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Graves' disease and thyroiditis can be differentiated using only free thyroid hormone levels

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ABSTRACT

Objectives: As the treatment approaches of Graves' disease and thyroiditis are different, differential diagnosis is important. In this study, we analyzed whether it is possible to perform a differential diagnosis for these two conditions by checking the increase ratio of free thyroid hormones.

Methods: In total 156 patients were taken into this study of which 29 were thyroiditis (17 had subacute thyroiditis, 6 had post-partum and 6 had silent thyroiditis) and 127 were Graves patients. The age, free T3 (FT3), free T4 (FT4), thyroid stimulating hormone (TSH) levels, FT3 index (FT3/FT3 upper limit of normal (ULN)), FT4 index (FT4/FT4 ULN) and free thyroid hormone index (FTHI) (FT3 index/FT4 index) of all patients were determined.

Results: A significant difference was found between the mean TSH, FT3 and FT3 index between Graves' disease and thyroiditis ($p = 0.036$, $p = 0.001$ and $p = 0.001$, respectively). When the groups were compared in terms of FTHI, the difference was found statistically significant ($p = 0.001$). FTHI was above 1 in all patients with Graves' disease whereas it was found below 1 in all patients with thyroiditis. There were no statistically significant difference between the Graves' disease and the thyroiditis in terms of age, FT4 and FT4 index ($p = 0.748$, $p = 0.389$ and $p = 0.392$, respectively).

Conclusion: Based on these results, considering the increases in free thyroid hormone values we can say that it is possible to perform a differential diagnosis of Graves' disease and thyroiditis, and that this may be used as a practical method to differentiate these two conditions.

Keywords: Graves' disease, thyroiditis, free thyroid hormone index

Thyrotoxicosis is a hypermetabolic condition characterized with excess serum thyroid hormones. It may occur as a result of exogenous thyroid hormone intake, release of previously synthesized hormone orhyperthyroidism. Hyperthyroidism is characterized by the high serum thyroid hormone levels as a result of excess synthesis and secretion of thyroid hormones from the thyroid gland. The most common causes are Graves'disease, toxic nodular goiter and toxic multinodular goiter [1, 2]. Graves'disease is an organ specific autoimmune disease. In Graves'disease the autoimmunity is against the thyroid stimulating hormone (TSH) receptor and the resultant TSH receptor antibodies cause hyperthyroidism [3, 4]. Graves'disease leads to diffuse extension in thyroid gland, ophtalmopathy in the eye, dermatopathy on the skin and acropachy in joints. In general, hyperthyroidism is treated through anti-thyroid drugs [5].

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Thyroiditis is also a common cause of thyrotoxicosis. Subacute thyroiditis is a condition that causes thyrotoxicosis as a result of stored thyroid hormone penetrating to blood after the inflammation of thyroid gland following upper respiratory tract infection. It is characterized with swelling in the neck region, pain and fever [1]. Post-partum thyroiditis is the inflammation of the thyroid gland after delivery. It causes painlessgoiter and temporary thyrotoxicosis. It is frequently observed between postpartum 6th week and 6th month, and generally, there is a family history for autoimmune diseases [1]. In the majority of the painless or silent thyroiditis patients, it is identified as an autoimmune disease characterized with antithyroid peroxidase (anti-TPO) positivity. Its pathological findings are characterized by lymphocyte infiltration in thyroid tissue. It is most frequent during postpartum period. Postpartum thyroiditis is accepted as a variant of silent thyroiditis. Silent thyroiditis may also occur in non-pregnant women and men. They show triphasic pattern; the differential diagnosis from GD should be performed at hyperthyroid phase and from Hashimoto thyroiditis at hypothyroid phase. While beta-blockers are used in all forms of thyrotoxicosis, as thyrotoxicosis in thyroiditis develops after destructive process, the anti-thyroid drugs have no effect and they are contraindicated [2, 6, 7]. For the proper treatment of thyrotoxicosis, accurate diagnosis is important.

