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Outcome of Thyroid Function in Graves' Patients Treated with Radioiodine: Role of Thyroid-Stimulating and Thyrotropin-Blocking Antibodies and of Radioiodine-Induced Thyroid Damage*

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ABSTRACT

We investigated the interrelationship and the influence of thyroid-stimulating antibodies (TSAb), TSH-blocking antibodies (TSHBAb), and of radioiodine (^{131}I)-induced thyroid damage in the early (within 1 yr) outcome of thyroid function in hyperthyroid patients with Graves' disease (GD) treated with ^{131}I. TSAb, TSHBAb, and ultrasound thyroid volume (as an index of thyroid damage) were simultaneously measured before and at 1, 3, 6, and 12 months after ^{131}I in 31 GD patients. One year after radioiodine, 9.7% of patients were hyperthyroid (Hyper-group), requiring methimazole; 12.9% were euthyroid (Eu-group); and 77.4% were hypothyroid (Hypo-group). Pretreatment thyroid volume in the Eu-group and Hyper-group was significantly greater ($P = 0.009$) than in the Hypo-group. Pre-^{131}I TSAb levels were higher in the Hyper-group *vs.* the Hypo-group ($P = 0.01$) or the Eu-group ($P = 0.03$). A significant post-^{131}I increase in TSAb levels occurred in 66% of patients developing hypothyroidism but not in those remaining hyperthyroid. After ^{131}I, TSHBAb appeared in 7 patients, in all but one associated with high levels of TSAb. One year after radioiodine: 1) the mean percent reduction in thyroid volume was greater in the Hypo-group (80.7%) or the Eu-group (83.5%) than in the Hyper-group (35.7%) ($P = 0.007$ and 0.033, respectively); 2) hypothyroid patients had smaller ($P = 0.0058$) post-^{131}I thyroids than hyperthyroid patients; and 3) TSAb were still elevated in 75% hypothyroid patients, but all of them had a thyroid volume $\leq$8 mL, indicating major postradioiodine gland damage. In conclusion: 1) the early outcome of thyroid function after ^{131}I for GD is mainly related to pretreatment thyroid volume and to the degree of its reduction after therapy; 2) high TSAb levels before ^{131}I are associated with a relative resistance to therapy; 3) a postradioiodine increase in TSAb levels is related to the development of hypothyroidism; and 4) the concomitant appearance of TSHBAb and disappearance of TSAb are not frequent after ^{131}I and play a role in the development of early postradioiodine hypothyroidism only in a minority of patients. (*J Clin Endocrinol Metab* **83:** 40–46, 1998)

RADIOIODINE (^{131}I) is increasingly used as the definitive treatment of choice in most patients with Graves' hyperthyroidism (1, 2). After a single radioiodine administration, patients may become hypothyroid, euthyroid, or remain hyperthyroid (3). Hypothyroidism may develop within the first few months after ^{131}I therapy or in subsequent years (2, 4, 5). The occurrence of hypothyroidism after radioiodine therapy largely depends on the dose of ^{131}I administered (6, 7).

Biological effects of ^{131}I include necrosis and impaired replication of nondestroyed follicular cells (8), atrophy, fibrosis, and a chronic inflammatory response, which may ultimately result in permanent thyroid failure (2). Changes in thyroid histology are associated with a reduction in thyroid volume (9), which reflects thyroid damage. Radioiodine treatment for Graves' disease (GD) is also followed by changes in thyroid autoimmunity, which may result in a transient increase of TSH-receptor antibodies (TRAb) with thyroid stimulating antibody (TSAb) activity (10, 11) and in the *de novo* appearance of TRAb with TSH-blocking activity (TSHBAb) (11–13). In a recent paper, TSHBAb were found in most patients developing early postradioiodine hypothyroidism, suggesting that the *de novo* appearance of TSHBAb could be responsible for the occurrence of thyroid failure (14). This observation remains to be confirmed. Longitudinal studies, comparing the outcome of thyroid function after ^{131}I with changes in thyroid volume and in the levels of TSAb and TSHBAb, also are lacking.

The aim of the present study was to establish the relative role of humoral thyroid autoimmunity and of radioiodine-induced thyroid damage in the development of early postradioiodine hypothyroidism in patients with GD. To this purpose, we measured thyroid volume, as an index of ^{131}I-induced tissue damage, TSAb, and TSHBAb before and at several time-intervals up to 1 yr after radioiodine therapy.

