

Research Article

Prevalence and Clinical Utility of TSH Receptor Antibody Positivity in Indian Hyperthyroid Subjects

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Citation: Anilkumar R, et al. Prevalence and Clinical Utility of TSH Receptor Antibody Positivity in Indian Hyperthyroid Subjects. Arch Endocrinol Disord. 2025;1(2):1-8.

<https://doi.org/10.46889/AED.2025.1202>

Received Date: 20-09-2025

Accepted Date: 07-10-2025

Published Date: 14-10-2025



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Abstract

We undertook a retrospective analysis of 52 subjects attending Karnataka institute of endocrinology and research, Bengaluru from March 2023 to August 2025. The study included subjects who had been diagnosed with hyperthyroidism and treated with anti-thyroid drugs. Informed consent was taken from all the participants.

Hyperthyroidism was defined as a suppressed TSH (<0.27 mU/L) and elevated free thyroxine (fT4) (>22.0 pmol/L). Demographic data, initial thyroid hormone levels, thyroid antibody titres, doses of ATDs, follow-up thyroid hormone levels and clinical course were reviewed. Patients included in this study were treated using carbimazole with a dose-titration regimen. Patients were reviewed every 4-6 weeks during the first few months of treatment until thyroid hormone levels have stabilized.

Results: TSH receptor antibody was positive in 80.8% of subjects studied. 55.8% of subjects were females. Family history of hyperthyroidism was present in only 2 subjects. Age of the subjects studied ranged from 18 to 80 years. Mean FT4 was 43.42 ± 25.82 and 29.06 ± 10.83 in TSH receptor antibody positive and negative subjects respectively. Mean TSH receptor antibody titres were 13.08 ± 13.47 and 0.83 ± 0.17 in TSH receptor antibody positive and negative subjects respectively. Anti TPO antibody was positive in 67.4% of the subjects studied.

Conclusions: TSH receptor antibody was positive in 80.8% of subjects studied in our study. So the 80.8% of the subjects had Graves' disease. The remaining 19.2% of subjects could be toxic multi nodular goitre, toxic adenoma, thyroiditis or TRAb negative Graves' disease. Graves orbitopathy was present in 13.5% of the subjects and they were all positive for TSH receptor antibodies.

Keywords: Hyperthyroidism; TSH Receptor Antibodies; FT4; TSH; Graves Disease; Anti TPO; Thyroiditis

Abbreviations

GD- Graves' Disease; ATD: Anti Thyroid Drugs; TSH: Thyroid Stimulating Hormone; RAI-Radioactive Iodine; FT4: Free Thyroxine; ATA: American Thyroid Association; TRAb: TSH Receptor Antibody; TPO: Thyroid Peroxidase

Introduction

Overt hyperthyroidism affects 1.3% of people in iodine-replete populations and if untreated is associated with a catabolic state characterized by weight loss, reduced bone mineral density, atrial fibrillation and thromboembolic events [1-3]. Graves' Disease (GD) is the commonest cause of hyperthyroidism in populations with sufficient dietary iodine intake. It accounts for up to 80% of cases, with a lifetime prevalence of 3% in women and 0.5% in men [4-7]. Recent evidence indicates that rapid control of hyperthyroidism in Graves' disease is desirable but it is also important to avoid over treatment. A low Thyroid Stimulating Hormone (TSH) level at one year after diagnosis was linked to a 55% rise in cardiovascular mortality, independent of the treatment approach [8]. Similarly, every 6 months, patients with hyperthyroidism who had suppressed TSH levels were linked

to an 11 to 13 percent higher chance of increased mortality [9]. So, keeping thyroid hormone levels normal is very important when treating people with Graves' disease [7].

