

## The High Ratio of Thyroiditis as a Main Cause of Thyrotoxicosis in Patients Referred to the Nuclear Medicine Department of Babol Shahid Beheshti Hospital

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### ABSTRACT

**BACKGROUND AND OBJECTIVE:** Thyrotoxicosis is a disease that results in excessive thyroid hormone activity in the blood. Common causes include Graves's disease, toxic nodular goiter (single or multiple) and thyroiditis. However, the cause of thyrotoxicosis may be different due to geographical areas, so in this study, the prevalence of thyrotoxicosis in the Babol County was investigated.

**METHODS:** In this cross-sectional study, 30 thyrotoxic patients who were referred for thyroid scan were evaluated. The thyroid scan was performed with radiopharmaceutical of technetium pertechnetate and based on the results of the scan; the patients were divided into two general groups. The first group increased the absorption of radiopharmaceutical or hyperthyroidism, which included graves and, toxic nodular goitre (single or multiple). The second group reduced the absorption of radiopharmaceutical, which included thyroiditis (subacute and painless).

**FINDINGS:** Of the 300 patients with thyrotoxicosis, 209 patients were women (69.7%) and 91 patients were men (30.3%). In thyroid scan, 135 cases of thyroiditis (45%), which 95 cases were women (70.4%) and 40 cases were men (29.6%), 96 patients of Graves (32%), 57 cases were women (4 (59%) and 39 cases were men (40.6%) and 69 cases of adenoma (23%), 57 cases were women (82.6%) and 12 cases were men (17.4%).

**CONCLUSION:** Thyroiditis in our region may be more frequent than Graves' disease and can be the most common cause of thyrotoxicosis, which can be important in medical decision-making.

**KEY WORDS:** *Thyrotoxicosis, Thyroiditis, Graves disease, Toxic Nodular Goiter and Thyroid Scan.*

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## Introduction

Thyrotoxicosis is a clinical condition that results from over-acting thyroid hormone in the blood and tissues of the body. Thyrotoxicosis can be caused by inappropriate stimulation of the thyroid gland and high levels of hormones secretion by stimulus factors. Passive release of thyroid hormone reserves following an infectious, autoimmune, chemical or mechanical stimulant can also be the cause of thyrotoxicosis.

Also, access and contact with non-thyroid sources of thyroid hormone include internal sources such as Stroma Ovaria, functional metastases of distinct thyroid cancers and external sources including fictitious thyroiditis are considered as the causes of this disease (1). Thyrotoxicosis is generally considered to be both clinical and subclinical type. Clinically defined as either low or undetectable TSH in the presence of increased T4 and T3, and subclinical type is defined as low or undetectable TSH in the presence of normal T4 and T3 (2). Clinical or subclinical thyrotoxicosis leads to a number of symptoms such as weight loss, appetite, limb shaking, heat intolerance, sweating, palpitations, nervous irritability, and exophthalmos particularly in Graves'. In some cases, unusual symptoms such as diffuse itching, vomiting, anorexia and cardiac symptoms, especially in adults, may be the predominant manifestation of the disease. In such cases, the diagnosis and treatment of the disease is usually delayed, which may have adverse consequences (3).

Graves' disease is one of the most common causes of hyperthyroidism. Although the toxic nodular Goiter is less prevalent than Graves' disease, its prevalence increases with age and in the iodine deficiency. In fact, toxic nodular Goiter in older people living in areas with iodine deficiency may be more common than Graves' disease. The less common cause of thyrotoxicosis is due to inflammation of the thyroid tissue and the release of existing hormones into the circulatory system, which includes sub-acute and painless thyroiditis. Painless thyroiditis in postpartum period may occur during treatment with lithium or cytokines, such as interferon alfa, and in 5 to 10% of patients treated with amiodarone. Sub-acute thyroiditis seems to be due to viral infection and it is characterized by fever and painful thyroiditis (1, 4, 6). The causes of thyrotoxicosis are divided into two general categories: 1- cases with hyperthyroidism including Graves' disease, toxic nodular goiter (including single toxic adenoma and multi toxic nodular goiter). 2- Cases without hyperthyroidism, which includes thyroiditis (painless thyroiditis and subacute thyroiditis), the use of certain

