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Original Article

99mTc-pertechnetate cut-off to distinguish Graves' disease from subacute thyroiditis

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Abstract

Background: The cause of thyrotoxicosis can be determined through the thyroid uptake of 99mTc-pertechnetate**.** The goal of the study was to calculate the cut-off value of 99mTc-pertechnetate of the thyroid gland for the differential diagnosis of Graves' disease from subacute thyroiditis.

Methods: A total of 60 patients were included in the study**.** Based on thyroid scan findings, 30 patients were in the Graves group and 30 of them had been diagnosed as subacute thyroiditis. Biochemical parameters, thyroid scintigraphy, and the percentage thyroidal 99mTc-pertechnetate uptake results were thoroughly assessed.

Results: The mean percentage 99mTc-pertechnetate uptake in Graves group was much higher than that of the subacute thyroiditis group, which was statistically significant (P <0.001). Receiver operating characteristic (ROC) analysis revealed that the uptake cut-off value of 1.1% had the sensitivity and specificity of 97% and 95%, respectively.

Conclusion: The findings depicted that the cutoff value of 1.1% for 99mTc-pertechnetate uptake could be a helpful index to differentiate Graves' disease from subacute thyroiditis, especially when it is difficult to distinguish between the two diseases using conventional diagnostic methods.

Keywords: Thyrotoxicosis, Technetium uptake, Graves' disease, Subacute thyroiditis.

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Thyrotoxicosis refers to a clinical condition resulting from the excess of thyroid hormone in body tissues. This condition can be caused by an over-synthesis of thyroid hormones (hyperthyroidism) or by a destructive process in the thyroid gland (subacute thyroiditis). Radioactive iodine uptake (RAI) test is recommended in the guidelines for the differential diagnosis of patients with thyrotoxicosis, especially patients who cannot be definitively diagnosed based on clinical and biochemical tests (1).

Common diagnostic methods for thyrotoxicosis include: the estimation of the ratio of free triiodothyronine to free thyroxine (FT3 / FT4 ratio), the measurement of the serum thyrotropin receptor antibody (TRAb) level, the semi-quantification of intra-thyroid vessels and the measurement of mean maximum systolic velocity (PSV) in thyroid arteries by ultrasonography, which are all appropriate and useful for determining the pathogenesis of thyrotoxicosis (2).

To ensure optimal treatment, it is important to differentiate between the causes of thyrotoxicosis. In this regard, it is important to distinguish between Graves' disease and subacute thyroiditis. In many cases, a radioactive iodine uptake (RAI) test is necessary to diagnose the cause of thyrotoxicosis, but it is often onerous and painstaking. Today, thyroid scintigraphy, one of the most widely used nuclear medicine imaging, is used to evaluate thyrotoxicosis and seems to be a qualified alternative technique. 99mTc-pertechnetate uptake test is a fast and cost-effective technique that can be applied instead of RAI uptake, and it is claimed that 99mTc-pertechnetate uptake test and RAI uptake have a good correlation (3, 4).

In general, few studies have been conducted in this area. In current years, with the remarkable use of programs to measure the uptake of 99mTc-pertechnetate, this method is becoming a routine method in nuclear medicine. Accordingly, several studies have been conducted to determine the normal range of 99mTc-pertechnetate uptake values (5-8). Therefore, determining the range of 99mTc-pertechnetate thyroid uptake in any particular geographic area is a great help in interpreting thyroid scintigraphy, especially to determine the cause of thyrotoxicosis. In our study, the thyroid uptake of 99mTc-pertechnetate in normal subjects ranged from 0.6 to 1.8% (9). In a study we conducted in 2017, subacute thyroiditis in our area was much higher than that of Graves' disease, which is deemed as the most common cause of thyrotoxicosis. In addition, the identification of these causes seems vital in medical decision-making; therefore, it is essential to determine the causes of thyrotoxicosis meticulously (10).