Treatment options for managing Graves' hyperthyroidism include Anti-Thyroid Drugs (ATD), Radioactive Iodine (RAI) therapy or removal of the entire thyroid gland. Anti-thyroid drugs are usually the first treatment chosen for Graves' hyperthyroidism. In Europe, ATD is commonly used as the first choice and about half of the patients achieve remission after taking the medication for 12 to 18 months [10,11]. In the past, radioactive iodine was the usual choice in the USA, but now the American Thyroid Association suggests that antithyroid drugs can also be used as the first treatment option [7,12].

ATDs can be given in two ways. One way is called a "dose titration" method, where the starting dose is high and then it is lowered over time. The other way is called a "block and replace" method, where the full dose of ATDs is used right away and at the same time, thyroxine is given to keep the thyroid hormone levels normal. Neither of these methods has been proven to be better in achieving remission [13]. However, the dose titration method uses lower doses of ATDs, which may mean fewer side effects, like agranulocytosis [14]. Also, people are less likely to stop treatment early because of side effects when using the dose titration method compared to the block and replace method [13-16]. In this study, we used the dose titration method to treat hyperthyroidism.

Many clinicians rely on experience-based approaches when prescribing antithyroid drugs. For instance, Abraham and colleagues suggest starting with a daily dose of 10-20 mg of carbimazole or methimazole if FT4 levels are below 40 pmol/l and 40 mg daily if FT4 is above 40 pmol/l and then halving the dose following 1 month of treatment [17].

Endocrinologists are now using Antithyroid Drugs (ATDs) more often than Radioactive Iodine (RAI) as the first treatment for Graves' disease, according to the ATA 2024 guidelines. A survey from 2011 showed that in the US, the percentage of doctors using I-131 as the first treatment dropped from 70% in 1990 to 60% by 2011. At the same time, the use of ATDs as the first treatment went up from 30% to 39% during that time. A 2020 study looking at US insurance records from 2005 to 2013 found that 33% of patients received I-131 first, while 60% were treated with ATDs first. A 2023 survey of endocrinologists in North America found that only 11% of them chose I-131 as the first treatment option for their patients with Graves' disease.

Objectives

This study was done to find out the prevalence of TSH receptor antibody positivity in Indian hyperthyroid subjects.

Materials and Methods

We undertook a retrospective analysis of 52 subjects attending Karnataka institute of endocrinology and research Bengaluru from March 2023 to August 2025 who had been diagnosed with hyperthyroidism and treated with anti-thyroid drugs carbimazole. Informed consent was taken from all the participants. Hyperthyroidism was defined as a suppressed TSH (<0.27 mU/L), elevated free thyroxine (fT4) (>22.0 pmol/L). Demographic data, initial thyroid hormone levels, thyroid antibody titres, doses of ATDs, follow-up thyroid hormone levels and clinical course were reviewed. Patients included in this study were treated with carbimazole in a dose-titration regimen. The highest initial dose for commencing treatment was carbimazole 60 mg daily for patients with elevated thyroid hormone levels. A lower dose was used for patients with lower levels of thyroid hormones, based on individual endocrinology physician's practice. Patients were reviewed every 4-6 weeks during the first few months of treatment until thyroid hormone levels have stabilized. Serum TSH, fT4, TSH receptor antibodies and anti TPO antibody levels were measured using automated chemiluminescent immunoassays. The TSH receptor is a G protein-coupled receptor synthesized as a 764 amino acid polypeptide. It undergoes post-translational cleavage of a 50 amino acid C-peptide to form TSH receptor A and B chains, linked by disulphide bonds. The extracellular A subunit is shed resulting in the generation of self-antigens which are presented in the context of MHC class II molecules, leading to activation of nonself-tolerant CD4⁺ T-cells, eventually resulting in the production of stimulatory antibodies. TRAb was discovered by Adams and Purves 60 years ago [18,19]. The sensitivity and specificity of a fully automated electrochemiluminescence assay evaluated in a multicentre trial were 99% at a cut-off value of 1.75 IU/l for the diagnosis of GD, with positive and negative predictive values of 95% and 100% respectively [20]. Anti TPO antibody >34 IU/ml is considered as positive.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made.

Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance. A t-test is a statistical test that is used to compare the means of two groups. It is often used in hypothesis testing to determine whether a process or treatment actually has an effect on the population of interest or whether two groups are different from one another with the null Hypothesis (H0) is that the true difference between these group means is zero and the alternate Hypothesis (Ha) is that the true difference is different from zero.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small also when expected frequencies are small (less than 5), the chi-square approximation may not be accurate. Yates' correction provides a more conservative result, reducing the risk of falsely rejecting the null hypothesis.

$$\chi^2_{Yates} = \sum \frac{(|f_o - f_e| - 0.5)^2}{f_e}$$

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value:0.01<P=0.05)

** Strongly significant (P value : P=0.01)

Statistical Software

The Statistical software namely SPSS 22.0 and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

Hyperthyroid subjects presented with common symptoms of loss of weight, palpitation, excessive sweating, insomnia, irritability, anxiety and heat intolerance. Uncommon symptoms are neck swelling, loose motions, amenorrhea in females. Graves's orbitopathy was present in 7 patients. Diabetes and hypertension was diagnosed in 14 subjects.

TSH receptor antibody positive in 80.8% of subjects studied. 55.8% of subjects were females. Family history of hyperthyroidism was present in only 2 subjects (Table 1). Age of the subjects studied ranged from 18 to 80 years. Mean FT4 was 43.42 \pm 25.82 and 29.06 \pm 10.83 in TSH receptor antibody positive and negative subjects respectively. Mean TSH receptor antibody titres were 13.08 \pm 13.47 and 0.83 \pm 0.17 in TSH receptor antibody positive and negative subjects respectively (Table 2-7). Anti TPO antibody was positive in 67.4% of the subjects studied.

Presenting Symptoms	Percent
Anterior neck swelling	50
Palpitation	80
Heat intolerance	70
Excessive sweating	80
Weight loss	90
Insomnia	70

Irritability	60
Exercise intolerance	60
Loose motions	30
Amenorrhea	40
Goitre	55
Tachycardia	80
Nervousness	80
Proptosis	13.5
Lid lag or lid retraction	13.5

Table 1: Patients symptoms and their percentages.

TSH Receptor AB	No. of Patients	%
Positive	42	80.8
Negative	10	19.2
Total	52	100.0

Table 2: TSH receptor Antibody distribution of subjects studied.

Variables	TSH Receptor AB		Total
	Positive	Negative	
Age in Years			
• <30	7(16.7%)	1(10%)	8(15.4%)
• 30-40	8(19%)	2(20%)	10(19.2%)
• 41-50	10(23.8%)	0(0%)	10(19.2%)
• >50	17(40.5%)	7(70%)	24(46.2%)
Gender			
• Female	24(57.1%)	5(50%)	29(55.8%)
• Male	18(42.9%)	5(50%)	23(44.2%)
Body Mass Index kg/m²			
• <18.5	8(19%)	2(20%)	10(19.2%)
• 18.5-24.9	17(40.5%)	2(20%)	19(36.5%)
• 25.0-29.9	12(28.6%)	2(20%)	14(26.9%)
• >30.0	5(11.9%)	4(40%)	9(17.3%)
WCR			
• <80	13(31%)	1(10%)	14(26.9%)
• 80-100	25(59.5%)	8(80%)	33(63.5%)
• >100	4(9.5%)	1(10%)	5(9.6%)
Family History			
• Negative	40(95.2%)	10(100%)	50(96.2%)
• Positive	2(4.8%)	0(0%)	2(3.8%)
Total	42(100%)	10(100%)	52(100%)

Table 3: Baseline details of patients in relation to TSH receptor antibody.

