $p<0.05$ was considered statistically significant.

Table 1. Criteria used in the diagnosis of Graves' Disease, Subacute thyroiditis and Toxic Nodular Goiter

Graves' Disease	Toxic Nodular Goiter	Subacute thyroiditis
1. Diffuse enlargement of the thyroid gland, presence of ophthalmyopathy/dermopathy 2. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 3. Increased TSH receptor antibody level 4. Increased blood flow on ultrasonography 5. Diffuse hyperplasic thyroid gland on scintigraphy	1. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 2. Nodular appearance on ultrasonography 3. Toxic adenoma appearance on scintigraphy	1. Painful, tender and hard thyroid gland 2. Elevated ESR, CRP 3. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 4. Ultrasonographically indistinct, hypoechoic areas with decreased blood supply, painful when pressing the probe

RESULTS

The mean age of the participants was 50±15 years. When the patients were evaluated in two groups as the hyperthyroidic group and destructive thyroiditis, the patients with destructive thyroiditis were seen to be younger (p<0.001). The gender distribution of hyperthyroidic patients and patients with destructive thyroiditis was similar (p=1.00). The fT3, fT3I, fT3/fT4 ratio and FTHI were found to be higher in hyperthyroid patients (p=0.04, p=0.04, p<0.001 and p<0.001; respectively) (**Table 2**). The optimal cut-off value for FTHI was determined as 0.97 and for fT3/fT4, 3.12 (**Table 3**).

Table 2. Comparisons of the demographic and laboratory values of the hyperthyroidic group and subacute thyroiditis group

	Hyperthyroidism (GD+TNG) n:100	Destructive thyroiditis (SAT) n:50	p
Age (years)	52 (22-87)	40 (27-71)	**<0.001**
Gender (F(%)/M(%))	74 (74%)/26(26%)	37(74%)/13(26%)	1.00
fT3 (pg/ml)	5.17 (2.60-30.00)	4.48 (2.37-11.28)	**0.04**
fT4 (ng/dl)	1.69 (0.61-7.77)	1.71 (0.83-4.55)	0.57
TSH (mIU/L)	0.007 (0.001-0.67)	0.02 (0.003-0.9)	0.88
TSH Index	0.18 (0.001-1.76)	0.53 (0.01-2.37)	0.88
fT3 Index	1.29 (0.65-7.50)	1.12 (0.59-2.82)	**0.04**
fT4 Index	1.35 (0.49-6.22)	1.37 (0.66-3.64)	0.57
fT3/fT4	3.83 (2.11-10-99)	2.56 (1.45-4.24)	**<0.001**
FTHI	1.19 (0.66-3.43)	0.80 (0.45-1.33)	**<0.001**
fT3/TSH	1005 (5.33-23900)	233.75 (4.99-3760)	0.11
fT3I/TSHI	95.48 (0.51-2270.50)	22.20 (0.47-357.20)	0.11

GD: Graves Disease, TNG: toxic nodular goiter, SAT: subacute thyroiditis FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

Table 3. Cut-off values for diagnosis of Hyperthyroidism according to ROC analysis

	Cut-off point	AUC	CI (95%)	Specificity (%)	Sensitivity (%)	p
FTHI	0.97	0.833	0.758-0.907	75	76.5	<0.001
fT3/fT4	3.12	0.833	0.758-0.907	76.3	75	<0.001
fT3	4.75	0.618	0.515-0.721	56.9	60.5	0.001

FTHI: Free Thyroid Hormone Index

Evaluation was made of 50 Graves patients, 50 toxic nodular goiter, and 50 subacute thyroiditis patients. The mean age of patients was 50.50 (30-75) years for GD, 60.50 (22-87) years for TNG, and 40 (27-71) years for SAT. No significant difference was found between the ages of GD and TNG patients (p=0.061). The age of SAT patients was found to be significantly younger than that of both GD and TNG patients (p<0.001 and p<0.001, respectively). No significant difference was found between the gender distribution of GD, TNG and SAT patients (p=0.19) (**Table 4**).