In this regard, few studies have been performed to discriminate between Graves' disease and subacute thyroiditis based on thyroid pattern scintigraphy and semi-quantitative calculation of percentage thyroid uptake of 99mTc-pertechnetate. Different cut-off values of uptake in different studies have been determined in recent years, ranging from 0.7 to 1.55 with the acceptable sensitivity and specificity (2, 8, 11). Since so far, such a study has not been reported in our geographical area, the aim of this study was to determine the percentage 99mTc-pertechnetate uptake in patients with Graves' disease and subacute thyroiditis and also to calculate the optimal cut-off value to differentiate between the two diseases.

Methods

This research was approved by the Ethics Committee of Babol University of Medical Sciences (ID number: 724133972; IR.MUBABOL.HRI.REC.1400.143). This cross-sectional study was performed to determine the cut-off value of thyroid uptake of radiopharmaceutical technetium pertechnetate in patients with Graves' disease and subacute thyroiditis who referred to the nuclear medicine department of Shahid Beheshti Hospital in Babol. The data were analyzed for all patients who had thyrotoxicosis in thyroid function tests and were referred to the Shahid Beheshti Hospital for thyroid scan from 2017 to 2020. In all patients, thyroid scan was performed as usual using 99mTc-pertechnetate. Also, the thyroid uptake percentage of 99mTc-pertechnetate was calculated by the following method. 99mTc-pertechnetate was injected at a dose of 5 mCi. The percentage 99mTc-pertechnetate uptake by the thyroid gland in 20 minutes was determined using nuclear imaging techniques. For this purpose, a gamma camera equipped with a low energy collimator and a parallel hole was used. Images were obtained with a 128 × 128 pixel matrix with a zoom of 1.5.

Images were taken from the syringe before and after the injection of 99mTc-pertechnetate to determine the exact amount of the prescribed dose to calculate the thyroid uptake. Images were taken from a syringe as well as from the front of the neck to image the thyroid for 60 seconds. A controlled image of the injection site was taken for the accuracy of the intravenous injection because extravasation is unacceptable for calculating the percentage of thyroid uptake. Thyroid uptake of Tc-99m pertechnetate is calculated for each participant using the following formula:

$$\%\ \text{uptake} = \frac{\text{Thyroid count} - \text{Background count}}{\text{pre injection syring count} - \text{post injection syring count}}$$

Patients with a history of heart, kidney and thyroid diseases were excluded from the study. Patients with a history of thyroid surgery and recent iodine-contrast radiographs and patients taking drugs affecting thyroid function were also excluded from the study. Patients who did not meet the exclusion criteria and were diagnosed with thyrotoxicosis based on laboratory tests and sent to our center for thyroid scan to diagnose the cause of thyrotoxicosis were included in the study. Thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) levels were measured in all patients. Also, the serum level of thyroid peroxidase antibody (TPOAb) in 43 patients (24 Graves, 19 thyroiditis) and thyrotropin receptor antibody (TRAb) in 37 patients (20 Graves, 17 thyroiditis) was measured using electrochemiluminescence analyzers (Roche Diagnostics GmbH, Germany). The patients were definitively examined and diagnosed by a qualified nuclear physician according to the thyroid pattern scan, laboratory results, and clinical records in the follow-up. The percentages thyroidal uptake of 99mTc-pertechnetate in both groups of Graves' disease and subacute thyroiditis were determined, and the best cut-off value for the differentiation of these two diseases was finally determined by statistical analysis.

Statistical analysis: The data were analyzed using SPSS software (Version 23.0, Chicago, IL, USA) with chi-square, t-test and Mann-Whitney tests. The *p*-value ($p < 0.05$) was considered significant. Also, with ROC analysis, the optimal cut-off value was determined with the best sensitivity and specificity.