Variables	TSH Receptor AB		Total	P Value
	Positive	Negative		
Age In Years	45.95 ± 16.75	53.8 ± 15.56	47.46 ± 16.67	0.184
Body Mass Index Kg/M ²	23.92 ± 4.59	26.03 ± 5.44	24.32 ± 4.78	0.212
WCR	85.69 ± 10.9	89.9 ± 9.13	86.5 ± 10.63	0.265
SBP	130.5 ± 20.22	138.5 ± 17.61	132.04 ± 19.84	0.256

DBP	75.26 ± 10.31	80 ± 13.32	76.17 ± 10.97	0.223
FT4	43.42 ± 25.82	29.06 ± 10.83	40.66 ± 24.27	0.093+
TC	149.57 ± 25.92	157.1 ± 36.26	151.02 ± 27.95	0.449
HDL	40.41 ± 6.12	38.09 ± 4.47	39.96 ± 5.87	0.266
LDL	93.55 ± 21.76	95.57 ± 34.04	93.94 ± 24.2	0.815
TG	115.76 ± 36.1	162.15 ± 126.57	124.68 ± 64.92	0.041*
TSH receptor Antibody	13.08 ± 13.47	0.83 ± 0.17	10.72 ± 13.02	0.006**

Table 4: Comparison of clinical variables/study variables in relation to incidence if TSH receptor AB of patients studied.

Duration	TSH Receptor AB		Total
	Positive	Negative	
New	19(45.23%)	8(80.00%)	27(64.29%)
<1 years	9(21.42%)	1(10.00%)	10(23.81%)
1-5 years	10(23.81%)	0	10(23.81%)
>5 years	4(9.53%)	1(10.00%)	5(11.91%)
Total	42(100%)	10(100%)	52(100%)

Table 5: Duration of hyperthyroidism distribution of subjects in relation to TSH receptor antibody.

Antithyroid Drug -Carbimazole	TSH Receptor AB		Total
	Positive	Negative	
10mg	5(11.94%)	3(30.00%)	8(19.04%)
20mg	15(35.71%)	6(60.00%)	21(50.00%)
30mg	4(9.52%)	0	4(9.52%)
40mg	15(35.71%)	1(10%)	16(38.06%)
60mg	3(7.14%)	0	3(7.14%)
Total	42(100%)	10(100%)	52(100%)

Table 6: Antithyroid drug initiation distribution of patients in relation to TSH receptor AB.

TSH Receptor Antibody	Anti TPO Antibody	Number	Percentage
Positive	Positive	32	61.6
Positive	Negative	10	19.2
Negative	Positive	3	5.8
Negative	Negative	7	13.4

Table 7: Antibody distribution of subjects.

Discussion

In our study, hyperthyroidism was diagnosed in symptomatic patients, most common symptoms being weight loss (90%), palpitations (80%), sweating (80%), nervousness and heat intolerance (70%). Clinical examination showed tachycardia in 80% patients, goitre in 55%, proptosis in 13.5% and lid retraction in 13.5% patients. 55.8% of the hyperthyroid subjects were women. 57.1% of the TSH receptor antibody positive subjects were women. There was no significant difference in the age, BMI or lipid profile amongst TSH receptor antibody positive and negative subjects. In our study, TSH receptor antibody was positive in 80.8% of subjects studied. Anti TPO antibody was positive in 67.4% of the subjects studied. Both antibodies were positive in 32 patients (61.6 %). Only TSH receptor antibody positive was positive in 10 patients (19.2%). Only anti TPO antibody was positive in 3 patients (5.8%). All 13.5% of Graves' orbitopathy subjects had positive TRAb. This indicates that TSH receptor antibody testing identifies more patients with autoimmune hyperthyroidism. There seems to be correlation between antithyroid drug dose and TSH receptor antibody positivity with large percentage of patients with antibody positive patients requiring higher doses.