drugs or thyroid hormones (such as amiodarone and levothyroxine). Although the clinical manifestations of thyrotoxicosis are more or less similar, it needs to be reasonably diagnosed for treatment (7, 8). Appropriate treatments in cases with hyperthyroidism (Graves' disease, toxic nodular goiter) are ant thyroid drugs (ATDs), iodine-131 and surgical treatment (thyroidectomy).

In cases without hyperthyroidism (thyroiditis), therapies are supportive and symptomatic. In addition, beta-blockers may be used in almost all forms of thyrotoxicosis, while they are only useful in some cases (1, 9). Thyroid dysfunction, especially thyrotoxicosis, is one of the cases faced by various groups of physicians (general, various specialties). Having a relatively similar approach in dealing with these disorders and requesting minimum testing and imaging will increase the patient's trust in the medical community and reduce the cost of treatment for families and reduce the loss of health care budgets in the country. Regarding the fact that treatment of thyrotoxicosis requires a precise diagnosis of the cause, it is seen frequently that the treatment is initiated empirically, in particular with ant thyroid drugs (ATDs), which is based on the prevalence of the cause of thyrotoxicosis mentioned in the reference books, which may be as inconsistent with our geographical area. Accordingly, in this study, the prevalence cause of thyrotoxicosis in the Babol region was studied.

## Methods

This cross-sectional study was approved by the Ethics Committee of Babol University of Medical Sciences with number MUBABOL.HRI.REC.1396.169 and totally in 1396 was performed on all patients referred for thyroid scan, in which thyrotoxicosis was confirmed by laboratory tests. In all patients, thyroid scan was performed using a radiopharmaceutical of technetium pertechnetate with 5-Millicurie with Gama Orbiter Siemens, equipped with a low-energy, high-resolution ( $128 \times 128$  matrix, 180 seconds and factor Zoom 1.5 in the anterior view). Then, based on the results of the scan, the patients were divided into two general groups. The first group increased the absorption of radiopharmaceutical or hyperthyroidism, which included Graves' and toxic nodular goiter (single or multiple). The second group reduced the absorption of radiopharmaceutical, which included cases of thyroiditis (subacute and painless). Thyroid laboratory tests were also collected and patients were divided into two groups of clinical thyrotoxicosis (low TSH, high T3

and T4) and subclinical thyrotoxicosis (low TSH, normal T3 and T4). By collecting accurate biography, patients who were taking drugs that caused changes in iodine absorption in the thyroid gland, like thyroid hormones, lithium, cytokines such as interferon alfa and amiodarone were removed from the study. Data were analyzed using SPSS-22 software and ANOVA, Tukey, Chi-square and Bonferroni test, analysis, and  $p < 0.05$  was considered statistically significant.

## Results

In this study, 300 patients with thyrotoxicosis were studied. Of these numbers, 209 people were women (69.7%) and 91 people were men (30.3%) (Table 1). Thyroid scan was performed on 135 patients with thyroiditis (45%), 96 cases of Graves (32%) and 69 of adenomas (23%). Figure 1 shows an example of the distribution of technetium pertechnetate absorption in the thyroid scan of patients in the triple group. Among three groups, there was a significant difference in terms of gender involvement, which women were more abundant in all three groups ( $p = 0.006$ ). The mean age of the patients was  $45.8 \pm 13.1$  years, which mean age in the thyroiditis group was  $45.7 \pm 13.7$  years, in the Graves group was  $42.7 \pm 12$  years and in the adenoma group was  $45.8 \pm 13.3$  years. There was no significant difference between groups in terms of age.