Results

A total of 60 patients, 26 (43.3%) male and 34 (56.7%) female, were included in the study. The mean age of patients participating in this study was 46.67±11.27 (from 23 to 67 years). Also, according to Shapiro-Wilk test, the age distribution of patients was not normal (P = 0.192). Based on thyroid scan findings, 30 were in the Graves group, and 30 were in the subacute thyroiditis group. In Graves group, there were 16 men (53.3%) and 14 women (46.7%). In subacute thyroiditis group, there were 10 men (33.3%) and 20 women (66.7%) (figure 1). Also, the gender distribution between the two groups was not significant (P = 0.118). The mean age for the Graves group was 44.31±11.99, and it was 48.67 ± 10.31 years for the subacute thyroiditis group. This difference of 4 years was not statistically significant (P = 0.171).

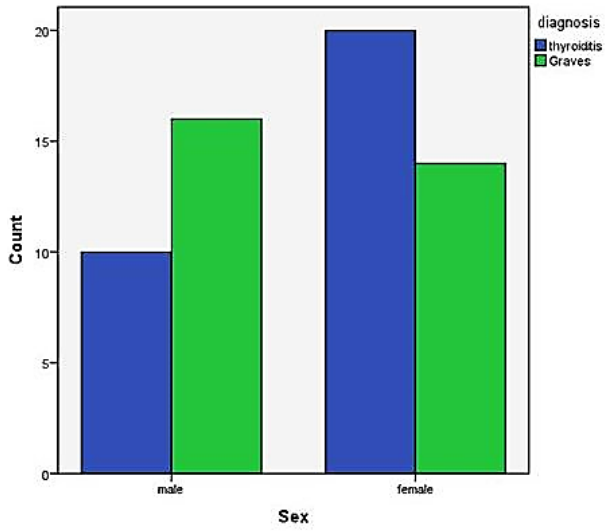

Figure 1. Diagram of gender distribution between Graves and subacute thyroiditis groups

In laboratory thyroid tests, only T4 test had a normal distribution in both groups, Graves (P = 0.523) and subacute thyroiditis (P = 0.512). But in laboratory tests, TSH and T3 did not meet the normality condition (p <0.001). The mean TSH level was 0.046±0.062 in Graves group and 0.075±0.136 in subacute thyroiditis group. Although the mean TSH level in Graves group was lower than that of the subacute thyroiditis group, this difference was not statistically significant using Mann-Whitney test (P = 0.097). The mean T3 level was 3.57±2.87 in Graves group and 2.74±1.87 in subacute thyroiditis group. Although the mean level of T3 in Graves group was higher than that of the subacute thyroiditis group, this difference was not statistically significant (P = 0.841). Also, the mean T4 level for the Graves group was 14.31±4.07, and it was 12.71±2.82 for the subacute thyroiditis group. The mean T4 level for Graves group was higher than that of the subacute thyroiditis group, but this difference was not statistically significant (P = 0.081). Patients with Graves' disease exhibited significantly higher serum TRAb and also positivity for TPOAb. The mean percentage radiopharmaceutical uptake of 99mTc-pertechnetate for Graves group was 6.5±4.95 and it was 0.45±0.10 for the subacute thyroiditis group. The mean percentage of uptake for Graves group was much higher than that of the subacute thyroiditis group, which was statistically significant (P <0.001).