Materials and Methods

Patients and radioiodine therapy

Thirty-one patients with hyperthyroid GD (7 males, 24 females; age range = 25–70 yr, mean age ± SD = 43.3 ± 12.2 yr) were included in this study. The diagnosis was based on common clinical and laboratory criteria. Twenty-three patients had Graves' ophthalmopathy that was mild in 17, moderate in 4, and severe in 2. One patient had pretibial

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myxedema. Before radioiodine therapy, all patients were treated with methimazole (MMI) for a mean period of 13 ± 9 months (range = 4–36 months). MMI was discontinued 1 week before ^{131}I therapy. Serum samples for free T_4, free T_3, TSH, and antithyroid antibodies were collected immediately before ^{131}I and at 1, 3, 6, and 12 months thereafter. Aliquots of sera were kept frozen at −20 C until used for specific assays. Sera and IgG, obtained from individual patients before and after ^{131}I, were run in the same assay.

The therapeutic dose of radioiodine was calculated with the formula:

$$\text{Dose (MBq)} = \frac{\text{thyroid weight (g)} \times 7.4\ \text{MBq/g}}{\text{24-h radioiodine uptake}}$$

Thyroid radioiodine uptake was measured at 3 and 24 h after an oral tracer dose (1.85 $\sqrt{\text{MBq}}$) of ^{131}I. Thyroid weight was estimated by assuming that 1 mL (ultrasound volume) corresponds to 1 g of tissue. The mean (±SD) therapeutic dose of ^{131}I was 518 ± 111 (range = 111–1258) MBq. Antithyroid drugs were not given shortly after ^{131}I. Treatment with MMI was reinstituted 3–6 months after radioiodine, in 3 patients with persistence of hyperthyroidism. To prevent an exacerbation of Graves' ophthalmopathy after radioiodine, 15 patients received prednisone at antiinflammatory doses after ^{131}I. Prednisone (20–30 mg/day; 0.4–0.5 mg/kg BW·day) was tapered 1 month later and discontinued within 3 months. Informed consent was obtained from patients under the guidance of the Ethical Committee, University of Pisa.

Thyroid ultrasonography

Thyroid ultrasonography was performed before ^{131}I and afterwards at 1, 3, 6 and 12 months, by the same examiner, using a linear transducer (7.5 MHz) attached to a real-time instrument (AU 590 Asynchronus Apparatus, Esaote Biomedica, Milan, Italy). Thyroid volume was calculated with the ellipsoid formula (15): width (mm) × length × thickness × 0.52 × each lobe = volume (mL). In a preliminary study, we found that thyroid volume in normal adults residing in an iodine-sufficient area in Italy was 11.3 ± 3.4 mL (mean ± SD) in males and 8.6 ± 2.2 mL in females.

Free thyroid hormones and TSH

Free T_4 was measured with FT4 Kit (normal range = 8.4–21.2 pmol/L), and free T_3 with FT3 Kit (4.0–8.4 pmol/L), both from Technogenetics, Milan, Italy. Serum TSH was measured with an immunofluorometric assay: Delfia hTSH, Pharmacia, Turku, Finland (normal range = 0.4–3.7 mU/L).

Antithyroglobulin antibody (TgAb) and antithyroperoxidase antibody (TPOAb)

TgAb and TPOAb were measured using commercial kits: TGAb IRMA Biocode, Sclessin, Belgium (normal values <50 U/mL), and DYNOtest anti-TPO_n BRAHMS Diagnostica GmbH, Berlin, Germany (normal values <30 U/mL).

TSAb and TSHBAb

IgG was prepared from sera of patients by separation on DEAE-Sephadex A 50, precipitation by ammonium sulphate, dialysis in TRIS buffer, and centrifugation at 3000 rpm (16). IgG concentration was measured by optical density at 280 nm (E = 1.46). By immunoelectrophoresis, the preparation contained 90% IgG and 10% of other proteins, mostly albumin.

Chinese hamster ovary (CHO) cells transfected with the recombinant human TSH receptor (CHO-R) (16) were cultured in RPMI-1640 medium plus 1 mmol/L glutamine, 10% FCS, and 0.4 g/L geneticin. CHO-R cells were seeded (30,000 cells/well) in 96-well plates (Costar, Cambridge, MA). Cells were fed fresh culture medium 24 h after seeding and were used for the assay of TSAb or TSHBAb the following day.

