Association of Thyroid Antibodies with Occurrence of Hypothyroidism after Radio-iodine Therapy in Patients with Graves' Disease Attending a Tertiary Level Hospital of Bangladesh

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ABSTRACT

Background: Graves' disease (GD) is an autoantibody-mediated autoimmune disease caused by direct stimulation of the thyroid epithelial cells. Thyrotropin Receptor Antibody and Thyroid Peroxidase Antibody are among the best-characterized autoantibodies for this pathology. Among different treatment modalities, radioiodine therapy (RAIT) is a proven safe and highly cost-effective therapeutic option, with the frequent side effect of developing hypothyroidism. Serum concentrations of various autoantibodies before and after RAIT may be used to predict the early or late onset of hypothyroidism.

Objective: To measure and statistically analyze the thyrotropin receptor antibody (TRAb) and thyroid peroxidase antibodies (TPOAb) in a group of hyperthyroid patients who did or did not develop early hypothyroidism after RAIT.

Patients and methods: This prospective comparative study was conducted at the thyroid division of the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, between March 2020 and June 2021. The study population was selected from diagnosed adult Graves' disease patients. A detailed history was taken, and a clinical examination was done for each patient. High-resolution ultrasound of the neck, thyroid scan, radioactive iodine uptake test, FT3, FT4, TSH, TPOAb, and TRAb were done one month before RAIT. After that, all patients were treated with a modified fixed dose of radioiodine (^{131}I) orally. Post-therapy follow-ups were done at the 3rd, 6th, and 9th months after therapy, during which serum FT3, FT4, TSH, TPOAb, and TRAb were estimated.

Result: Out of 60 enrolled patients, 54 completed their scheduled visits. They were divided into two groups based on the early (within three months) or late (after three months) occurrence of hypothyroidism after therapy. There was no significant difference observed between the two groups regarding gender, age, duration of disease, or ^{131}I dose. No significant difference was noted between the pre-therapy serum FT3, FT4, and TSH levels of group A and B patients. At the third month, all three parameters were significantly different between the groups. But at 6 months, a significant statistical difference was observed between the groups regarding serum FT3 and TSH but not FT4. The TPOAb was found to be significantly higher in group A before therapy and in each follow-up. However, TRAb was significantly higher in group A only at the 6-month follow-up.

Conclusion: Higher levels of serum TRAb and TPOAb in patients with Graves' disease at diagnosis are closely associated with the occurrence of early hypothyroidism.

Key words: Thyroid antibodies, Grave's disease, radioiodine therapy, hypothyroidism.

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INTRODUCTION

Graves' disease (GD) is an autoantibody-mediated autoimmune disease caused by direct stimulation of the thyroid epithelial cells by Thyroid Stimulating Hormone Receptor (TSHR)-stimulating antibodies (1). The diagnosis is based on biochemistry (Thyroid Stimulating Hormone, Thyroxine, and Triiodothyronine), imaging (ultrasound of the thyroid gland and power Doppler), and serology, i.e., thyroid peroxidase antibodies (TPOAb) and thyrotropin receptor autoantibodies (TRAb). In overt hyperthyroidism, both free thyroxine (FT4) and triiodothyronine (T3) concentrations are elevated, and serum Thyroid Stimulating

Hormone (TSH) is suppressed; however, in milder hyperthyroidism, serum total T4 and FT4 levels can be normal, and only free triiodothyronine (FT3) may be elevated, with an undetectable serum TSH (2).

TRAb and TPOAb are among the best-characterized autoantibodies in GD. The detection of these antibodies has significantly increased sensitivity with the improvement of assay technique in the last decades. TRAb measurement is a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism (3). The TRAb-causing GDs are characterized by their specific binding to the leucine-rich domain of TSHR and their ability to stimulate the TSHR, resulting in a signaling cascade that stimulates thyrocytes to synthesize and secrete thyroid hormones (4, 5).

Current therapeutic approaches include anti-thyroid drugs (ATD) and either thyroid ablation with radioactive iodine (RAI) or surgery. Radioiodine therapy is a proven safe and highly cost-effective therapeutic option for GD, despite its high recurrence and relapse rate (3). One of the most inevitable side effects of RAIT is hypothyroidism. Many factors influence its occurrence after RAIT, such as ^{131}I dosage, age, gender, size of the thyroid gland, initial FT4, FT3, TSH levels, radioactive iodine uptake, duration of disease, administration of ATD, and the presence of thyroid antibodies. With increasing TRAb concentrations before RAI, the chances of treatment failure increase. The level of these antibodies' concentration before and after RAIT may predict the early or late onset of hypothyroidism (6). There are very few previously conducted studies to compare and analyze this. Hence, this study was designed to measure and statistically analyze TRAb and TPOAb in a group of patients who did or did not develop early hypothyroidism after RAIT.