TSH levels of GD patients were 0.003 (0.001-0.35) mIU/L. TSH levels of GD patients were lower than TNG and SAT patients (p>0.001 and p=0.04, respectively). There was no difference between the TSH of the SAT and TNG groups (p=0.70).

There was no difference between the fT3 levels of SAT and TNG patients (p=0.95). The fT3 level of GD patients was higher than that of both TNG and SAT patients (p<0.001). The fT3I of GD patients was 2.34 (1.03-7.50). The fT3I value was higher in GD patients than in TNG and SAT patients (p<0.001). No difference was found between the fT3I values of TNG and SAT patients (p=0.95) (**Table 5**).

The fT4 level was 2.36 (0.87-7.77) ng/dl in patients with GD, 1.050 (0.61-4.00) ng/dl in TNG patients, and 1.71 (0.83-4.55) ng/dl in SAT patients. The fT4 levels of all three groups were significantly different from each other (p<0.001). The fT4I level was 0.84 (0.49-3.20) in GD patients, 1.37 (0.66-3.64) in SAT patients, and 0.84 (0.49-3.20) in TNG patients. The fT4I values of all three groups were significantly different from each other (p<0.001) (**Table 5**).

The fT3/fT4 ratio of SAT patients was 2.56 (1.45-4.24), which was significantly lower than that of GD and TNG patients (p<0.001). The fT3/fT4 ratio of the Graves disease and TNG groups did not differ (p=0.99). The FTHI value was lower in SAT patients than in GD and TNG patients (p<0.001). There was no difference in the FTHI values of GD and TNG patients (p=0.99) (**Table 5**).

Table 4. Comparisons of the demographic and laboratory values of patients with subacute thyroiditis, toxic nodular goiter and Graves' disease

	Graves Disease	Toxic Nodular Goiter	Subacute thyroiditis	p
Age (years)	50.50 (30-75)	60.50 (22-87)	40 (27-71)	<0.001
Gender (F(%)/M(%))	33(66%)/17(34%)	41(82%)/9(18%)	37(74%)/13(26%)	0.19
fT3 (pg/ml)	9.38 (4.14-30.00)	4.12 (2.60-20.00)	4.48 (2.37-11.28)	<0.001
fT4 (ng/dl)	2.36 (0.87-7.77)	1.050 (0.61-4.00)	1.71 (0.83-4.55)	<0.001
TSH (mIU/L)	0.003 (0.001-0.35)	0.04 (0.003-0.67)	0.02 (0.003-0.9)	<0.001
TSH Index (TSHI)	0.008 (0.00-0.92)	0.105(0.01-1.76)	0.53(0.01-2.37)	<0.001
fT3I	2.34 (1.03-7.50)	1.03 (0.65-5.00)	1.12 (0.59-2.82)	<0.001
fT4I	1.88 (0.70-6.22)	0.84 (0.49-3.20)	1.37 (0.66-3.64)	<0.001
fT3/fT4	3.72 (2.51-8.23)	3.95 (2.11-1.99)	2.56 (1.45-4.24)	<0.001
FTHI	1.16 (0.79-2.57)	1.23 (0.66-3.43)	0.80 (0.45-1.33)	<0.001
fT3/TSH	2118.33 (12.77-23900)	101.05 (5.33-2963.33)	233.75 (4.99-3760)	<0.001
fT3I/TSHI	201.24 (1.21-2270.50)	9.60 (0.51-281.52)	22.20 (0.47-357.20)	<0.001

FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

Table 5. Post hoc analysis results of the demographic and laboratory values of patients with Graves' Disease, toxic nodular goiter and subacute thyroiditis.

