CLINICAL STUDY

Serum thyrotropin-receptor autoantibodies levels after ^{131}I therapy in Graves' patients: effect of pretreatment with methimazole evaluated by a prospective, randomized study

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Abstract

Objective: Radioiodine therapy (^{131}I) in hyperthyroid Graves' disease is generally followed by a transitory increase in levels of thyrotropin receptors antibodies (TRAb). Immunosuppressive effects of antithyroid drugs are still a matter of debate. In this study we evaluated the effect of methimazole pretreatment on the TRAb boost induced by ^{131}I .

Design: A randomized, prospective clinical trial.

Methods: 61 patients were randomly assigned to receive ^{131}I alone (32 patients) or ^{131}I plus pretreatment with methimazole (30 mg/day; 29 patients). Serum TRAb levels were measured on the day of ^{131}I dosing (D0), and at 1, 3, 6 and 12 months after ^{131}I administration.

Results: The mean serum TRAb levels decreased significantly from baseline to D0 in patients treated with methimazole (80.8 vs 48.8 U/l; $P < 0.05$). After ^{131}I treatment, TRAb levels increased at 3 months (48.8 to 60 U/l; 19%) and they were still elevated at 6 months compared with D0 values (99.9 U/l; 105%). Thereafter, TRAb levels decreased to baseline values (47.8 U/l) at 12 months. In hyperthyroid patients, TRAb levels increased significantly from D0 to 1 month (45.0 to 78 U/l; 73%) reaching their highest levels at 3 months (225 U/l; 400%). After this, we observed a progressive decrease to the baseline levels at 12 months (40.0 U/l). The course of TRAb levels after ^{131}I treatment was significantly different between the two groups ($P < 0.05$). Multiple regression analysis identified serum TRAb levels on D0 as independent predictors of TRAb increment after ^{131}I therapy ($r^2 = 0.34$; $P = 0.001$). A higher increment in serum TRAb levels was associated with hypothyroidism after 1 year of follow-up.

Conclusion: Methimazole pretreatment attenuates the ^{131}I -induced rise in serum TRAb levels. The effects of methimazole could be attributed to a direct immunomodulatory action or may be due to its effects on the control of hyperthyroidism, which is a known cause of immune dysregulation.

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Introduction

Antithyroid drugs have been one of the standard modalities of therapy for Graves' hyperthyroidism either as first choice therapy or as pretreatment prior to radioactive iodine (^{131}I) in selected patients. Pretreatment with antithyroid drugs before ^{131}I therapy is usually recommended in order to deplete preformed stores of thyroid hormones and to decrease the risk of hyperthyroidism exacerbation (1) although recent studies have shown that thyroid hormone levels do not increase after radioiodine dosing (2, 3). Pretreatment with methimazole does not interfere with the efficacy of ^{131}I therapy (4, 5).

Radioiodine therapy has been widely used in hyperthyroid Graves' patients and its popularity among physicians is growing in view of its safety and

effectiveness. Serum thyrotropin receptors antibodies (TRAb) are detected in serum of most patients with Graves' disease and are the cause of clinical thyrotoxicosis due to activation of the thyrotropin receptor. It is well recognized that ^{131}I administration is associated with a transitory increase in TRAb levels (6–8). A similar immunological response is also observed in about 5% of patients treated with ^{131}I for nodular goiter, with induction of a Graves'-like disease (9). Possible immunosuppressive effects of antithyroid drugs on the suppression of TRAb production are still a matter of debate in the literature (8, 10–12). Some studies have demonstrated that TRAb production following ^{131}I administration is influenced by therapy, with methimazole but not betamethasone abolishing the observed increase in TRAb levels (7, 13). However, in both study designs methimazole was adjunctive to

^{131}I therapy and was maintained for 3–12 months thereafter, which meant that the role of specific parameters associated with the antithyroid treatment could not be addressed.

In the present study we evaluated the effect of methimazole pretreatment to determine if the expected decrease in serum TRAb levels and hyperthyroidism control would be enough to block the ^{131}I -induced rise in TRAb levels.