TSAb and TSHBAb were measured using previously described methods (16, 17). IgGs were diluted in hypotonic buffer containing 4 g/L BSA and 0.5 mmol/L isobutylmethylxanthine. In the TSAb assay, cell cultures were incubated with IgG alone (1 g/L). In the TSHBAb assay, cell cultures were incubated with IgG alone (1 g/L), TSH alone (10 mU/L), or IgG plus TSH. Hypotonic buffer-BSA-isobutylmethylxanthine alone was added to some cultures in each experiment to measure basal cAMP production. After 2-h incubation at 37 C in 5% CO_2/95% air atmosphere, cAMP was measured in extracellular medium by RIA. Experiments were performed in triplicate; and results (pmol/well) were expressed as the average of these. The mean (± SD) cAMP production, obtained with IgGs from 50 normal subjects, was 98 ± 16% of basal value. IgGs increasing cAMP production >2 SD from the mean of normals (>130% of basal) were considered positive for TSAb. To measure TSHBAb, an index of inhibition of TSH-dependent cAMP production (TSH-inhibition index, TSH-II) was calculated with the formula:

$$\left[1 - \frac{\text{cAMP (TSH + sample IgG)} - \text{cAMP (sample IgG)}}{\text{cAMP (TSH)} - \text{cAMP (control buffer)}}\right] \times 100$$

IgGs producing a reduction of TSH-stimulated cAMP increase ≥30% were considered positive for TSHBAb (17).

Statistical analysis

Nonparametric tests were used. Results obtained in different groups of patients were compared by χ^2 test with Yeates correction, Mann-Whitney, or Kruskal-Wallis tests as appropriate. Sequential results in each subgroup of patients were analyzed by Wilcoxon signed-rank test.

Results

Changes in thyroid status after radioiodine

One year after radioiodine, 3 of 31 patients (9.7%) were hyperthyroid (Hyper-group), requiring MMI treatment; 4 of 31 (12.9%) were euthyroid (Eu-group); and 24 of 31 (77.4%) patients were hypothyroid (Hypo-group). In the Hypo-group, 4 of 24 (16.7%) patients became hypothyroid at 1 month after ^{131}I, 12 of 24 (50%) at 3 months, 6 of 24 (25%) at 6 months, and 2 of 24 (8.3%) at 12 months. Hypothyroidism was subclinical in 11 patients and overt in 13 patients. To exclude transient hypothyroidism, L-thyroxine therapy was started at a suboptimal dose that was not increased until evidence for persistently elevated serum TSH was obtained. In the Eu-group, 2 patients experienced transient hypothyroidism 3–6 months after ^{131}I but spontaneously recovered at 1 yr.

Thyroid volume before and after radioiodine

Before radioiodine, the median thyroid vol was 30 mL (mean ± SD = 37.8 ± 28.4 mL) in the whole study group, 29 mL (mean = 57.2 ± 51.7 mL) in the Hyper-group, 76.5 mL (mean = 75.7 ± 18.0 mL) in the Eu-group, and 27.5 mL (mean = 29.1 ± 19 mL) in the Hypo-group. Differences among subgroups of patients were not statistically significant. When patients in the Eu-group and Hyper-group were considered together, their pretreatment thyroid vol (median = 65 mL, mean = 67.8 ± 34.1 mL) was significantly greater ($P = 0.009$) than in the Hypo-group.

After radioiodine, a progressive reduction in thyroid volume occurred that was already significant 1 month after ^{131}I ($P = 0.001$) (Fig. 1A). One year after ^{131}I, the percent reduction of thyroid volume in the whole study group ranged from 24–96% (mean % reduction = 76.4%). The mean percent reduction in thyroid volume was greater in hypothyroid (80.7%) than in hyperthyroid (35.7%) ($P = 0.007$) patients. Euthyroid patients experienced a mean percent reduction in thyroid volume (83.5%) that was greater, compared with hyperthyroid ($P = 0.033$) but not with hypothyroid patients.