The mean serum level of TSH, T3 and T4 in the thyroiditis group were  $0.09 \pm 0.19$ ,  $3.7 \pm 3.7$ , and  $13.9 \pm 3.8$ , respectively, and in Graves group they were  $0.07 \pm 0.09$ ,  $3.6 \pm 2.4$  and  $15.6 \pm 5.5$  in the adenoma group they were  $0.17 \pm 0.20$ ,  $2.9 \pm 2.9$  and  $10.7 \pm 2.5$  (Table 2). According to the results of one-way ANOVA, there was a significant difference between mean TSH in the studied groups ( $p < 0.001$ ). The results of Tukey's post hoc test showed that there was a significant difference between the mean serum level of TSH between thyroiditis and toxic nodular goiter and also between Graves' and toxic nodular goiter groups ( $p < 0.001$ ). Also

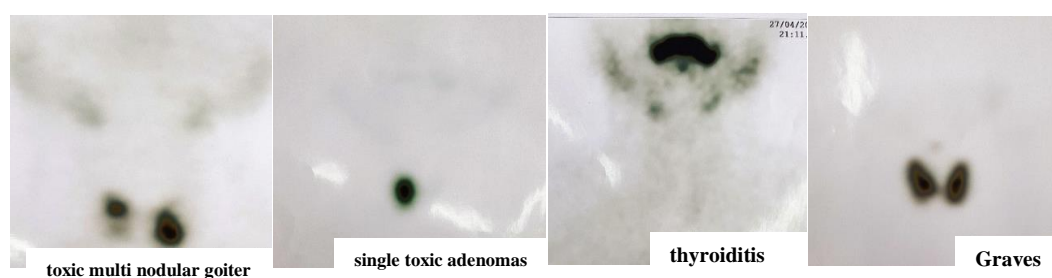
the results of one-way analysis of ANOVA and Tukey's post hoc test showed a significant difference between the mean serum level of T4 ( $p < 0.001$ ). However, this difference was not significant in the mean serum level of T3. Of the 300 patients that were studied, 178 (59.3%) patients suffered from clinical thyrotoxicosis and 122 patients (40.7%) suffered from subclinical thyrotoxicosis (Table 3). Of the 135 patients in the thyroiditis group, 87 patients suffered from clinical thyrotoxicosis (64.4%) and 48 patients suffered from subclinical thyrotoxicosis (35.6%), of which in the Graves group 70 patients suffered from clinical thyrotoxicosis (72.9%) and 26 patients suffered from subclinical thyrotoxicosis (27.1%) and in the toxic nodular goiter group 21 cases suffered from clinical thyrotoxicosis (30.4%) and 48 cases suffered from subclinical thyrotoxicosis (69.6%).

Chi-square test showed a significant relationship between thyrotoxicosis and triple groups ( $p < 0.001$ ). Using Bonferron's modified test, it was found that in the clinical type, the toxic nodular goiter was significantly less than Graves and thyroiditis, but in the subclinical type it was significantly higher. Also in Table 4, the mean serum level of thyroid factors in triple groups is shown in terms of thyrotoxicosis. The results of one-way ANOVA showed that there was no significant difference of TSH between the three groups in clinical thyrotoxicosis, but there was a significant difference of T4 between the thyroiditis and Graves groups and between the toxic nodular goiter and graves groups ( $p < 0.001$ ).

On the other hand, the result of above tests showed that there was a significant difference of TSH between thyroiditis and toxic nodular goiter and between grave and toxic nodular goiter ( $p = 0.01$ ), difference of T4 between thyroid and the toxic nodular goiter groups was significant ( $p = 0.001$ ). Also, there was no significant difference for T3 in both types of clinical and non-clinical thyrotoxicosis between the three groups (Table 4).