Materials and methods

Subjects

The study was carried out between February 1997 and June 2002. Consecutive patients with a diagnosis of Graves' disease attending the Endocrine Division at the Hospital de Clínicas de Porto Alegre were eligible. Graves' hyperthyroidism was diagnosed on the basis of suppressed thyroid-stimulating hormone (TSH) levels by sensitive assay, elevated serum thyroid hormone levels, 24-h radioiodine uptake, and detectable levels of anti-TSH receptor antibody. Exclusion criteria were previous treatment with radioiodine or thyroidectomy, signs of moderate or severe ophthalmopathy (proptosis >22 mm, ophthalmoplegia, chemosis or lagophthalmos), severe heart disease (symptomatic coronary heart disease, class III heart failure, New York Heart Association criteria), debilitating conditions, and large and compressive goiters (>150 g). Patients previously treated with antithyroid drugs whose treatment had been interrupted at least 3 months before the study were included.

Sixty-eight patients were enrolled. Five patients were lost before randomization. Two patients were withdrawn from the study shortly after randomization, one because of pregnancy and the other because of atrial fibrillation. Thus, this study includes 61 patients. Of these, 51 patients were newly diagnosed and 10 patients had previously been treated with antithyroid drugs.

During the enrolment period the patients underwent a complete physical examination, including ocular examination (assessment for soft tissue inflammation, lagophthalmos, extraocular muscle involvement and/or exophthalmos using Hertel's prism exophthalmometer) and electrocardiogram. Data about duration of the disease, previous antithyroid drug therapy, and history of smoking were recorded, and thyroid volume was assessed by ultrasound, always by the same observer. The Ethics Committee at the Hospital approved the study protocol, and all patients gave their written, informed consent.

Treatment protocol and serial evaluation

Patients were randomly assigned to receive ^{131}I alone (32 patients) or ^{131}I plus methimazole (MMI) until

biochemical euthyroidism was achieved (29 patients). In the first group, patients received a single dose of radioiodine on the day of treatment (D0; 200 $\mu\text{Ci/g}$ of thyroid tissue as estimated by ultrasound, divided by the fractional 24-h uptake value). The treatment day was scheduled approximately one week after the diagnosis was established. A clinical and laboratory assessment was performed on the day of treatment and monthly for 1 year after ^{131}I treatment.

In the second group, patients were treated with methimazole (30 mg daily) until biochemical euthyroidism was achieved. Patients were considered to have reached euthyroidism when serum thyroid hormone levels were within the laboratory reference range. Patients received ^{131}I dosing 4 days after antithyroid drug discontinuation. The ^{131}I dose was calculated in the same way as for the first group, based on a second 24-h radioiodine uptake performed on the day of treatment. A clinical and laboratory assessment was carried out 4 days before radioiodine therapy, on day 0 (D0) and then monthly for 1 year after ^{131}I therapy.

Serum levels of thyroxine (T_4), free thyroxine (FT_4), triiodothyronine (T_3) and TSH were measured in the morning on the days scheduled for clinical and laboratory assessment, as described above. Serum TRAb levels were measured on D0 and at 1, 3, 6 and 12 months after radioiodine therapy. None of the patients received antithyroid drug therapy after radioiodine therapy. The β -adrenergic blocking agent, propranolol (80–120 mg/day), was given to patients if tachycardia >120 beats/min occurred.

Successful therapy was defined as euthyroidism or permanent hypothyroidism based on FT_4 measurements obtained at each monthly visit. To avoid misclassification of the thyroid status, we used two consecutive serum FT_4 measurements in the normal or low range, or, in cases of borderline upper range values, three serum FT_4 values. The time of cure (month) was considered as the time when the first serum FT_4 measurement reached and persisted in the normal or low range. Therapy failure was defined as the need to repeat ^{131}I treatment or as persistent elevated serum thyroid hormone levels after 1 year of ^{131}I dosing.

Serum hormone measurements

Assays were performed on batched serum samples (duplicates) that had been stored at -20°C pending study completion. Serum T_4 and T_3 levels were measured using radioimmunoassays (Diagnostic Products, Los Angeles, CA, USA; Immunotech, Marseille, France), and serum FT_4 levels were measured using Coat-a-Count (Immunotech, Marseille, France). Intra-assay coefficients of variation in euthyroid controls were: T_4 , 3–8%; T_3 , 7–10%; and FT_4 , 3–6%. For values in the hyperthyroid and hypothyroid

ranges, intra-assay coefficients of variation were: T₄, 6–9%; T₃, 6–12%; and FT₄, 4–8% and T₄, 5–7%; T₃, 6–10%; and FT₄, 4–6% respectively. Interassay coefficients of variation were (euthyroid controls): T₄, 10%; T₃, 12%; and FT₄, 7%. TSH levels were measured by a double-antibody sensitive assay (Immulite, Diagnostic Products). Serum TRAb levels were determined by radioreceptor assay (porcine thyrotropin receptor (pTSHR), CIS-Bio International, Cardiff, France). The intra-assay and interassay coefficients of variation were 3.4–6.5% and 15.2% respectively. The reference ranges for each of these assays is shown in Table 1.