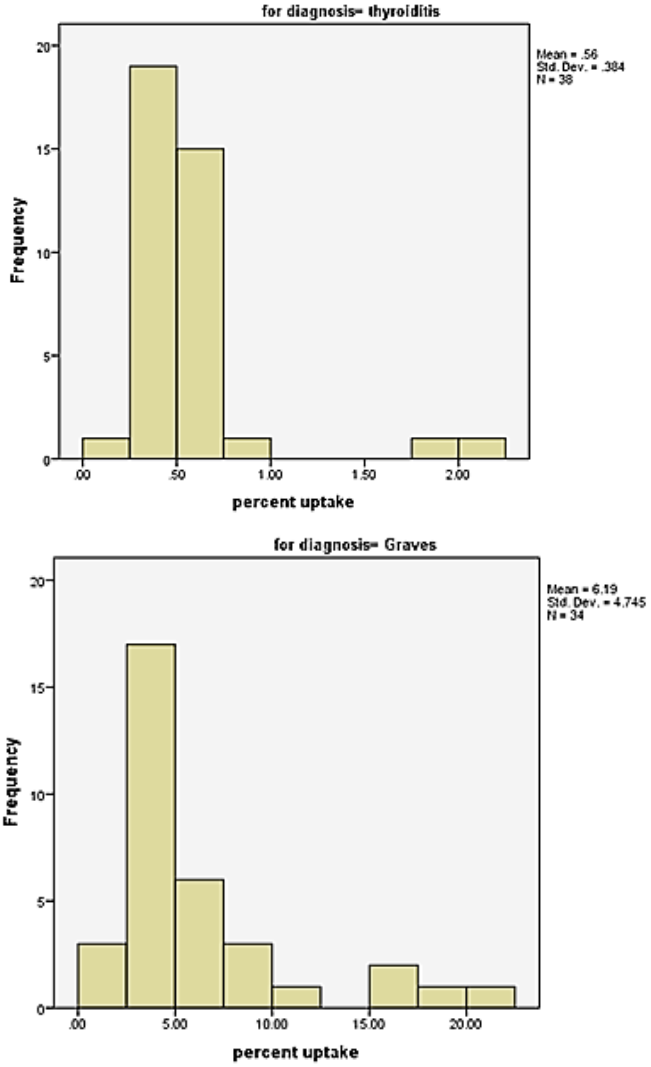

Figure 2. Histogram of percentage uptake in the Graves (up) and subacute thyroiditis (down) groups

To differentiate between the Graves group and the subacute thyroiditis group and also to determine the validity of the percentage 99mTc-pertechnetate uptake, we utilized receiver operating characteristic curve analysis (ROC curve). According to the results of this analysis, the optimal cutoff value with 97% sensitivity and 95% specificity was 1.11%.

Table1. Demographic characteristics and information about functional hormones and percentage of thyroid uptake in the two groups

Variables		Graves	Subacute thyroiditis	P-value
Sex N (%)	Female	14 (46/7)	20 (66/7)	0.118
	Male	16 (53/3)	10 (33/3)	
Age (Mean±SD)		44.67±12	48.67±10.31	0.171[b]
TSH (Mean±SD) mIU/mL		0.046±0.062	0.075±0.136	0.097[a]
TRAb (Mean±SD) (IU/L)		6.3 (1.7-10.6)	1.2 (1.0-2.5)	<0.001[a]
TPOAb (Mean±SD) (IU/mL)		305.4±480.4	65.7±98.1	<0.001[a]
T_3 (Mean±SD) ng/mL		3.57±2.87	2.74±1.87	0.841[a]
T4 (Mean±SD) ug/dL		14.3 ±4.07	12.71±2.82	0.081[b]
Percent Uptake (Mean±SD)		6.51±4.95	0.45±0.11	<0.001[a]

a: Mann-Whitney, b: Independent t-test, TSH: Thyroid Stimulating Hormone, TRAb: Thyrotropin Receptor Antibodies, TPOAb: Thyroid Peroxidase Antibodies, T3: Triiodothyronine, T4: Thyroxine.

Discussion

In this study, the optimal cut-off value for 99mTc-pertechnetate uptake was determined to help differentiate between Graves' disease and subacute thyroiditis. Based on our results, the percentage 99mTc-pertechnetate uptake in the Graves group was meaningfully higher than that of the subacute thyroiditis group. Also, when we implemented the ROC analysis, the cut-off value for the 99mTc-pertechnetate uptake for the distinction of the two diseases was 1.1%, which showed 97% sensitivity and 95% specificity.