In this study, we analyzed the increase ratio of free T3 (FT3) and free T4 (FT4) compared to their upper limit of normal (ULN) and the free thyroid hormone indices (FTHI) (FT3 index/F4 index) and examined whether these parameters may be used in the differential diagnosis of Graves'disease and thyroiditis.

METHODS

In total 156 patients were taken into this study of which 127 patients (69 female, 54.3%) were Graves'disease (6 patients under 18 years of age) and 29 cases (18 female, 62%) were thyroiditis (17 subacute thyroiditis, 6 post-partum and 6 silent thyroiditis, 3 patients under 18 years of age) who were all diagnosed through differential diagnosis. For this study, the permission was obtained from the ethical committee of our university. Patients with TSH value below 0.1 were accepted to the study.

The age, FT3 (normal reference range: 2-4.4 ug/ml), FT4 (normal reference range: 0.8-1.7 ng/dl), TSH (normal reference range: 0.27-4.2 U/ml), FT3 index (FT3/FT3 ULN), FT4 index (FT4/FT4 ULN) and FTHI criteria of the patients included to the study were controlled. FT3, FT4 and TSH levels were measured by the chemiluminescent immunoassay using Beckman Coulter DxI 800 immune-analyzer with original reagents.

Table 1. Characteristics of the groups

	Graves' disease				Thyroiditis				*p* value
	Min	Max.	Median	Mean ± SD	Min	Max.	Median	Mean ± SD	
Age (years)	15	74	38	39.14 ± 14.18	16	72	37	38.58 ± 16.24	0.748
FT3 (ug/ml)	4.43	32.55	10.24	12.24 ± 6.78	3.79	16.44	5.48	6.35 ± 2.64	**0.001**
FT3I	1.01	7.40	2.32	2.76 ± 1.50	0.86	3.74	1.10	1.42 ± 0.61	**0.001**
FT4 (ng/dl)	1.12	7.77	2.79	3.24 ± 1.71	1.76	7.77	2.34	2.81 ± 1.30	0.389
FT4I	0.66	4.77	1.68	1.91 ± 1.01	1.04	4.57	1.37	1.65 ± 0.76	0.392
TSH (U/ml)	0.01	0.01	0.01	0.01 ± 0.01	0.01	0.10	0.01	0.02 ± 0.02	**0.036**
FTHI	1.02	3.28	1.34	1.46 ± 0.37	0.48	0.99	0.91	0.87 ± 0.12	**0.001**

FT3 = Free T3, FT3I = FT3 index, FT4 = Free T4, FT4I = FT4 index, TSH = Thyroid stimulating hormone, FTHI = free thyroid hormone index, Min = Minumum, Max = Maximum, SD = Standard Deviation

Statistical Analysis

The data of our study were uploaded to SPSS 22.0 program and Man Whitney U test was used for the evaluation of the data as it was not possible to perform parametric test assumption (Kolmogorov-Smirnov) and the level of significance was accepted as 0.05.

RESULTS

The findings of the patient groups are shown in table 1.No statistically significant difference was found between the Graves'disease group and the thyroiditis group in terms of age, FT4, and FT4 index (p = 0.748, p = 0.389 and p = 0.392, respectively) (Table 1). When the groups were compared in terms of TSH, FT3 and FT3 index, statistically significant difference was found (p = 0.036, p = 0.001 and p = 0.001, respectively) (Table 1), however no differentiating threshold was found. When the groups were compared in terms of FTHI, the difference was found statistically significant (p = 0.001) (Table 1) (Figure 1). FTHI was above 1 in all patients in Graves'disease group whereas it was found below 1 in all patients in thyroiditis group (Fig. 1).