PATIENTS AND METHODS

This prospective comparative study was conducted at the thyroid division of the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2020 to June 2021. The study population was selected through consecutive purposive sampling techniques from diagnosed adult Graves' disease patients who came to NINMAS. Patients with a history of thyroid surgery or definite surgical indications, recent corticosteroid treatment, any other autoimmune disease, dual thyroid pathology, Graves' ophthalmopathy, severe heart disease, poor liver and kidney function, pregnancy, or lactation were excluded from the study. Before enrolling the patients in the study, proper ethical clearance and informed written consent were obtained.

The total number of subjects was 60, who were divided into two groups based on the occurrence of hypothyroidism after RAIT (during follow-up). The first group (Group A) consisted of patients with an early onset of hypothyroidism occurring within 3 months of RAIT. The second group (Group B) included patients with a late onset of hypothyroidism occurring after 3 months of RAIT.

A detailed history was taken, a clinical examination was done for each patient, and the required data were recorded on a predesigned data collection sheet. High-resolution ultrasound (HRUS) of the neck, thyroid scan, radioactive iodine uptake (RAIU) test, FT3, FT4, TSH, TPOAb, and TRAb were done one month before RAIT. After that, all patients were treated with a modified fixed dose of ^{131}I at 10–15 mCi (370–555 MBq) orally, a single dose in an empty stomach. Post-therapy follow-up was done at the 3rd, 6th, and 9th months after RAIT, during which serum FT3, FT4, TSH, TPOAb, and TRAb were measured.

After the completion of data collection, all the data were scientifically analyzed. Statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences) version 26.0 statistical software. The findings of the study were presented by frequency and percentage in tables. Means and standard deviations for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample. Associations of quantitative data were assessed using the Student t test, while qualitative data were assessed by the Chi-square test and the Fisher exact test. $P<0.05$ was considered significant, and all P values were two-sided.

RESULT

Out of 60 enrolled patients, 54 completed their scheduled visits, and six were lost to follow-up. Their age ranged from 18 to 55 years, with the majority in the 28 to 37-year-old group (46.4% in Group A and 53.8% in Group B). There was no significant difference observed between the two groups regarding gender, age, duration of disease, and 131I dose ($p > 0.05$) (Table 1).

Table 1: Comparison between baseline clinical data of groups A and B (n=54)

Group	No of patients	Male/ Female	Age (in years)	Duration of disease (in months)	^{131}I dose (mCi)
Group A	28 (51.8%)	11/17	34.3± 8.5	9.0± 4.2	12.1 ± 1.4
Group B	26 (48.2%)	8/18	35.9± 7.5	10.5 ±2.5	12.3 ± 1.6

No significant difference was noted between the pre-therapy serum FT3, FT4, and TSH levels of group A and B patients. In the next follow-up at 3 months after RAIT, serum FT3 and FT4 were significantly lower, and TSH was significantly higher in group A compared to group B ($p<0.001$). At the 6th month, a significant statistical difference was observed between the groups regarding serum FT3 and TSH but not FT4. However, at the 9th month, no significant statistical difference was observed between the groups regarding serum FT3, FT4, and TSH levels ($p > 0.05$) (Tables 2, 3, and 4).

Table 2: Serum FT3 hormone lavels in groups A and B (n=54)

Time Period	Serum FT3 (pmol/L)		p value
	Group A	Group B	
Before RAIT	11.3 ± 5.4	9.7 ± 4.4	0.251*
At 3rd month	4.1 ± 4.1	14.6 ± 4.7	**<0.001***
At 6th month	6.7 ± 2.9	10.9 ± 6.0	**0.003***
At 9th month	6.5 ± 2.7	7.4 ± 3.7	0.441*

* p value obtained from Independent sample t test and bold indicated significant p value

Table 3: Comparison of Serum FT4 levels between two groups (n=54)

Serum FT4	Group A	Group B	p value
Before RAI therapy	17.6 ± 13.1	12.3 ± 7.1	0.075
At 3rd month	7.4 ± 5.3	19.1 ± 6.5	**<0.001**
At 6th month	12.4 ± 2.8	14.5 ± 6.3	0.121
At 9th month	12.1 ± 2.9	13.6 ± 5.4	0.194