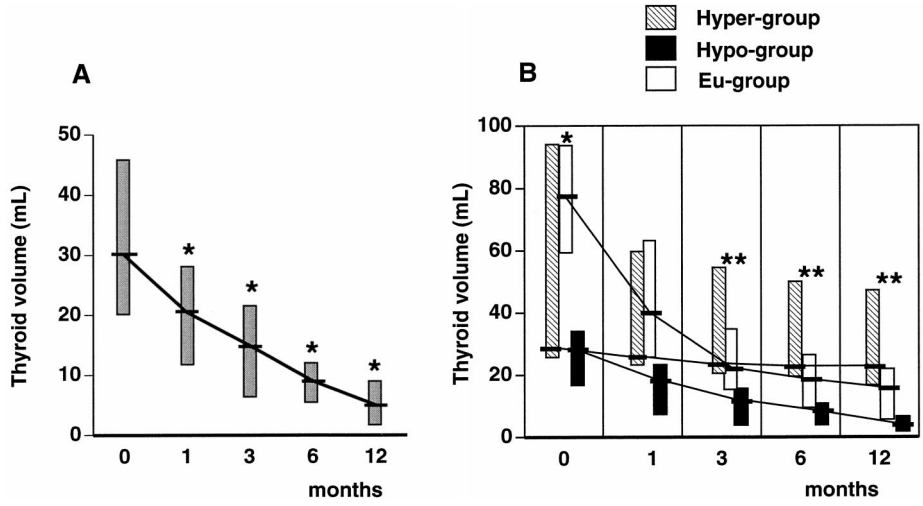

FIG. 1. Ultrasound thyroid volume [median and interquartile (25th-75th percentile) distribution] before (time zero) and at various time intervals after radioiodine therapy in the whole study group (*, significantly different *vs.* pretreatment, $P < 0.001$) (Panel A), and in different groups of patients subdivided according to the outcome of their thyroid function (Panel B) (*, significantly greater in the Hyper-group and Eu-group *vs.* Hypo-group, $P = 0.01$; **, significantly greater in Hyper-group *vs.* Hypo-group, $P < 0.01$). The *lines* drawn over the *bars* go through medians of the *bars*.

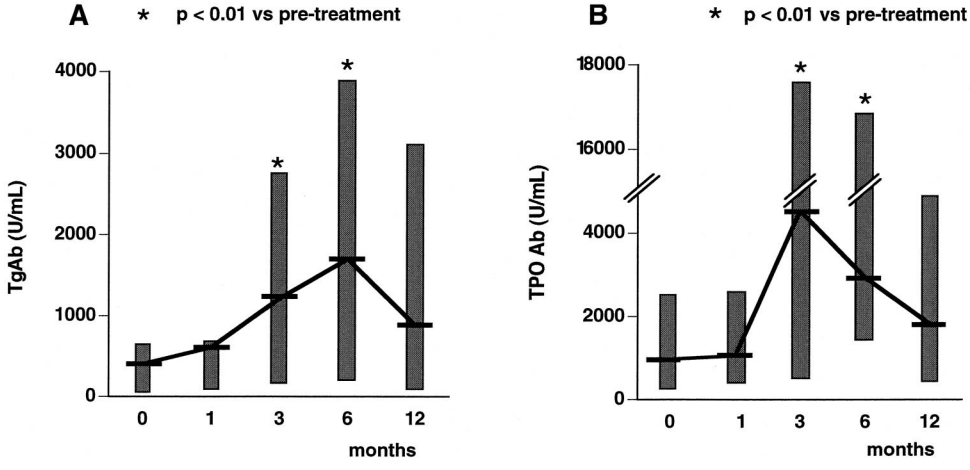

FIG. 2. Serum levels [median and interquartile (25th-75th percentile) distribution] of TgAb (Panel A) and TPOAb (Panel B) before (time zero) and at various time intervals after radioiodine therapy.

Changes in thyroid volume after ^{131}I in different subgroups of patients are shown in Fig. 1B. One year after radioiodine, the median thyroid vol was 4 mL (mean = 4.4 ± 2.5 mL) in the Hypo-group, 14.5 mL (mean = 12.7 ± 8.4 mL) in the Eu-group, and 22 mL (mean = 31.3 ± 20.6 mL) in the Hyper-group. Hypothyroid patients had smaller ($P = 0.0058$) thyroids than hyperthyroid patients. Euthyroid patients had an intermediate thyroid volume between that of hypothyroid and hyperthyroid patients, but the difference was not statistically significant. All hypothyroid patients had a thyroid vol ≤8 mL. With one exception, all euthyroid and hyperthyroid patients had a thyroid vol >11 mL.