	Graves Diasease	Toxic Nodular Goiter	p	Graves Diasease	Subacute thyroiditis	p	Toxic Nodular Goiter	Subacute thyroiditis	p
Age (years)	50.50 (30-75)	60.50 (22-87)	0.61	50.50 (30-75)	40 (27-71)	<0.001	60.50 (22-87)	40 (27-71)	<0.001
fT3 (pg/ml)	9.38 (4.14-30.00)	4.12 (2.60-20.00)	<0.001	9.38 (4.14-30.00)	4.48 (2.37-11.28)	<0.001	4.12 (2.60-20.00)	4.48 (2.37-11.28)	0.955
fT4 (ng/dl)	2.36 (0.87-7.77)	1.050 (0.61-4.00)	<0.001	2.36 (0.87-7.77)	1.71 (0.83-4.55)	0.003	1.050 (0.61-4.00)	1.71 (0.83-4.55)	<0.001
TSH (mIU/L)	0.003 (0.001-0.35)	0.04 (0.003-0.67)	0.001	0.003 (0.001-0.35)	0.02 (0.003-0.9)	0.04	0.04 (0.003-0.67)	0.02 (0.003-0.9)	0.705
TSH Index (TSHI)	0.008 (0.00-0.92)	0.105 (0.01-1.76)	0.001	0.008 (0.00-0.92)	0.53 (0.01-2.37)	0.04	0.105 (0.01-1.76)	0.53 (0.01-2.37)	0.705
sT3I	2.34 (1.03-7.50)	1.03 (0.65-5.00)	<0.001	2.34 (1.03-7.50)	1.12 (0.59-2.82)	<0.001	1.03 (0.65-5.00)	1.12 (0.59-2.82)	0.955
sT4I	1.88 (0.70-6.22)	0.84 (0.49-3.20)	<0.001	1.88 (0.70-6.22)	1.37 (0.66-3.64)	0.003	0.84 (0.49-3.20)	1.37 (0.66-3.64)	<0.001
fT3/fT4	3.72 (2.51-8.23)	3.95 (2.11-1.99)	0.99	3.72 (2.51-8.23)	2.56 (1.45-4.24)	<0.001	3.95 (2.11-1.99)	2.56 (1.45-4.24)	<0.001
FTHI	1.16 (0.79-2.57)	1.23 (0.66-3.43)	0.99	1.16 (0.79-2.57)	0.80 (0.45-1.33)	<0.001	1.23 (0.66-3.43)	0.80 (0.45-1.33)	<0.001
fT3/TSH	2118.33 (12.77-23900)	101.05 (5.33-2963.33)	<0.001	2118.33 (12.77-23900)	233.75 (4.99-3760)	0.001	101.05 (5.33-2963.33)	233.75 (4.99-3760)	0.476
fT3I/TSHI	201.24 (1.21-2270.50)	9.60 (0.51-281.52)	<0.001	201.24 (1.21-2270.50)	22.20 (0.47-357.20)	0.001	9.60 (0.51-281.52)	22.20 (0.47-357.20)	0.476

FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

For GD-TNG differential diagnosis, the fT3I/TSHI ratio of 324.58 was determined as the cut-off point for Graves' disease with 77.8% sensitivity and 86.1% specificity (AUC: 0.882 , 95%CI: 0.804-0.961, p<0.001) (**Figure 1**).