Statistical analysis

Results are presented as median and 95% confidence interval (CI) or means $\pm$ S.E.M. Clinical and laboratory characteristics between groups were compared using the χ^2 test or Fisher's exact test for qualitative variables, or by Student's *t*-test or Mann–Whitney's U-test/Kruskal–Wallis test for quantitative variables. The correlations between serum TRAb levels and clinical and laboratory parameters were assessed using Spearman's rank. In each group, the variation of serum TRAb levels over time was assessed by analysis of variance by repeated measures (Friedman's test), followed by Dunnett's test. Comparison of variation in serum TRAb levels between the two groups of patients was assessed by the general linear model for repeated measures followed by Mann–Whitney test. Multiple linear regression analysis was used to identify predictors of serum TRAb increment after ¹³¹I administration. The variation in serum TRAb levels between the treatment day and at 3 months were logarithmically transformed (log10TRAb) and forward selection was used. *P* values

of less than 0.05 were considered statistically significant. The Statistical Package for Social Science 10.0 professional software (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Subjects

The characteristics of the 61 patients with Graves' disease that were randomly assigned to receive ¹³¹I therapy alone (32 patients) or to receive ¹³¹I after treatment with antithyroid drugs (29 patients) are shown in Table 1. There were no significant differences between the two groups with respect to any of the characteristics listed, except for the thyroid hormone levels.

The median period of time required to achieve biochemical euthyroidism in the group of patients pretreated with antithyroid drugs was 12 weeks (2 to 48 weeks). At the time methimazole was stopped (4 days before radioactive administration), the mean serum T₃ and FT₄ levels were 2.2 ± 0.5 nmol/l and 17.7 ± 5.3 pmol/l respectively. The mean ¹³¹I dose (10.6 ± 5.7 vs 8.9 ± 4.6 mCi) and the number of patients using propranolol (3 vs 2) and/or oral contraceptives (9 vs 8) were similar in both groups. Methimazole was replaced with propylthiouracil (300 mg/day) in three patients who developed a cutaneous rash. All patients remained clinically stable throughout the study (2, 4). Five patients used the β -adrenergic blocking agent propranolol (80–120 mg/day) due to tachycardia >120 beats/min and one patient in the methimazole group required a second dose of ¹³¹I before 1 year due to persistently elevated serum levels of thyroid hormones and development of atrial

Table 1 Characteristics of patients with Graves' disease on the day of ¹³¹I administration. Values represent means $\pm$ S.D. or median (range).

	Hyperthyroid patients (<i>n</i> = 32)	MMI-treated patients (<i>n</i> = 29)
Age (years)	35.1 $\pm$ 7.6	37.4 $\pm$ 7.8
Sex (M/F)	4/28	2/27
Smokers (<i>n</i>)	15 (46.9%)	12 (41.4%)
Range of disease duration	7 (1–72)	12 (1–156)
Thyroid volume (ml)†	38.4 $\pm$ 19.8	31.3 $\pm$ 15.2
24-h radioiodine uptake (%)§	73.3 $\pm$ 17.5	70.0 $\pm$ 22.9
Dose ¹³¹ I (mCi)	10.6 $\pm$ 5.7	8.9 $\pm$ 4.6
Thyroxine (nmol/l)	302.4 $\pm$ 95.2	155.7 $\pm$ 60.5*
Free thyroxine (pmol/l)	56.6 $\pm$ 19.7	21.6 $\pm$ 4.6*
Triiodothyronine (nmol/l)	7.95 $\pm$ 3.8	3.78 $\pm$ 1.9*
Thyrotropin concentration (mU/l)	< 0.03	< 0.03
TRAb (U/l)	62.2 (10.6–407)	77.5 (11.5–311.4)

MMI, methimazole.