TgAb and TPOAb before and after radioiodine

Before radioiodine, TgAb were detected in 10 of 31 (32%) patients (median value = 402 U/L; mean = 636 ± 804 U/L). TgAb levels significantly increased at 3 ($P = 0.0037$) and 6 ($P = 0.009$) months after ^{131}I and then declined at 1 yr (Fig. 2A). Before radioiodine, TPOAb were detected in 27 of 31 (87%) patients (median = 970 U/L; mean = 3008 ± 5156 U/L). TPOAb levels significantly increased at 3 ($P = 0.005$) and 6 ($P = 0.001$) months after radioiodine and then decreased at 12 months (Fig. 2B). Serum levels of TgAb and TPOAb significantly increased after radioiodine in the Hypo-group ($P = 0.002$ and $P = 0.006$, respectively) but not in the Hyper-group.

TSAb before and after radioiodine

Before ^{131}I, TSAb were found in 19 of 31 (61.2%) patients (median value = 216%; mean = 461 ± 433%): all 3 patients in the Hyper-group (median = 1010%; mean = 1061 ± 147%), 13 of 24 (54.1%) in the Hypo-group (median = 185%; mean = 380 ± 406%), and 3 of 4 in the Eu-group (median = 216%; mean = 214 ± 29%). Pretreatment TSAb levels in the Hyper-group were higher than in the Hypo-group ($P = 0.01$) or in the Eu-group ($P = 0.03$).

Six months after ^{131}I, the number of patients with detectable TSAb significantly increased to 26 of 31 (83.8%) ($P = 0.04$), and TSAb levels were higher ($P = 0.04$), compared with pretreatment values (Table 1). One year after ^{131}I, TSAb were detectable in 25 of 31 (80.6%) patients, but their levels had decreased ($P = 0.006$ *vs.* 6 months after ^{131}I) and did not differ from pretreatment results.

TSAb remained detectable up to 1 yr after ^{131}I in all hyperthyroid patients, but serum levels decreased in 2 of them (Fig. 3A). In the Eu-group, 1 more patient had detectable TSAb after ^{131}I, and a significant increase in TSAb levels was

TABLE 1. Serum levels of TSAb and percentage of patients with detectable TSAb before (pretreatment) and at various time intervals (1–12 months) after radioiodine therapy

	Pretreatment	1 month	3 months	6 months	12 months
Mean ± SD	461 ± 433	329 ± 258	634 ± 761	863 ± 1365	456 ± 461
25th percentile	168	143	216	200	179
Median	216	182	312	288[a]	253
75th percentile	422	638	780	780	532
% positive	61.2%	67.4%	77.4%	83.8%[a]	80.6%

TSAb are expressed as % of basal cAMP production.
[a] *, Significantly different *vs.* pretreatment ($P = 0.04$).

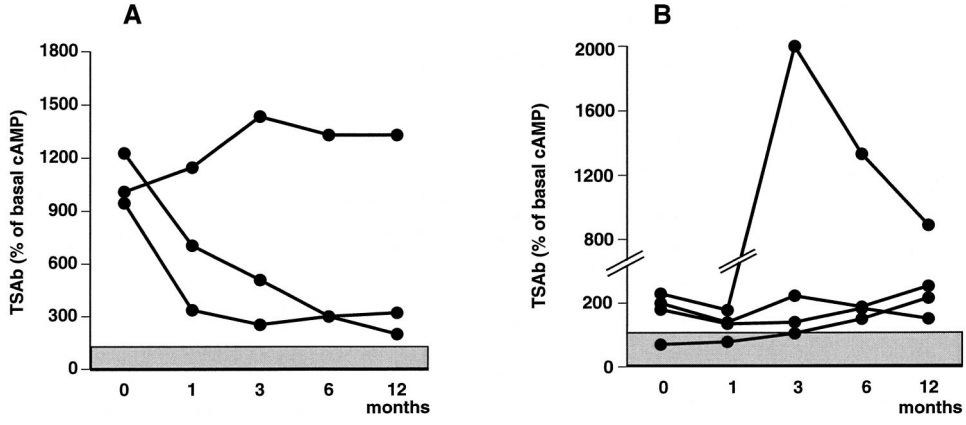

FIG. 3. Serum levels of TSAb before (time zero) and at various time intervals after radioiodine therapy in patients of Hyper-group (Panel A) and Eu-group (Panel B). The *shaded area* denotes the normal range.