**Table1. Demographic characteristics of studied patients**

Thyroid scan findings		Thyroiditis N(%)	Graves N(%)	Toxic nodular goiter N(%)	Total	P-value
Sex	Female	95(70.4)	57(59.4)	57(82.6)	209(69.7)	0.006
	Male	40(29.6)	39(40.6)	12(17.14)	91(30.3)	
Age		$45.7 \pm 13.7$	$42.7 \pm 12$	$45.8 \pm 13.3$	$45.8 \pm 13.1$	0.16



**Figure 1.** Distribution of absorption of technetium pertechnetate in thyroid scan of patients with triple groups; from right to left: Graves (increased diffusion absorption), thyroiditis (decreased or not absorbed), single toxic adenomas (increased single focus absorption), and toxic multi nodular goiter (increased multiple focuses absorption )

**Table2.** The mean serum level of thyroid factors in triple groups

Laboratory Parameters	Thyroiditis N(%)	Graves N(%)	Toxic nodular goiter N(%)	P-value
TSH, mean (SD), mIU/l	0.09(0.11)	0.07(0.09)	0.18(0.2)	<0.001
Total T3, mean (SD), ug/dl	3.9(7.2)	3.6(2.4)	2(0.9)	0.42
Total T4, mean (SD), ug/dl	13.9(3.8)	15.6(5.5)	10.7(2.5)	<0.001

**Table3.** Classification of triple groups based on type of thyrotoxicosis

Type of thyrotoxicosis	Thyroiditis N(%)	Graves N(%)	Toxic nodular goiter N(%)	P-value
Clinical	87(64.4)	70(72.9)	21(30.4)	<0.001
Sub-Clinical	48(35.6)	26(27.1)	48(69.6)	

**Table4.** Average serum level of laboratory tests in different groups according to type of thyrotoxicosis

Type of thyrotoxicosis	Laboratory Parameters	Thyroiditis N(%)	Graves N(%)	Toxic nodular goiter N(%)	P-value
Clinical	TSH, mean (SD), mIU/l	0.06(0.09)	0.05(0.07)	0.07(0.15)	0.46
	Total T4, mean (SD), ug/dl	15.6(3.46)	17.8(4.9)	14(1.9)	<0.001
	Total T3, mean (SD), ug/dl	5.3(9.17)	4.3(2.3)	2.7(1.11)	0.64
Sub-Clinical	TSH, mean (SD), mIU/l	0.14(0.14)	0.3(0.11)	0.23(0.2)	0.01
	Total T4, mean (SD), ug/dl	10.6(1.41)	9.8(1.5)	9.5(1.37)	0.001
	Total T3, mean (SD), ug/dl	1.85(0.33)	1.1(0.46)	1.61(0.53)	0.16

## Discussion

The results of this study indicate that thyroiditis in our study area is more prevalent than Graves and other causes of thyrotoxicosis and can be considered as the most common cause of this disease. Thyrotoxicosis is one of the most common thyroid diseases, with prevalence of 1.5-1.5%, that incidence rate in women is 5-10 times more than it's incidence in men (1,2). In our study, although the number of female patients was more frequent, from the 300 patients studied, 209 (69.7%) patients were female, but a high incidence was observed in men. The ratio of female-to-male involvement was 2 to 1, which may indicate higher involvement in males. Therefore, our study can be roughly similar to that of Bell and colleagues, of which 317 patients (24%) were female (78%). The mean age of patients in the current study was 45.8 years, which is

consistent with the prevalence of the disease in middle ages. In the Lauren Bell study, the mean age of patients was 45 years, which is similar to our study (10). In various studies, Graves' disease is one of the most common causes of thyrotoxicosis, and in some sources its prevalence is reported to be 80% (1, 2 and 9). In a study conducted by Avs et al., 60 patients suffered from thyrotoxicosis, 45 cases suffered from Graves (75%), 10 cases suffered from thyroiditis (17%) and 5 cases suffered from toxic adenomas (8%) (11). However, our study found that thyroiditis was the most common cause of thyrotoxicosis (45% of cases) and Graves were seen only in 32% of patients. In this regard, our findings are close to the study of Sang et al. in South Korea, in which the study stated that thyroiditis is high in the area, with 30% of patients with thyroiditis (12). Like most thyroid disorders, in our study thyroiditis was more prevalent in

