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ORIGINAL ARTICLE

Biochemical and immunological changes after antithyroid drugs, radioactive iodine, or thyroidectomy in Graves' disease: a retrospective comparative study

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Running title: Nuhanović et al. Laboratory changes in Graves' disease

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ABSTRACT

Aim: To compare changes in thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin receptor antibodies (TRAb) after antithyroid drugs, radioactive iodine, or total thyroidectomy in patients with Graves' disease.

Methods: This retrospective comparative cohort study included 60 adults treated at the University Clinical Centre Tuzla between 2021 and 2025, with 20 patients in each treatment group. Laboratory values obtained before treatment and at the first documented follow-up were analysed. The primary analysis compared change scores among treatment groups; within-group changes and correlations were secondary analyses.

Results: Baseline FT4 and TRAb differed among the treatment groups ($p = 0.022$ and $p = 0.005$, respectively). After thyroidectomy, FT3 and TRAb changed significantly ($p = 0.004$ and $p < 0.001$), whereas TSH and FT3 changed significantly within the radioactive iodine group ($p = 0.014$ and $p = 0.027$). No significant within-group changes were observed after antithyroid drug treatment. Change scores did not differ significantly among the groups for TSH, FT3, FT4, or TRAb. Changes in FT3 and FT4 were positively correlated ($\rho = 0.649$; $p < 0.001$), whereas changes in TSH were negatively correlated with FT3 and FT4.

Conclusion: Selected laboratory parameters changed within the thyroidectomy and radioactive iodine groups, but change scores did not differ significantly among the three treatment groups. These comparisons should be interpreted in view of baseline imbalance, small group sizes, non-consecutive sampling, and non-standardised follow-up.

Keywords: antithyroid agents; Graves' disease; iodine radioisotopes; thyroidectomy; treatment outcome

INTRODUCTION

Graves' disease is an autoimmune cause of hyperthyroidism in which antibodies directed against the thyrotropin receptor stimulate thyroid hormone synthesis and thyroid growth (1). Thyrotropin receptor antibodies (TRAb) support diagnosis and may also provide information about persistent autoimmune activity and the likelihood of relapse (2).

Current treatment options include antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy (3). These approaches differ in mechanism, time to biochemical control, adverse-effect profile, and durability of response: ATDs suppress hormone synthesis, RAI produces progressive thyroid ablation, and thyroidectomy immediately removes functioning thyroid mass (4). Real-world practice patterns vary considerably (5).

Hormonal and immunological recovery do not necessarily occur in parallel. Thyroid-stimulating hormone (TSH) may remain suppressed after free triiodothyronine (FT3) and free thyroxine (FT4) have normalised, whereas TRAb may persist or transiently increase after treatment, particularly after RAI (6). Treatment selection is influenced by baseline disease severity, thyroid size, orbitopathy, previous response, contraindications, and patient preference, making observational comparisons susceptible to confounding by indication (2).

Despite the widespread use of ATDs, RAI, and thyroidectomy for Graves' disease, comparative real-world data on hormonal and immunological trajectories remain limited, particularly in Bosnia and Herzegovina and the Western Balkans. Differences in healthcare organisation, treatment selection, and patient characteristics may influence observed laboratory patterns. Baseline disease characteristics also influence subsequent biochemical course and relapse (7), supporting cautious interpretation of region-specific observational data.

The aim of this study was to compare pre-treatment and first documented follow-up TSH, FT3, FT4, and TRAb values among patients treated with ATDs, RAI, or total thyroidectomy and to assess differences in change scores among the three treatment groups.

MATERIAL AND METHODS

Patients and study design

This retrospective comparative cohort study was conducted at the Department of Nuclear Medicine, Clinic for Radiology and Nuclear Medicine, University Clinical Centre Tuzla. Medical records of patients with Graves' disease evaluated and treated between 2021 and 2025 were reviewed.

Eligible patients were aged 15 years or older and had a documented diagnosis of Graves' disease with elevated TRAb.

Exclusion criteria were age 14 years or younger, absence of confirmed Graves' disease or positive TRAb, insufficient pre-treatment or follow-up laboratory data for all study outcomes, another cause of hyperthyroidism, or definitive treatment outside the study period. Complete data for every individual laboratory parameter were not required; one patient with a missing pre-treatment FT3 value was excluded only from FT3-specific analyses but remained in the study cohort.