The reference ranges for laboratory values are: thyroxine, 56.3–160.9 nmol/l (4.5–12.5 μ g/dl); free thyroxine, 8.4–23.2 pmol/l (0.6–1.8 ng/dl); triiodothyronine, 1.19–2.8 nmol/l (78–182 ng/dl); thyrotropin, 0.4–4.5 mU/l. Normal values for thyrotropin–receptor antibody are <11 U/l. To convert thyroxine values to μ g/dl and free thyroxine values to ng/dl, divide by 12.87. To convert triiodothyronine values to ng/dl, divide by 0.01536.

* *P* values for the comparisons between groups < 0.05.

† Thyroid volume was measured by ultrasonography.

§ Iodine uptake was measured 24 hours after the oral administration of 5 μ Ci (185 kBq) of ¹³¹I and are expressed as a percentage of the administered dose; reference values are 15–35%.

fibrillation. No patients presented symptoms or signs of clinical ophthalmopathy. Hypothyroid patients received L-thyroxine replacement therapy.

Serum TSH receptor antibodies

At baseline all patients but 2 (3%), both randomized to the hyperthyroid group, tested positive for TRAb. In the group pretreated with methimazole, median serum TRAb levels decreased significantly from baseline to D0 (80.5 (95% CI 11.8 to 278.6) vs 48.8 (95% CI 4.7 to 196.9) U/l; $P < 0.05$). Accordingly, 25% of patients from this group tested negative for TRAb at ^{131}I dosing. In hyperthyroid patients, we observed a decrease in median serum TRAb levels between baseline and D0 (68.3 (95% CI 10.3 to 423.9) vs 45.0 U/l (95% CI 10.9 to 241.1)), but it was not statistically significant (Fig. 1). Serum TRAb levels on the day of ^{131}I administration presented a significant correlation with serum T_3 levels ($r = 0.590$; $P < 0.001$), duration of disease ($r = -0.325$; $P = 0.028$) and 24-h radioiodine uptake ($r = 0.351$; $P = 0.018$). Age ($P = 0.708$), sex ($P = 0.117$), thyroid volume ($P = 0.135$) and smoking habit ($P = 0.807$) were not associated with serum TRAb levels on the day of ^{131}I administration.

Serum TSH receptor antibodies after ^{131}I administration

Radioactive iodine treatment induced a significant increase in serum TRAb levels in both patient groups (Fig. 1A). In the group of patients treated with methimazole, serum TRAb levels did not change between D0 and month 1 (48.8 (95% CI 4.8 to 196.9) vs 33.1 (95% CI 6.8 to 231) U/l) whereas a significant increase (19%) from 48.8 (95% CI 4.8 to 196.9) to 60 (95% CI 8.8 to 875.5) U/l was observed by month 3. Six months after ^{131}I administration median serum TRAb levels were still significantly elevated compared with baseline values (99.9 (95% CI 3.3 to 364.7) U/l; 105%); thereafter, we observed a progressive decrease until month 12, when median serum TRAb levels reached baseline values (47.6 (95% CI 4.7 to 207.10) U/l).

In the hyperthyroid group a significant increase (45.0 (95% CI 10.9 to 241.1) to 78.0 (95% CI 7.6 to 1106) U/l; 73%) was observed as early as 1 month after ^{131}I administration. Serum TRAb levels peaked at 3 months (225 (95% CI 14.7 to 1162.6) U/l; 400%), followed by a progressive decrease to baseline levels at 12 months (40.0 (95% CI 3.4 to 365.9) U/l).

As illustrated in Fig. 1A, the course of median serum TRAb levels after ^{131}I administration was significantly different in the two patient groups ($P < 0.05$). Median serum TRAb levels were significantly higher in the hyperthyroid group than in pretreated patients at 1 and 3 months ($P = 0.027$ and $P = 0.033$ respectively). After 1 year of ^{131}I administration, there was no

difference in the median serum TRAb levels between the groups ($P = 0.801$).

Prognostic factors of ^{131}I -induced rise in serum TRAb levels

In order to identify possible factors associated with the ^{131}I -induced rise in serum TRAb levels, all patients were grouped for analysis. A multiple regression analysis was performed with the variation between the serum TRAb levels on the day of treatment and at 3 months ($\log_{10}\text{TRAb}$) as the dependent variable. The following potential predictor factors were included as independent variables: sex, age, duration of disease, thyroid volume, serum TRAb and T_3 levels on the day of treatment, and smoking habit. Only serum TRAb levels remained significantly associated with the peak increment of serum TRAb levels at 3 months ($r^2 = 0.34$; $P = 0.001$). All other variables were eliminated from the model.