women, but the mean age of the conflict was not different from other groups. Graves' disease is clearly more prevalent in female than male, as the estrogen hormone, as a female hormone, can play a role in this (9), which is more common in women than men (5:1) (13). For example, in the study of Allahabadia et al., 536 patient with Graves 444 patients were female (82.8%) and 92 patients were male (17.2%) with a ratio of 4.8: 1 (14). But in our study, Graves' group was 59.4% female and 40.6% male, which is approximately 1.5: 1. In our study, Graves was observed in men with a higher prevalence. Perhaps the role of environmental factors in our area of life, including stress and smoking, may be effective. In the toxic nodular goiter group, 30% of patients suffered from multinodular goiter with an average age of 50 years and were more likely to be seen in women (8: 1), with respect to the age of conflict and the frequency of sex was consistent with the findings of Carle et al. at the age of 50 and at a frequency of 6: 1 in female sex (15).

On the other hand, 70% of patients suffered from the single adenomas with an average age of 44 years, that had lower mean age than the multinodular goiter group, which is consistent with previous findings (2). In the study of laboratory parameters, the mean TSH in comparison between the groups showed a significant difference between the thyroiditis and the toxic nodular goiter groups and between the Graves and the toxic nodular goiter groups, but there was no significant difference between Graves and thyroiditis groups. Mean level of T4 had a significant difference between the thyroiditis and the toxic nodular goiter groups, and between Graves and the toxic nodular goiter groups but there was no significant difference between the Graves' and the thyroiditis groups. However, there was no such difference between the groups in terms of the mean level of T3. In the present study, approximately 60% of patients suffered from clinical thyrotoxicosis and 40% suffered from subclinical thyrotoxicosis. In a similar study, by Shekhar et al in 2018 found that 73% of patients suffered from clinical thyrotoxicosis and 27% suffered from subclinical thyrotoxicosis (16). In another study by Shashi et al. in 2015, 65% of patients suffered from clinical thyrotoxicosis and 35% suffered from subclinical thyrotoxicosis, which was similar in our study in terms of distribution in both clinical and subclinical thyrotoxicosis groups (17). In terms of categorization, groups based on the type of thyrotoxicosis (clinical and subclinical) showed a significant difference between the groups. For example,

most clinical cases of thyrotoxicosis were found in the Graves group (approximately 73%) and the thyroiditis group (approximately 65%), which showed a significant difference in comparison with the toxic nodular goiter group (approximately 27%). In contrast, in toxic nodular goiter group, most patients (approximately 70%) suffered from subclinical thyrotoxicosis. Such findings are commonly expected, since to occur clinical thyrotoxicosis, the size of the adenoma diameter should be greater than 3 centimeters, and in lesser sizes, thyrotoxicosis is usually seen subclinically (2). There was no significant difference between graves and thyroiditis groups according to the type of thyrotoxicosis (clinical and subclinical). Therefore, based on the laboratory findings, it was not possible to categorize definitive categorization of the patient into triple groups, especially between graves and thyroiditis. The findings of this study indicate that contrary to the findings in reference literature derived from the study of patients in the advanced Western countries, and in particular the United States, thyroiditis in our region is more prevalent than Graves and can be considered as the most common cause of thyrotoxicosis. Because Since anti-thyroid drugs such as methimazole are not suitable choice in treatment of thyroiditis, it is desirable that due to the high prevalence of thyroiditis in our area, treatment of thyrotoxicosis should be performed after definitive diagnosis, and avoid empirical treatment. The limitations of this study, were the low volume of the sample considering the two-year study period, which requires continuation of the study in a longer period and in cooperation with other centers. It is also possible that some patients with graves will not be referred for thyroid scan, since an extra thyroid manifestation, such as ophthalmopathy, may occasionally cause a definitive diagnosis. Although this may have some effect on the prevalence of Graves, it does not seem to be significant, and requires further examination with the help of endocrine specialists.

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