DISCUSSION

If a patient with moderate to severe hyperthyroidism and has a symmetrically enlarged thyroid gland and a new-onset ophthalmopathy, these are sufficient for Graves'disease diagnosis, and no further analysis are required for a differential diagnosis for hyperthyroidism. When there is a doubt about the diagnosis, the radioactive iodine uptake (RAIU) test should be performed to differentiate from the causes of thyrotoxicosis. RAIU test is generally high in Graves'disease. RAIU test is found close to zero in painless, postpartum or subacute thyroiditis cases, excess thyroid hormone intake or in new excess iodine intake cases.

In technetium scintigraphy (TcO4), pertechnetate captured but not organified by thyroid is used. While this results in a low range of normal uptake and high background activity, total body radiation exposure is less than for 123I scintiscans; either type of scan can be useful in determining the etiology of hyperthyroidism in the presence of thyroid nodularity [6].

Subacute thyroiditis is generally painful and the gland is stiff in palpation. Erythrocyte sedimentation

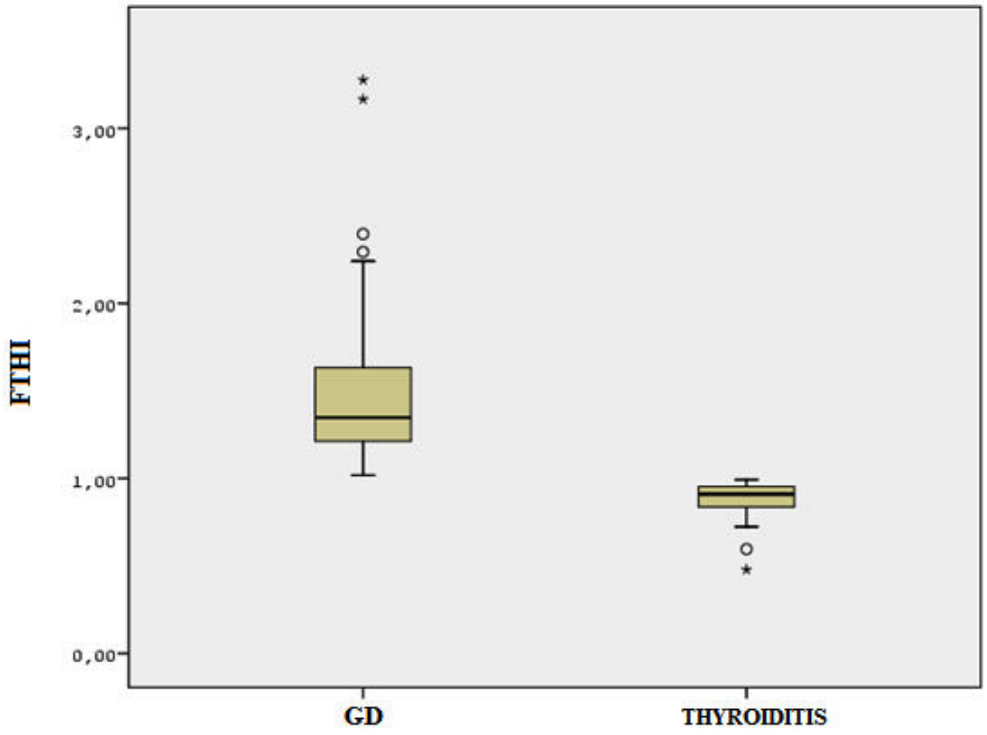

Fig. 1. Comparison of groups according to free thyroid hormone index. GD = Graves' disease, FTHI = Free thyroid hormone index

rate is > 50 mm/h almost in all and sometimes above 100 mm/h. In patients with painless thyroiditis, there is a self or family history of autoimmune thyroid disease, and it is generally observed during postpartum period. There is anti-TPO antibody positivity at a low or moderate level [8].

The use of ultrasonography for the differential diagnosis of thyrotoxicosis is disputable. However, during pregnancy and breastfeeding period, in case of new iodine exposure while RAIU test is contraindicated, color flow Doppler ultrasonography may assist in diagnosing thyroid hyperactivity and to differentiate Graves'disease from destructive thyroiditis [9].