Relationship between thyroid function outcome and change in serum TRAb levels

One year after ^{131}I administration no statistical differences were observed between pretreated or not-pretreated patients with respect to permanent hypothyroidism (55.2% vs 56.3%), euthyroidism (31.0% vs 28.1%) or persistent hyperthyroidism (13.8% vs 15.6%). In addition, there was no correlation between the course of thyroid function after ^{131}I dosing, as determined by the mean serum T_3 and FT_4 levels, and the course of mean serum TRAb levels (Fig. 1A–C). However, patients who became hypothyroid presented a higher increment in serum TRAb levels (24 patients, median 191.0, interquartile range 17.9 to 661.1) than those in euthyroidism (8 patients, median 0.94, interquartile range –11.5 to 44.2) or hyperthyroidism after 1 year of ^{131}I therapy (Fig. 2A; $P = 0.038$). Nevertheless, at the end of 1 year there was no statistical difference in the serum TRAb levels among euthyroid, hyperthyroid, or hypothyroid patients (Fig. 2B). Furthermore, despite the treatment group or thyroid function outcome, 1 year after receiving ^{131}I therapy for Graves' hyperthyroidism, 80% of patients from the hyperthyroid group and 85% of pretreated patients remained positive for TRAb (Fig. 2B).

Discussion

The analysis of serum TRAb after radioiodine dosing showed that the decrease in basal serum TRAb levels achieved by methimazole pretreatment before ^{131}I therapy attenuates the radioiodine-induced increases in TRAb levels. Multiple regression analysis identified serum TRAb levels on treatment day as an independent predictor of TRAb increment after ^{131}I administration.

Figure 1 Changes in serum TRAb (A), FT_4 (B) and T_3 (C) levels in patients with Graves' disease who were treated with radioiodine alone (hyperthyroidism) or methimazole + radioiodine (MMI-treated). The dotted lines denote the reference range. TRAb levels are presented as median (95% CI) while FT_4 and T_3 values are presented as means $\pm$ S.E.M. * $P < 0.05$ for the comparison with the value on the day of ^{131}I dosing (D0). # $P < 0.05$ for the comparison between groups.

A higher increment in serum TRAb levels was associated with hypothyroidism after 1 year of follow-up.

It is well recognized that the onset of Graves' disease and the recurrence of hyperthyroidism following therapy are associated with elevated levels of antibody receptors (14–16). There is controversial evidence that antithyroid drugs have immunosuppressive actions that may contribute to the suppression of TSH receptor antibodies. By tracking oxygen radicals produced by macrophages in response to a variety of stimuli, it is believed that methimazole probably interferes with antigen processing of the macrophages, leading to decreased T cell response and antibodies production. The decrease in serum TRAb levels and

the increased remission rate in Graves' disease after methimazole compared with propranolol treatment, as well as an *in vitro* effect of methimazole on immunocytes (11) are among the results which favor an immunosuppressive effect of antithyroid drugs. However, the decreased lymphocyte production and/or secretion of immunoglobulins shown *in vitro* occur at methimazole concentrations much higher than those found in crude thyroid homogenates of patients taking methimazole (17, 18).

The finding that adjunctive methimazole treatment blocks the transitory increase in serum TRAb levels observed after ^{131}I administration in hyperthyroid Graves' patients (7, 19), has been suggested as evidence

Figure 2 (A) Serum TRAb variations and (B) serum TRAb levels 1 year after ^{131}I treatment in patients with euthyroidism, persistent hyperthyroidism, or hypothyroidism. The dashed line denotes the upper normal values for TRAb ($<11\text{ U/l}$). * $P < 0.05$ for the comparison with euthyroid and hyperthyroid groups (Kruskal–Wallis ANOVA). RAI, radioactive iodine.