The final analytic sample comprised 60 patients who met the predefined eligibility criteria, with 20 patients in each treatment group: antithyroid drugs (ATDs), radioactive iodine (RAI), and total thyroidectomy. Although the protocol permitted inclusion from 15 years of age, all patients in the analytic sample were adults.

The study included a non-consecutive sample of eligible records. Because a screening log was unavailable, the total numbers of records screened and excluded and the reasons for exclusion could not be reconstructed. Treatment was selected during routine clinical care according to

clinical indications, previous disease course, treatment response, contraindications, and patient preference when documented; the investigators did not assign treatment.

Methods

Data were obtained from outpatient records and the institutional nuclear medicine database. Pre-treatment values were defined as the most recent laboratory measurements obtained before the relevant treatment.

For the ATD group, the index date was defined as the date of initiation of antithyroid drug therapy, and the post-treatment value was defined as the first available laboratory assessment after treatment initiation. For the RAI and total thyroidectomy groups, post-treatment values were defined as the first available laboratory measurements documented after the respective procedure. Post-treatment laboratory assessments were performed during routine clinical care and were not obtained at standardised intervals. Exact intervals between treatment initiation or procedure and assessment could not be consistently retrieved. The first documented follow-up was not intended to represent biochemical remission. Because follow-up timing directly affects hormone and antibody kinetics, comparisons of change scores were interpreted cautiously and were not considered estimates of comparative treatment effectiveness.

The primary outcome was the between-group difference in change scores, calculated as the first documented follow-up value minus the pre-treatment value, for TSH, FT3, FT4, and TRAb. Secondary analyses evaluated pre-treatment to follow-up changes within each group and correlations among changes in the four laboratory parameters.

Serum TSH, FT3, and FT4 were measured using electrochemiluminescence immunoassays on the cobas e 601 immunoassay module of the cobas 6000 analyser series (Roche Diagnostics, Mannheim, Germany). The reference intervals were 0.27–4.20 mIU/L for TSH, 3.1–6.8 pmol/L for FT3, and 12.0–22.0 pmol/L for FT4.

Serum TRAb was measured using the Elecsys Anti-TSHR electrochemiluminescence immunoassay on the same cobas e 601 module. According to the manufacturer's documentation, the diagnostic cut-off was 1.75 IU/L, and values > 1.75 IU/L were considered positive.

Statistical analysis

Statistical analyses were performed using JASP (version 0.19.1, JASP Team, Amsterdam, the Netherlands). Continuous variables were summarised using means ± standard deviations (SDs) or medians and interquartile ranges (IQRs), as available; categorical variables were presented as numbers and percentages. Group-specific age data were available as medians (IQRs), whereas overall age was available as a mean ± SD. Baseline continuous variables and change scores were compared among groups using the Kruskal–Wallis test. Sex was compared using the Fisher–Freeman–Halton exact test, and family history was compared using Pearson's chi-square test. Normality of paired differences was assessed using the Shapiro–Wilk test and Q–Q plots. Paired-samples t tests or Wilcoxon signed-rank tests were used for within-group comparisons, as appropriate. Spearman rank correlation evaluated associations among change scores. FT3 analyses included 59 patients because one patient in the thyroidectomy group lacked a pre-treatment FT3 value. Holm correction was applied to the four primary between-group change-score comparisons. Secondary within-group and correlation analyses were not adjusted for multiple comparisons. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 60 patients were included, comprising 49 (81.7%) women and 11 (18.3%) men (Table 1). Each treatment group included 20 patients; women predominated in all three groups (Table 1). Baseline demographic characteristics are shown in Table 1. Group-specific median ages and the overall mean age are reported according to the available summaries; age did not differ

significantly among the groups. Baseline laboratory values are presented in Table 2. TSH and FT3 did not differ significantly among the groups, whereas baseline FT4 and TRAb did ($p = 0.022$ and $p = 0.005$, respectively), indicating incomplete baseline comparability.