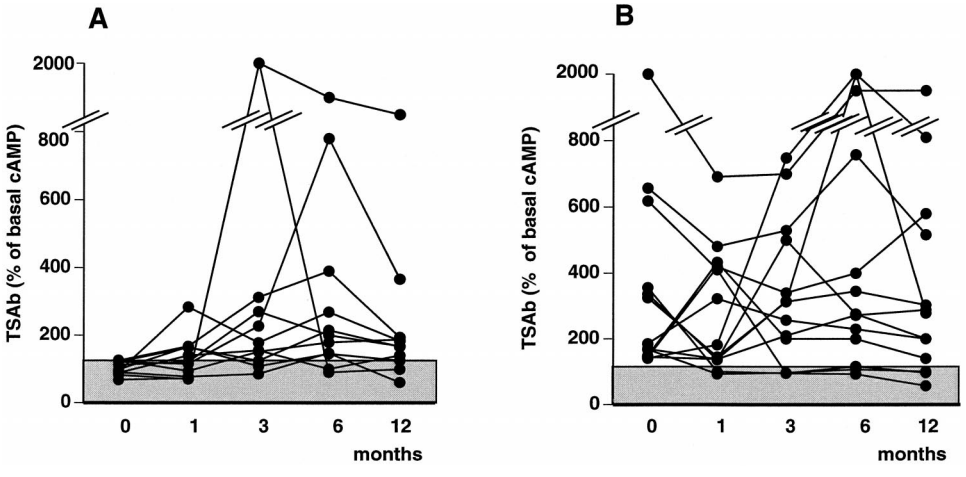

FIG. 4. Serum levels of TSAb before (time zero) and at various time intervals after radioiodine therapy in patients of Hypo-group. Patients are subdivided according to the finding of undetectable (Panel A) or detectable (Panel B) TSAb before ^{131}I administration. The *shaded area* denotes the normal range.

observed in another one (Fig. 3B). One year after ^{131}I, all euthyroid patients were positive for TSAb (range = 151–812%). Six months after radioiodine, TSAb levels significantly increased in hypothyroid patients ($P = 0.02$). In this group, 9 of 11 (81.8%) patients with undetectable TSAb before ^{131}I became positive for this antibody 3–6 months after therapy ($P = 0.003$) (Fig. 4A). Among patients with detectable TSAb before ^{131}I, 7 of 13 (53.8%) showed an increase greater than 30% in TSAb levels after therapy (Fig. 4B). In the remaining 6 patients, TSAb levels did not change in 2 and decreased in 4. Altogether, an increase in TSAb levels was found in 66.6% of patients with postradioiodine hypothyroidism. One year after ^{131}I, TSAb were found in 18 of 24 (75%) hypothyroid patients (median = 239%; mean = 454 ± 479%). At that time, there was no significant difference in TSAb levels among hyperthyroid, euthyroid, or hypothyroid patients.

TSHBAb before and after radioiodine

Before ^{131}I, 4 patients (13%) had TSHBAb associated with strong TSAb activity (Table 2). The coexistence of TSAb and TSHBAb was not associated with a specific outcome of thyroid status (2 patients remained hyperthyroid, and 2 developed hypothyroidism). After ^{131}I, 7 more patients developed TSHBAb, and 2 became negative. TSHBAb were associated with TSAb in all patients but one, in whom TSAb disappeared 3 months after ^{131}I being replaced by TSHBAb (Table 2). One year after ^{131}I, TSHBAb were found in 1 of 4 (25%) euthyroid, in 1 of 3 (33%) hyperthyroid, and in 5 of 24 (20.8%) hypothyroid patients, in all but one associated with TSAb.