of an organ-specific immunity effect. However, our results indicate that the improvement in Graves' immune dysregulation (as assessed by TRAb measurements) achieved by methimazole pretreatment is enough to lessen the immune system response to ^{131}I therapy. In not-pretreated patients receiving ^{131}I we observed a significant increase in mean serum TRAb levels as early as 30 days after ^{131}I dosing, reaching peak levels 3 months later. By contrast, in the group of patients pretreated with methimazole, in whom a significant decrease in serum TRAb levels had occurred, the observed increase in mean serum TRAb levels occurred only after 3 months, with much less intensity. The observed TRAb response pattern in the group who received ^{131}I alone was very similar to response patterns reported by other studies (20, 21) while the course of serum TRAb levels over 1 year in methimazole pretreated patients was virtually identical to that reported by others in patients using methimazole during the 1-year observed period (7, 8). The fact that

methimazole had been stopped 4 days before ^{131}I administration suggests that the immune status at the time of ^{131}I administration is the main determinant of the ^{131}I -induced rise in serum TRAb levels in Graves' patients.

However, the study design does not allow us to solve an important question regarding the immune effects of antithyroid drugs *in vivo* since methimazole pretreatment also improved the hyperthyroidism, a known cause of immune disorder. The strong correlation observed between serum TRAb and thyroid hormone levels on the treatment day demonstrates how complex it is to interpret the results independently. Nevertheless, in a multiple regression analysis model including both variables, only serum TRAb levels on the treatment day remained significantly associated with the level of the increment in serum TRAb levels in response to ^{131}I administration. This result may indicate that serum TRAb levels at the time of ^{131}I iodine dosing are the principal determinant of the subsequent boost in TRAb levels. Furthermore, the lack of correlation between the thyroid hormone concentrations after ^{131}I treatment and the course of serum TRAb levels suggests that once the release of thyroid cells antigens has occurred the immune response pattern is independent of thyroid hormone status.

The clinical implications of the increase in serum TRAb levels after ^{131}I therapy is still a matter of speculation. Chiovato *et al.* (8) has suggested that the increase in serum TRAb levels is caused by the release of TSH receptor molecules from disrupted follicular cells. Because the TSH receptor is a membrane protein, the post-radioiodine increase in serum levels of this antibody would be a marker of thyroid cell damage produced by ^{131}I , and a favorable prognostic factor for cure. In our series, permanent hypothyroidism 1 year after ^{131}I administration was present in about 55% of patients pretreated or not treated with methimazole. The high incidence of hypothyroidism could, at least in part, be explained by our high dose protocol and by the fact that none of the patients received antithyroid drug therapy after ^{131}I dosing (22). We also observed that the patients who became hypothyroid presented a larger increment in serum TRAb levels than patients who were hyperthyroid or euthyroid at the end of the study. Assuming that the serum TRAb levels are a marker of thyroid damage, it is interesting to note the similarity in the increase in serum TRAb levels between euthyroid patients and those who did not respond to ^{131}I therapy. Similar to what has been reported by others 1 year after ^{131}I therapy, most patients regardless of thyroid outcome remained positive for TRAb, emphasizing that the underlying autoimmune dysfunction is still present (23).

Increased serum TRAb levels have also been observed in patients with nodular thyroid disease treated with radioactive iodine, and concomitant development of hyperthyroidism (9). Since recent studies

have demonstrated that methimazole pretreatment does not interfere with ¹³¹I efficacy (4, 5), this therapy approach could be considered in high risk patients such as those with elevated anti-tireoperoxidase pretreatment titers (9). Some studies have also associated ¹³¹I therapy with worsening of Graves' ophthalmopathy (24–26), and it has been hypothesized that the radiation damage would result in the release of thyroid antigens, which would promote an immune response against orbital components that share antigenic epitopes with the thyroid (27). Based on this assumption the role of methimazole in the course of ophthalmopathy after ¹³¹I treatment has been addressed by some studies (13). The authors concluded that although methimazole was able to suppress the surge of TRAb after ¹³¹I treatment, it was not of prognostic significance for the development of Graves' ophthalmopathy. Even though our study protocol has excluded patients with moderate or severe eye disease, it was interesting to note that none of our patients from either group developed clinical ophthalmopathy during the 1-year follow-up.

In conclusion, our results demonstrated that in patients with Graves' disease, serum TRAb levels at the time of ¹³¹I administration mainly influence the mechanisms regulating autoantibody production after radioactive iodine therapy. The ¹³¹I treatment-induced rise in serum TRAb levels was associated with the development of hypothyroidism after 1-year of follow-up.

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