Within-group changes at the first documented follow-up are presented in Table 2. After thyroidectomy, FT3 and TRAb changed significantly ($p = 0.004$ and $p < 0.001$, respectively), whereas TSH and FT4 did not. In the RAI group, TSH and FT3 changed significantly ($p = 0.014$ and $p = 0.027$), but FT4 and TRAb did not. No significant change was observed in the ATD group; the reduction in TRAb did not reach statistical significance ($p = 0.077$).

Change scores did not differ significantly among the treatment groups for TSH (unadjusted $p = 0.135$; Holm-adjusted $p = 0.294$), FT3 (unadjusted $p = 0.054$; Holm-adjusted $p = 0.216$), FT4 (unadjusted $p = 0.098$; Holm-adjusted $p = 0.294$), or TRAb (unadjusted $p = 0.200$; Holm-adjusted $p = 0.294$) (Table 2). Thus, significant within-group findings did not translate into evidence of differential change among the treatment modalities.

Changes in TSH were negatively correlated with changes in FT3 ($\rho = -0.447$; $p < 0.001$) and FT4 ($\rho = -0.518$; $p < 0.001$), whereas changes in FT3 and FT4 were positively correlated ($\rho = 0.649$; $p < 0.001$). A negative correlation was observed between changes in FT4 and TRAb ($\rho = -0.334$; $p = 0.009$). Correlations of TRAb change with TSH and FT3 thechange were not statistically significant (Table 3).

DISCUSSION

This retrospective comparative study evaluated biochemical and immunological changes following the three standard treatment modalities for Graves' disease within the same clinical cohort. Significant changes in selected laboratory parameters were observed within the thyroidectomy and RAI groups; however, the primary between-group analysis did not demonstrate significant differences in change scores among treatment modalities.

Previous studies have compared clinical remission, recurrence, or outcomes after individual Graves' disease treatments (8). The present study adds regional comparative data on parallel changes in thyroid hormones and TRAb across all three treatment modalities. Nevertheless, the findings should be interpreted in the context of non-random treatment selection, baseline imbalance, and non-standardised follow-up rather than as evidence that one treatment is superior. Baseline FT4 and TRAb differed across the treatment groups, consistent with non-random treatment selection. Patients referred for RAI or thyroidectomy may differ from those continuing ATDs in disease severity, thyroid size, previous response, orbitopathy, comorbidities, and treatment preference. According to the European Thyroid Association guidelines, these clinical characteristics are among the principal determinants of treatment selection (2). The American Thyroid Association guidelines similarly recommend individualised therapeutic decisions based on disease severity, patient preference, reproductive plans, and associated clinical conditions (3). Such confounding by indication can influence both baseline measurements and subsequent change, and it cannot be eliminated by unadjusted comparisons in a small cohort. Liu et al. also reported significant baseline differences among patients undergoing ATDs, RAI, or thyroidectomy, emphasising that treatment allocation in routine clinical practice is strongly influenced by disease severity rather than random assignment (8). Similarly, Engelbrecht-Wiggans et al. highlighted that comparisons between definitive treatment modalities should always be interpreted in the context of baseline disease characteristics and treatment indications (9).

The absence of statistically significant changes in the ATD group should not be interpreted as evidence of ineffectiveness. ATD response depends on treatment duration, dose, adherence, baseline hormone concentrations, and timing of assessment (10). Relapse risk also varies with age, thyroid volume, goitre size, and baseline FT3 and FT4 concentrations (7). Recent studies

have shown that prolonged low-dose methimazole therapy can be an effective and safe long-term strategy in appropriately selected patients, with higher remission rates and gradual reductions in TRAb concentrations (11). Similarly, Azizi et al. reported that long-term ATD therapy may reduce relapse risk while allowing many patients to avoid definitive treatment (12). These factors were not consistently available in the present dataset and may partly explain the absence of significant laboratory changes in the ATD group. Chen et al. identified high baseline TRAb levels as a predictor of persistent TRAb positivity during long-term ATD therapy (13).