In patients with symptoms and thyroid profile confirming thyrotoxicosis, further evaluation is needed to confirm the cause of thyrotoxicosis as Graves' disease, thyroiditis, toxic multi nodular goitre or toxic adenoma. While radionuclide uptake scan is

helpful to differentiate these conditions by showing increased uptake in Graves' disease, low uptake in thyroiditis and hot nodules in toxic nodular goitre, its availability and contraindication in pregnancy/lactation remains a drawback. On the other hand, TRAb is a specific marker for Graves' disease (Fig. 1) and plays an important role in diagnosing, predicting the course of the disease, assessing risk levels and managing Graves' disease in adults, pregnant women and newborns. Graves' disease is entirely dependent on, the interaction of an autoantibody with its autoantigen. Hence, testing for the TSH receptor antibody is useful in the diagnosis of Graves' disease. Hence, TRAbs are commonly used in developed countries for managing Graves' disease, as shown by different guidelines that recommend using TRAbs in various situations [21,22]. The third generation TRAbs tests that are approved and currently used have a strong ability to correctly identify Graves' disease. It is now understood that using TRAbs tests as recommended by the approved guidelines and procedures can be a good use of money, even though the test itself is expensive at first and it can also speed up getting a diagnosis [23].

By confirming the exact diagnosis of Graves' disease, the TRAbs test also reduces the necessity to use other methods like USG and RAI uptake, thereby improving patient satisfaction [24]. The rational use of TRAbs will help in the diagnosis, monitoring and management of persons with Graves' disease. Hence, TRAb tests are now being recommended for a reliable diagnosis of Graves' disease, thus allowing us to reserve expensive radionuclide uptake scan to selected situations.