* p value obtained from Independent sample t test and bold indicated significant p value

Table 4: Comparison of patients by thyroid stimulating hormone (TSH) (n=54)

TSH	Group A	Group B	p value
Before RAI therapy	0.03 ± 0.04	0.06 ± 0.08	0.053
At 3rd month	85.9 ± 47.3	0.1 ± 0.1	**<0.001**
At 6th month	3.3 ± 0.5	15.0 ± 15.1	**<0.001**
At 9th month	2.1 ± 0.9	3.5 ± 1.1	0.474

* p value obtained from Independent sample t test and bold indicated significant p value

Before RAIT, in group A, mean TPOAb was 1100.7± 340.6, while in group B, mean TPOAb was 612.2± 480.7. An independent sample t test showed that the TPOAb was significantly higher in group A compared to group B ($p<0.001$). The TPOAb was found to be significantly higher in group A in each follow-up ($p<0.05$) (Figure 1).

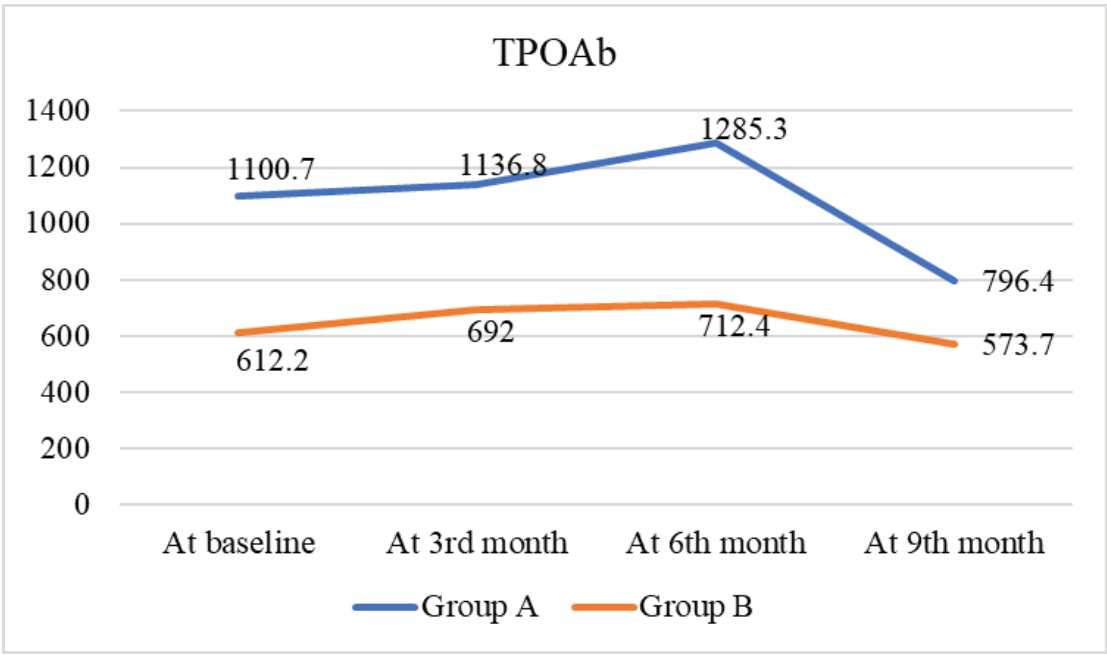

Figure 1: Thyroid peroxidase antibodies (TPOAb) levels at different time points (N=54)

Mean TRAb was 8.4± 11.8 in group A, before RAIT and in the 6th month, it reached its peak of 33.7±10.9. Then, on the 9th month, it decreased to 15.2±10.2. Again, in group B, at baseline, mean TRAb was 9.4± 17.4, and in the 6th month, it reached its peak of 17.2±23.3. Then, on the 9th month, it decreased to 12.5±20.6. TRAb was significantly higher in group A at the 6th month follow-up compared to group B ($p = 0.002$) (Figure 2).