TABLE 2. TSAb, TSHBAb, and ultrasound thyroid volume in patients with detectable TSHBAb at any time before (pre-treatment) or after radioiodine therapy

Patient	Pretreatment			1 month			3 months			6 months			12 months			Thyroid function outcome
	TSAb %	TSH BAb %	Vol mL	TSAb %	TSH BAb %	Vol mL	TSAb %	TSH BAb %	Vol mL	TSAb %	TSH BAb %	Vol mL	TSAb %	TSH BAb %	Vol mL	
RM	**1228**	**83**	117	**705**	0	71	**509**	29	65	**300**	10	60	**155**	0	55	Hyper
FM	**1010**	**65**	26	**1147**	**100**	25	**1434**	**100**	21	**1330**	**100**	20	**1330**	**100**	17	Hyper
PT	**211**	27	55	**178**	11	31	**1650**	**49**	16	**1166**	**100**	9	**812**	**38**	2	Eu
CA	**1594**	**67**	42	**691**	4	15	**814**	29	14	**1429**	**69**	11	**1493**	**41**	4	Hypo 3 m
TF	82	25	63	70	4	41	**3000**	**100**	17	**3000**	**100**	10	**1737**	**85**	7	Hypo 3 m
CA	68	0	42	72	0	30	**2510**	**100**	27	90	21	25	99	24	8	Hypo 3 m
CG[a]	**618**	0	91	**410**	21	40	95	**82**	28	116	**60**	9	97	**49**	8	Hypo 3 m
CM	**133**	15	21	**433**	0	20	**200**	**73**	11	**200**	**42**	9	**180**	**51**	3	Hypo 3 m
MA	**134**	29	9	**419**	**36**	4	**340**	**58**	3	**400**	**60**	3	**580**	**81**	2	Hypo 3 m
MI	**132**	18	36	**182**	12	21	**748**	**44**	16	**2500**	**100**	8	**1059**	28	7	Hypo 6 m
DC	**336**	**100**	19	**136**	**50**	11	**500**	**100**	7	**276**	**75**	8	**200**	17	5	Hypo 6 m

[a] The patient (CG) who experienced postradioiodine disappearance of TSAb associated with appearance of TSHBAb.

Vol, Ultrasound thyroid volume (mL); Hyper, hyperthyroid; Eu, euthyroid; Hypo, hypothyroid; 3m and 6m indicate the postradioiodine time-interval (3 months and 6 months, respectively) when patients became hypothyroid. Positive results for TSAb (>130%) and for TSHBAb (≥30%) are highlighted using *bold*.

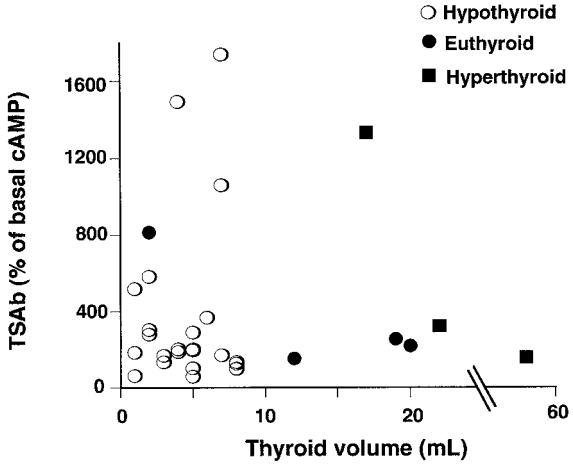

FIG. 5. Relationship between serum levels of TSAb and ultrasound thyroid volume at 1 yr after ^{131}I treatment in patients with persistent hyperthyroidism, euthyroidism, or hypothyroidism.

Relationship between thyroid status, thyroid volume, and TSAb or TSHBAb changes after radioiodine

One year after ^{131}I, all patients with a thyroid vol ≤8 mL but one were hypothyroid, in spite of persistent TSAb in 75% of them (Fig. 5). The patient who developed TSHBAb without TSAb after ^{131}I became hypothyroid with a thyroid vol of 28 mL (Table 2). However, hypothyroidism occurred 3 months after ^{131}I in another patient, who had a thyroid vol of 29 mL and circulating TSAb without TSHBAb.

One year after ^{131}I, hyperthyroid patients had either a large thyroid (55 mL) with low TSAb levels (155%) or slightly enlarged thyroids and medium-high levels of TSAb (312–1330%) (Fig. 5). Among patients with a thyroid vol ≤8 mL, only one was euthyroid, caused by strong TSAb activity in his serum (812%). The other euthyroid patients had normal or slightly increased thyroid volumes and low TSAb level (151–250%).