There have been only a handful of research studies focusing on the cut-off percentage 99mTc-pertechnetate uptake to differentiate between Graves' disease and subacute thyroiditis. In a study by Fadime in 2020, 99mTc-pertechnetate uptake was considerably higher in patients with Graves' disease than in patients with subacute thyroiditis. By ROC analysis, the cut-off value of 1.55% for 99mTc-pertechnetate had an accuracy of 92.9%, with a sensitivity and specificity of 92% and 87%. The results of that study showed that 99mTc-pertechnetate uptake test can be helpful in distinguishing diagnosis of Graves' disease and subacute thyroiditis (P <0.001) (11). In another study, Zuhur *et al.* measured 99mTc-pertechnetate uptake prospectively and reported the uptake of 3% as the cut-off value (12). This cutoff value of 3% was significantly higher than what was supposed in the current study. This study included two topics, which makes it difficult to be compared with the present study. Initially, their study was to investigate the cut-off number of 99mTc-pertechnetate uptake, but it focused on the upper boundary of the normal reference range of 99mTc-pertechnetate uptake in normal people (0.7%-3%) to differentiate Graves' disease from subacute thyroiditis. Therefore, it is possible that patients with Graves' disease with 99mTc-pertechnetate uptake of less than 3%, as stated by Ikekubo *et al.* are classified as subacute thyroiditis. Second, in this research, which was conducted on patients with thyrotoxicosis with different severities, some patients with Graves' disease had an obvious clinical pattern based on which they did not need to be screened to distinguish from subacute thyroiditis. In fact, only 9% of Graves's patients in that study had a 99mTc-pertechnetate uptake of less than 3% (13).

In addition, Kidokoro-Kunii et *al.* described 0.9% as the cut-off value for 99mTc-pertechnetate uptake for 57 patients with Graves' disease and 7 patients with subacute thyroiditis (14). The lower cut-off value of 99mTc-pertechnetate uptake in their study, compared to our study, could be due to smaller changes in 99mTc-pertechnetate uptake in a small number of patients in the subacute

thyroiditis group (7 subacute thyroiditis vs. 57 Graves patients). Uchida et al. in 2016 stated that a cut-off value of 1% with a sensitivity and specificity of 96.6% and 97.1%, respectively, is effective in distinguishing these two diseases, which was similar to our study. The application of this number of incisions for patients with thyrotoxicosis showed a positive and negative predictive value of 100% and 88.9% in Graves' disease, respectively. They stated that a 1% cutoff value was useful for the uptake of 99mTc-pertechnetate to distinguish between Graves' disease and subacute thyroiditis (2). In another study in Korea in 2021, their cut-off number was below 1% (0.7%), which was smaller than that of our study. This difference in the cut-off values could be attributed to differences in the geographic area and dietary iodine intake (8). Different cut-off values were obtained in previous studies. In the present study, the cut-off value was 1.1, which was similar to other studies that were able to differentiate between Graves' disease and subacute thyroiditis with high sensitivity and specificity, although the sensitivity and specificity of our study were slightly higher than those of other studies.

In this study, the lower limit of 99mTc-pertechnetate thyroidal uptake range in patients with Graves' disease had overlaps (uptake range from 1.6 to 18%), with the upper range of uptake in individuals with normal thyroid uptake (uptake range of 0.54 to 1.8%, performed at this center). Therefore, this issue may sometimes cause problems to differentiate Graves' disease with less thyroid uptake than patients with normal uptake (9). One of the limitations of the current research was the small sample size and the implementation of the study in one center only. Also, we could not obtain information about the estimated iodine intake in the diet and the possible difference in iodine status in our geographical area compared to other parts of the country. In addition, the potential impact of iodine intake on the sensitivity / specificity of 99mTc-pertechnetate uptake was not determined, either. Therefore, it is suggested that a large-scale prospective study with a larger population in several centers in different parts of the country be conducted to confirm the size of the cut-off value more accurately. The findings of the current research show that the cut-off value of 1.1% for the 99mTc-pertechnetate uptake can be helpful in differentiating Graves' disease from subacute thyroiditis. It is suggested to conduct a multicenter study with more samples for more accurate results.

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Authors' contribution: A.Gh, and SH.M.A. designed the study, writing of the article, interpreted the data and the revision of its content, M.S. collected data, H.Sh. analyzed data, all authors approved the manuscript and its final version.

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