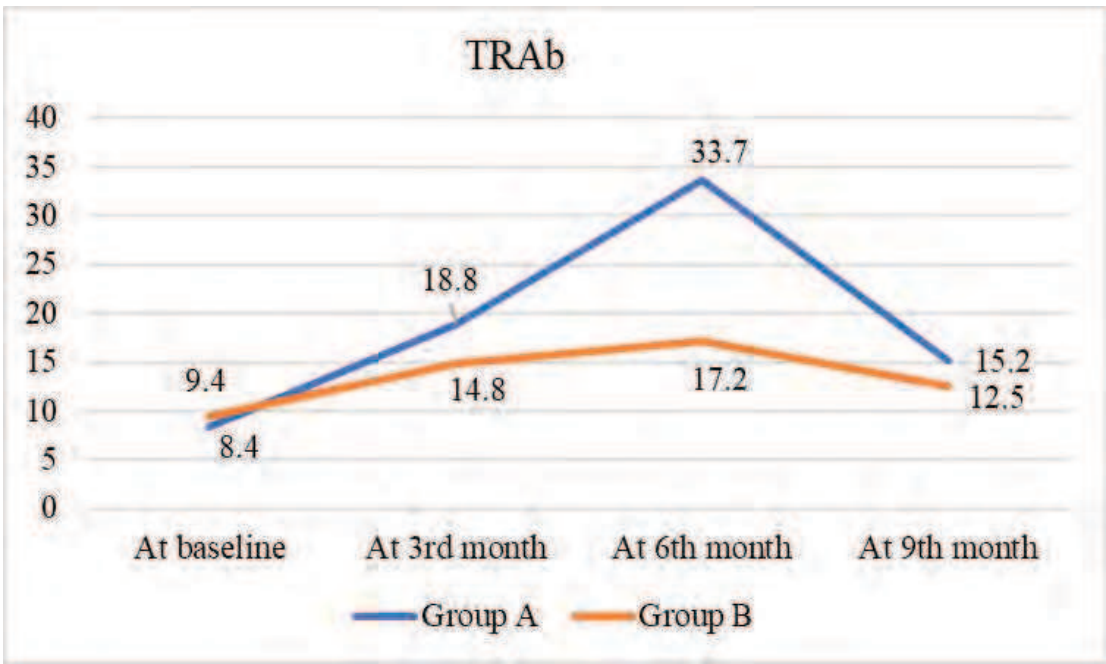

Figure 2: thyrotropin receptor antibody (TRAb) levels at different time points (N=54)

DISCUSSION

Radioactive iodine (RAI) is a safe and effective modality for the treatment of GD (7). About 80% of patients developed hypothyroidism after a dose of RAI (8). In this study, the levels of thyroid autoantibodies (TRAb and TPOAb) were recorded and compared, and the attainment of early and late hypothyroidism after RAIT in GD was observed. The majority of the patients were in the 30- to 50-year-old age group, which did not match the findings of other authors. Girgis et al. observed a peak incidence of GD between 40 and 60 years of age (9). However, most of the study subjects were female. Other studies also supported this finding (10).

Among the 54 patients in the current study, the majority (51.8%) developed early and 48.2% late hypothyroidism. Among the 26 patients with late-onset hypothyroidism, 12 became hypothyroid at 6 months. After nine months, all patients became euthyroid. Age, sex, baseline serum FT3, FT4, and TSH levels showed no statistical difference between the two groups of patients. This indicated that these factors are not responsible for the development of early hypothyroidism.

This study found that TPOAb was significantly higher in the early hypothyroidism group than the non-early hypothyroidism group before and after RAIT. TPOAb level was at its peak at the 6th month in both groups, which was supported by other studies (10). TPOAb seems to have a predictive value for hypothyroidism after RAIT, as it showed dynamic changes that increased at three months, elevated to peak at six months, and decreased at 12 months in both groups. It is suggested that TPOAb probably plays a positive role in the development of hypothyroidism.

TRAb plays a key role in the pathogenesis of GD, and its levels correlate with the clinical course. Its level increases for a year following RAIT, with a gradual fall thereafter. TRAb level >12 IU/l at diagnosis of GD is associated with a 60% risk of relapse at two years and an 84% risk at four years (11). Significant differences were observed between group A and group B regarding TRAb at 6 months following RAIT in this study, which peaked at 33.7 ±10.9 U/L in group A and only 17.2±23.3 U/L in group B. Dong et al. observed that TRAb levels showed a significant difference before and after RAI treatment in the early hypothyroidism group, which matches with this study (10).

CONCLUSION

In this study, it has been found that higher levels of serum TRAb and TPOAb in patients with Graves' disease at diagnosis are closely associated with the occurrence of early hypothyroidism. TRAb and TPOAb may be used in the prediction of the development of hypothyroidism, as they seem to be important factors responsible for the therapy outcome.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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