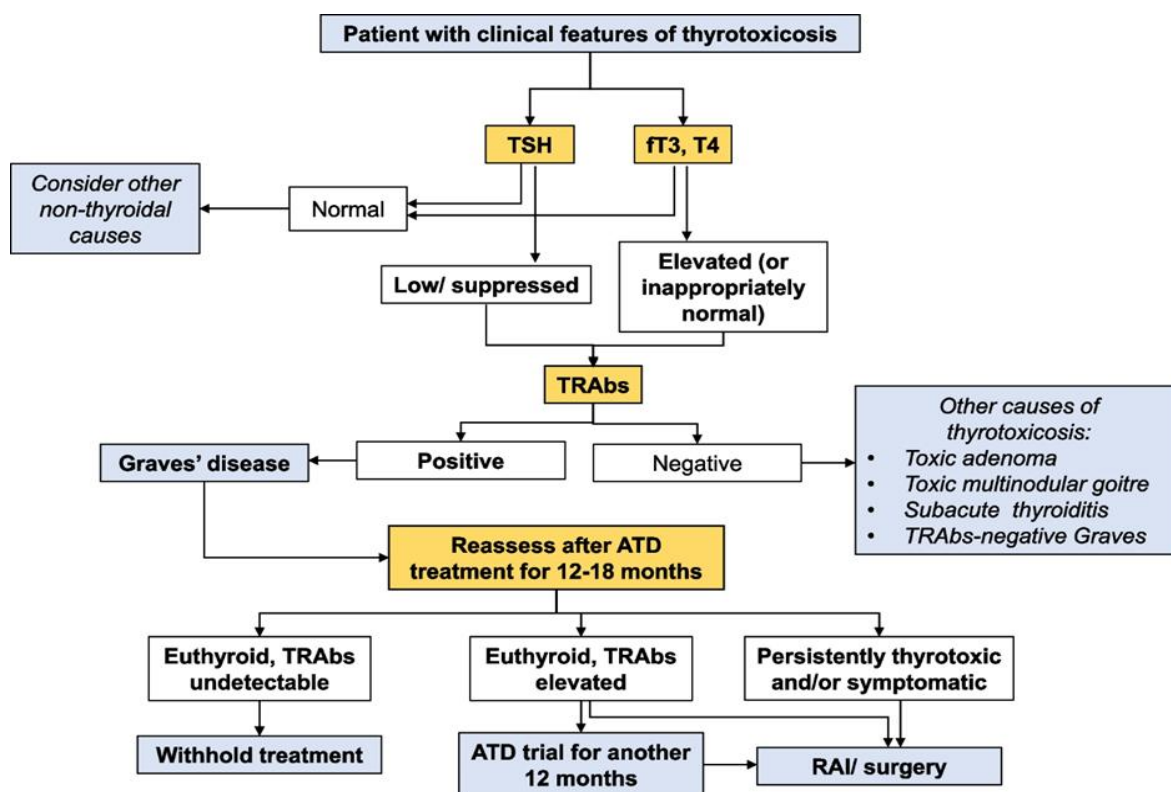


Figure 1: Utility of TSH receptor antibodies in differential diagnosis of hyperthyroidism.

Additional utility of TRAbs is found in deciding the duration of ATD use for hyperthyroidism. Majority of patients with Graves' hyperthyroidism treated with ATD become euthyroid within months. A pertinent question in such patients is how long therapy should continue. Based on a limited number of studies current recommendation is that this should be 12-18 months [26]. After withdrawal of ATD, around half of patients will experience a relapse of their hyperthyroidism [25,26]. Few studies have designed relapse risk score to estimate the relapse rate after stopping antithyroid drugs. TSH receptor antibody titers and base line FT4 levels were used in GREAT scoring (Graves Recurrence Events After Therapy) [26]. Higher serum free T4, higher thyrotropin-binding inhibitor immunoglobulin, younger age and larger goitre were associated with higher relapse risk. Abbara, et al., of department of endocrinology Imperial College, London United kingdom has devised a hyperthyroidism relapse risk score by using baseline variables: initial ft4, TSH receptor antibodies, gender, smoking status and ethnicity [26]. Following withdrawal of antithyroid drug treatment, the risk of relapse was greater in patients with higher initial ft4, initial TSH receptor antibody titre, males, smokers and British Caucasian ethnicity.

Studies have found that TRAb levels decline gradually under ATD treatment until they disappear in about 70 to 80% of patients after 18 months [26]. It is suggested that TSH receptor antibody estimation at the diagnosis of hyperthyroidism and 18 months after treatment with anti thyroid drugs will help in assessing the relapse of hyperthyroidism. In view of all these evidences, it would be appropriate to conclude that TSH receptor antibody measurement is mandatory in the following indications:

1. Hyperthyroidism during pregnancy when thyroid uptake scan is contraindicated
2. Pregnant women with history of Graves's disease to determine possible foetal and neonatal hyperthyroidism as these antibodies cross placenta
3. Patients with possible Grave's orbitopathy without biochemical hyperthyroidism
4. Patients with recent history of large iodine load where thyroid uptake scan cannot be reliable, e.g., recent amiodarone use, recent imaging studies with iodinated contrast
5. To determine the prognosis of hyperthyroidism who are being treated

Conclusion

In subjects with hyperthyroidism, TSH receptor antibody was positive in 80.8% of subjects in our study. These subjects can be concluded to be having Grave's disease. The remaining 19.2% of subjects could be toxic multi nodular goitre, toxic adenoma, thyroiditis and TRAb negative Graves' disease and further testing is needed in these subjects to arrive at the diagnosis. TSH receptor antibody testing identifies more patients with autoimmune hyperthyroidism compared to anti TPO. There seems to be correlation between antithyroid drug dose and TSH receptor antibody positivity with large percentage of patients with antibody positive patients requiring higher doses. Grave's orbitopathy was present in 13.5% of the subjects and they were all positive for TSH receptor antibodies suggesting that autoimmunity aggravates orbitopathy. All these factors suggest that evaluation for hyperthyroidism should include TRAb test as a first step to reliably identify patients with Graves' disease, avoiding the need for any additional tests.

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial Disclosure

This research did not receive any grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgement

Niharika S and Sushma Nayak for creation of Tables, Listing and Graphs (TLG) and Statistical Analysis Reporting (SAR) and Dr. K.P.Suresh, Ph.D (Biostatistics) for reviewing methodology and results.

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