After RAI, TSH and FT3 changed significantly, whereas TRAb did not. TRAb kinetics after RAI are time-dependent: antibody concentrations may increase during the first year and subsequently decline (6). Because post-treatment assessment was not standardised, measurements obtained at different stages of this trajectory may have increased variability and obscured a consistent immunological pattern. Ma et al. reported an early increase in TRAb followed by a later decline among patients achieving remission; the present RAI cohort did not show a statistically significant TRAb change (14). Bartalena et al. also emphasised that baseline autoimmune activity and Graves' orbitopathy should be considered when interpreting post-treatment laboratory findings and selecting treatment (15).

After thyroidectomy, FT3 and TRAb changed significantly. Removal of thyroid tissue eliminates the principal source of hormone production and may reduce ongoing antigenic stimulation. Previous studies have reported progressive TRAb decline after total thyroidectomy, although the rate of decline depends on preoperative TRAb, age, thyroid size, and duration of follow-up (16). Engelbrecht-Wiggans et al. also demonstrated favourable long-term biochemical outcomes following thyroidectomy while emphasising that treatment response should always be interpreted according to baseline disease severity and clinical indication for surgery (9). The present findings

are compatible with these observations but cannot establish a comparative advantage because between-group change scores were not significantly different.

The observed correlations were physiologically coherent. TSH changes were inversely related to FT3 and FT4 changes, and FT3 and FT4 changes were positively related. The weaker relationships between TRAb and thyroid hormones further support that biochemical and immunological recovery may not occur synchronously. Similar observations have been reported in previous studies demonstrating that restoration of thyroid function and normalisation of autoimmune activity follow different temporal patterns after treatment for Graves' disease (1). This may explain why significant hormonal improvement can occur despite persistent TRAb positivity during the early post-treatment period (6).

This study has several limitations. The retrospective, non-randomised design is susceptible to selection bias and confounding by indication. The non-consecutive sample and unavailable screening denominator limit representativeness. Exact treatment-to-follow-up intervals could not be reconstructed; consequently, change scores may compare measurements obtained at different points in hormone and antibody trajectories. The sample included only 20 patients per group, limiting precision and precluding reliable multivariable adjustment, and baseline FT4 and TRAb differed among groups. Treatment dose, ATD type and duration, administered RAI activity, previous treatment, and adherence were not consistently available. One patient lacked a baseline FT3 measurement and was omitted from FT3-specific analyses. Secondary analyses were not adjusted for multiple comparisons and should therefore be interpreted cautiously. Sustained biochemical remission, relapse, clinical outcomes, adverse effects, and long-term follow-up were not evaluated. These limitations preclude causal or comparative-effectiveness conclusions but do not alter the study's retrospective comparative design.

CONCLUSION

At the first documented follow-up, selected hormonal and immunological parameters changed within the thyroidectomy and RAI groups, whereas change scores did not differ significantly among the ATD, RAI, and thyroidectomy groups. The findings provide a retrospective comparison of observed laboratory changes but do not establish the superiority of any treatment modality because of non-consecutive sampling, non-standardised follow-up, baseline imbalance, and small group sizes.

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Conflicts of interest: None to declare.

Author contributions (CRediT): Conceptualisation—D.N., A.B., and B.I.; methodology—E.B.Č., S.Ć., and D.N.; formal analysis—M.G., S.Č., and D.G.; investigation—A.B., D.N., and B.I.; data curation—E.B.Č., S.Ć., and S.Č.; writing—original draft—D.N., A.B., E.B.Č., and B.I.; writing—review and editing—S.Ć., D.G., and A.B.; supervision—B.I. and S.Č.; project administration—D.N., A.B., and M.G. All authors reviewed and approved the final manuscript.

Ethics statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Clinical Centre Tuzla (Approval No. 02-09/2-100-4/24; 22 April 2025). Data were anonymised before analysis.

Data availability statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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TABLES

Table 1. Baseline demographic characteristics of included patients

Variable	Thyroidectomy (N = 20)	Radioactive iodine (N = 20)	Antithyroid drugs (N = 20)	Total (N = 60)	p
		Median (IQR)		Mean ± SD	
Age, years	43.5 (31.0)	49.0 (21.0)	52.0 (17.0)	48.32 ± 12.8	0.700
			n (%)		
Sex					
Male	3 (15.0)	6 (30.0)	2 (10.0)	11 (18.3)	0.339
Female	17 (85.0)	14 (70.0)	18 (90.0)	49 (81.7)	
Family history					
Negative	17 (85.0)	13 (65.0)	12 (60.0)	42 (70.0)	0.194
Positive	3 (15.0)	7 (35.0)	8 (40.0)	18 (30.0)	

Categorical variables are n (%). The age p value is from the Kruskal–Wallis test; the sex p value is from the Fisher–Freeman–Halton exact test; the family-history p value is from Pearson's chi-square test.