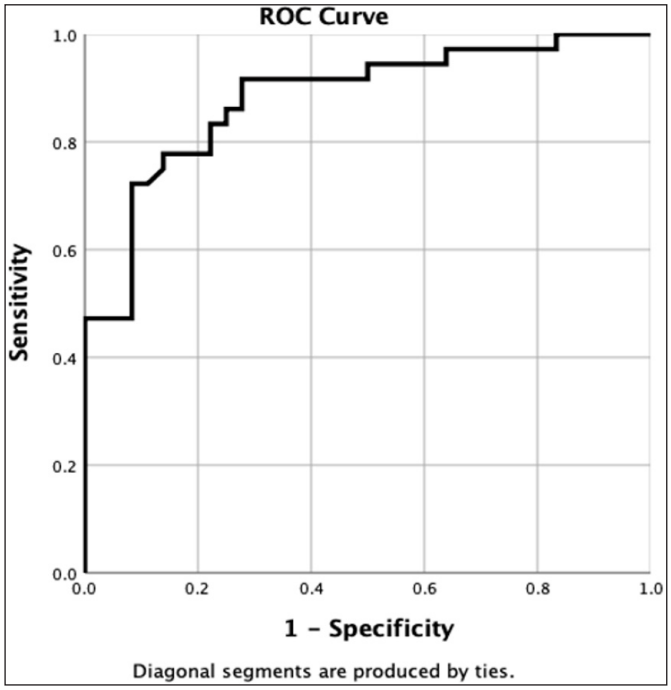

Figure 1. ROC curve analysis for FT3 index/TSH index

DISCUSSION

Ultrasonography, TSH receptor antibody level, and thyroid scintigraphy are the recommended methods in the differential diagnosis of Graves disease, TNG and SAT (19). In the current study, evaluations were made of the tests that can be applied for differential diagnosis in cases where these methods cannot be used. The results of the study demonstrated that FTHI and fT3/fT4 ratio can be used in the differential diagnosis of hyperthyroidism-destructive thyroiditis with 75% sensitivity and 76.5% specificity. It was observed that both fT3/fT4 ratio and FTHI were insufficient in distinguishing GD-TNG in hyperthyroid patients. From ROC analysis, it was determined that the fT3/TSH ratio has diagnostic value for GD-TNG differentiation. Thyrotoxicosis was seen to be more severe in GD patients.

Many studies have found the fT3/fT4 ratio to be useful in distinguishing between hyperthyroidism and destructive thyroiditis. Bahadır et al. (13) determined the optimal cut-off value for GD as 2.96 with sensitivity of 71.7% and specificity of 91.4%. Sriphrapradang (15) defined the fT3/fT4 cut-off value as 4.4 with 47.2% sensitivity and 92.8% specificity. There are also studies which have reported a cut-off value of 0.41, 0.86 and 2.8 for the fT3/fT4 ratio (10, 17, 20). The cut-off value of the fT3/fT4 ratio differs in all these studies, which can be attributed to the

different measurement units and reference range used. In addition, as in the study by Chen et al. (20), study design differences such as the participation of healthy control subjects in the ROC analysis change the results.

It can be considered that a differential diagnosis made using a method independent of measurement units, such as FTHI, will yield more objective results. In a study by Sumbul et al. (17), although a significant difference was found between hyperthyroid and destructive thyroiditis patients in terms of FTHI, ROC analysis was not performed. However, while the FTHI was >1 in all patients in the GD group, it was <1 in all patients in the thyroiditis group. Similarly in the current study, a cut-off value of 0.97 was determined for FTHI for the differential diagnosis of hyperthyroidism and subacute thyroiditis. However FTHI was insufficient in the differential diagnosis Graves' disease and TNG.

In a recent study by Wu et al. (16), the fT3/TSH ratio was found to be beneficial in the differential diagnosis of hyperthyroidism -thyrotoxicosis, although the hyperthyroidism group in that study only consisted of GD patients. In the current study, the fT3I/TSHI ratio was used because it is independent of the measurement method. The fT3I/TSHI ratio was found to be significantly higher in GD patients. The fT3/TSH ratio in Graves' patients was also found to be higher than in TNG patients. This is because thyrotoxicosis is more severe in Graves patients.

The FTHI cut-off point of >0.97 was found to be significant for hyperthyroidism and the fT3I/TSHI cut-off point of >324.58 was significant for GD. Therefore, in the case of FTHI>0.97 and fT3I/TSHI>324.58, the diagnosis of GD may be considered in the foreground. TNG can be considered if FTHI>0.97 and fT3I/TSHI<324.58. In case of FTHI<0.97 and fT3I/TSHI<324.58, SAT can be considered.

The main limitation of this study was that it was a single center, retrospective study. The small sample size was another limitation. In addition, iodine levels may change fT3 and fT4 levels. As it was a retrospective study, patients were not evaluated for iodine levels. Since this study was conducted in an iodine-deficient region, these results can be valid for iodine-deficient regions.

CONCLUSION

According our results, FTHI and fT3I/TSHI are useful criteria in the differential diagnosis of hyperthyroidism-thyrotoxicosis, with cut-off points of 0.97 and 324.58, respectively. The fact that they are independent of measurement units increases the universality of these methods. It may be appropriate to use FTHI and sT3I/TSHI methods together. Nevertheless, further studies are needed to confirm these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision no:109/39).

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.

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