An alternative method to differentiate Graves'disease is measuring the TSH receptor antibody (TRAb). This approach is used in the absence of thyroid scintigraphy and uptake or when these are contraindicated. TRAb may also be measured in patients with postpartum thyroiditis but it shows Graves'disease in high titers [6, 10].

In the absence of thyroid scintigraphy and uptake or when these are contraindicated, the ratio of total T3 and total T4 may be useful in evaluating the etiology of thyrotoxicosis. As T3 synthesis from the hyperactive gland is more than T4, this ratio (ng/mcg) is > 20 in GD and < 20 in painless or postpartum thyroiditis [11]. ATA/AACE guidelines recommend TRAb measurement and total T3/total T4 ratio as an alternative method for the diagnosis of GD in the absence of thyroid scintigraphy and uptake or when these are contraindicated [6]. As serum thyroxine-binding globulin may affect many conditions in an unfavorable manner, total T4 and T3 measurements may be affected.

Today, free thyroid hormone (FT4 and FT3) measurement are used as gold standard test for the diagnosis of thyrotoxicosis [11]. TSH receptor antibody measurement is not performed in many centers, it is expensive and the results take time. In this study, we intended to perform a differential diagnosis for these two conditions by checking the increase ratio of free thyroid hormones.

In our study, we analyzed how much FT3 and FT4 was increased compared to ULN and the ratio of these increases. There was a significant difference between the groups in terms of FT3 and FT3 index, but there was no differentiating threshold value for the diseases. There was no difference between the groups in terms of FT4 and FT4 index. In our study, FT3 index increased more than FT4 indexin all GD patients and FTHI was above 1. On all thyroiditis patients FT4 index increased more than FT3 index and FTHI was below 1.

CONCLUSION

As a result, we demonstrated that we could perform a differential diagnosis for Graves'disease and thyroiditis by only checking the increase ratios in free thyroid hormones. The increase in the free thyroid hormone values in the absence of thyroid scintigraphy and uptake or when these are contraindicated may be used as an alternative method for the differential diagnosis of Graves'disease. This is a new finding but due to the limited number of patients in our study, there is a need for studies with more patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

[1] Devereaux D, Tewelde SZ. Hyperthyroidism and thyrotoxicosis. Emerg Med Clin N Am 2014;32:277-92.

[2] Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet 2012;379:1155-66.

[3] Grigoriu C, Cezar C, Grigoras M, Horhoianu I, Parau C, Vîrtej P, et al. Management of hyperthyroidism in pregnancy. J Med Life 2008;1:390-6.

[4] Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013;1:238-49.

[5] Menconi F, Marcocci C, Marinò M. Diagnosis and classification of Graves' disease. Autoimmun Rev 2014;13:398-402.

[6] Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al.;American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21:593-646.

[7] Samuels MH. Subacute, silent, and postpartum thyroiditis.

Med Clin North Am 2012;96:223-33.
[8] Woolf PD. Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? Endocr Rev 1980;1:411-20.
[9] Bogazzi F, Vitti P. Could improved ultrasound and power Doppler replace thyroidal radioiodine uptake to assess thyroid disease? Nat Clin Pract Endocrinol Metab 2008;4:70-1. [10] Gorman CA. Radioiodine and pregnancy. Thyroid 1999;9:721-6.
[11] Shigemasa C, Abe K, Taniguchi S, Mitani Y, Ueda Y, Adachi T, et al. Lower serum free thyroxine (T4) levels in painless thyroiditis compared with Graves' disease despite similar serum total T4 levels. J Clin Endocrinol Metab 1987;65:359-63.
[12] Dufour DR. Laboratory tests of thyroid function: uses and limitations. Endocrinol Metab Clin N Am 2008;36:579-94.