Table 2. Laboratory findings before treatment and at the first documented follow-up by treatment group

Variable	Thyroidectomy (N = 20)	Radioactive iodine (N = 20)	Antithyroid drugs (N = 20)	Total (N = 60)	p*
TSH (mIU/L), mean ± SD					
Before treatment	4.65 ± 9.64	1.26 ± 2.42	5.06 ± 12.50	3.66 ± 9.23	0.059
After treatment	12.28 ± 25.35	12.92 ± 24.15	2.78 ± 3.15	9.33 ± 20.49	0.518
ΔTSH	7.63 ± 28.24	11.66 ± 24.80	−2.28 ± 10.14	5.67 ± 22.87	0.135
p**	0.349	0.014	0.869	—	—
FT3 (pmol/L), mean ± SD					
Before treatment	5.37 ± 2.35	9.66 ± 11.72	4.53 ± 1.78	6.54 ± 7.28	0.168
After treatment	3.42 ± 1.26	4.52 ± 2.70	5.94 ± 6.96	4.65 ± 4.45	0.187
ΔFT3	−1.95 ± 2.61	−5.14 ± 11.90	1.41 ± 7.18	−1.89 ± 8.53	0.054
p**	0.004	0.027	0.701	—	—
FT4 (pmol/L), mean ± SD					
Before treatment	13.30 ± 9.81	26.07 ± 26.78	12.45 ± 5.75	17.27 ± 17.67	0.022
After treatment	15.85 ± 8.11	16.34 ± 8.18	14.37 ± 5.52	15.52 ± 7.30	0.301
ΔFT4	2.54 ± 11.15	−9.73 ± 27.93	1.92 ± 6.33	−1.75 ± 18.35	0.098
p**	0.320	0.184	0.190	—	—
TRAb (IU/L), mean ± SD					
Before treatment	16.94 ± 12.35	6.62 ± 5.78	8.16 ± 8.35	10.57 ± 10.17	0.005
After treatment	8.35 ± 10.10	6.09 ± 7.81	6.74 ± 9.98	7.06 ± 9.25	0.889
ΔTRAb	−8.59 ± 10.40	−0.54 ± 9.81	−1.42 ± 13.85	−3.51 ± 11.86	0.200
p**	<0.001	0.421	0.077	—	—

*Unadjusted Kruskal–Wallis p values for differences between groups; Holm-adjusted p values for the four primary change-score comparisons were 0.294 for TSH, 0.216 for FT3, 0.294 for FT4, and 0.294 for TRAb. **Unadjusted paired-samples t test or Wilcoxon signed-rank test for within-group change, selected according to the distribution of paired differences. FT3 analyses included 19 patients in the thyroidectomy group and 20 in each other group (total n = 59).

ATD, antithyroid drug; FT3, free triiodothyronine; FT4, free thyroxine; IQR, interquartile range; RAI, radioactive iodine; SD, standard deviation; TRAb, thyrotropin receptor antibodies; TSH, thyroid-stimulating hormone; Δ, first documented follow-up minus pre-treatment value

Table 3. Spearman correlations among changes in laboratory parameters

Variable pair	ρ	p
ΔTSH–ΔFT3	−0.447	< 0.001
ΔTSH–ΔFT4	−0.518	< 0.001
ΔTSH–ΔTRAb	0.249	0.055
ΔFT3–ΔFT4	0.649	< 0.001
ΔFT3–ΔTRAb	−0.010	0.943
ΔFT4–ΔTRAb	−0.334	0.009

Δ, first documented follow-up minus pre-treatment value; FT3, free triiodothyronine; FT4, free thyroxine; TRAb, thyrotropin receptor antibodies; TSH, thyroid-stimulating hormone; ρ, Spearman correlation coefficient. Correlations involving FT3 included 59 patients; all other correlations included 60 patients