Effect of prednisone therapy

Ten of 24 patients (42%) in the Hypo-group, 2 of 4 patients in the Eu-group, and all 3 patients with persistent hyperthyroidism received prednisone after ^{131}I. Differences among subgroups of patients were not statistically significant, even when patients in the Eu-group and Hyper-group were considered together and compared with the Hypo-group. Pre- and posttreatment thyroid volumes did not significantly differ in patients taking or not taking prednisone. Pretreatment TSAb levels were higher ($P = 0.03$) in patients given prednisone, but this difference was not any longer evident after ^{131}I. The number of patients with detectable TSHBAb, both before and after radioiodine, did not differ in relation to steroid therapy. Pretreatment TPOAb and TGAb levels were similar in patients treated or not treated with prednisone, but the post-^{131}I increase in the levels of these antibodies was lower in patients receiving steroid therapy.

Discussion

Radioiodine therapy for Graves' hyperthyroidism was followed by a progressive reduction in thyroid volume (67% and 76% of pretreatment volume at 6 and 12 months, respectively). These findings are similar to those reported by Peters *et al.* (9) in patients given a standard dose (555 MBq) of ^{131}I, but in the latter paper, the relationship between degree of reduction in thyroid volume and outcome of thyroid function was not investigated. In our study, pre- and posttreatment thyroid volume was the best predictor of early (within 1 yr) outcome of thyroid function. Hypothyroid patients after ^{131}I had smaller pretreatment glands than those undergoing euthyroidism or hyperthyroidism and experienced a significantly greater reduction in thyroid volume than those remaining hyperthyroid (80.7% *vs.* 35.7% at 1 yr, respectively). Thyroid volume reduction (83.5%) in euthyroid patients did not differ from that in hypothyroid patients, but their starting thyroid volume was greater. One year after ^{131}I, hypothyroid patients had smaller glands ($P = 0.0058$) than hyperthyroid patients, and their thyroid vol was ≤8 mL. The relevance of postradioiodine thyroid volume reduction for the outcome of thyroid function was reported by Murakami at al. (18), but in that study, no relationship was evident between pretreatment thyroid volume and postradioiodine thyroid function. Although no influence of pre-

treatment thyroid volume on the outcome of radioiodine treatment was also reported by Tsuruta *et al.* (19), most previous studies indicated that large Graves' goiters are more resistant to ^{131}I (2, 20). Administration of MMI shortly after radioiodine, that can reduce the effect of radiometabolic therapy (3), and the use of a relatively low dose of ^{131}I might influence the results of Murakami *et al.* (18). In that study, 50% of hyperthyroid patients treated with ^{131}I were not cured (18).

Pretreatment TSAb levels were significantly higher in patients with persistent hyperthyroidism than in those becoming hypothyroid ($P = 0.01$) or euthyroid ($P = 0.03$) after ^{131}I. This finding confirms data from other studies (18, 21), and is consistent with the fact that hyperthyroid patients after radioiodine had larger pretreatment thyroids and experienced a lower reduction in thyroid volume than those developing hypothyroidism. Indeed, the *in vitro* growth-promoting effect of most TRAb parallels their thyroid-stimulating activity, measured in adenylate-cyclase stimulation assays (22).

The number of patients with detectable TSAb and TSAb levels increased 3–6 months after ^{131}I in patients developing hypothyroidism but not in those with persistent hyperthyroidism. This difference in postradioiodine TSAb changes agrees with previous observations (11, 12, 23). In our view, the increase in TSAb levels is caused by the release of TSH receptor molecules from disrupted follicular cells and to the subsequent boosting of the autoimmune response (10). A significant increase in TPOAb levels was also observed after ^{131}I in patients developing hypothyroidism but not in those remaining hyperthyroid. Because both the TSH receptor and TPO are membrane proteins, the postradioiodine increase in serum levels of the correspondent autoantibodies may be regarded as marker of thyroid cell damage produced by ^{131}I. Conceivably, this phenomenon is related to the degree of thyroid damage produced by ^{131}I, to the subsequent reduction in thyroid volume, and to the development of hypothyroidism. The observation that serum TSAb were still elevated in 75% of hypothyroid patients 1 yr after ^{131}I, underscores the importance of postradioiodine reduction in thyroid volume for the development of hypothyroidism. An exception to this rule was a patient with high levels of TSAb (812%) who was euthyroid in spite of a thyroid markedly reduced in size (2 mL).

The coexistence of TSAb and TSHBAb was observed in a minority of patients (13%) before ^{131}I and was not associated with a specific outcome of thyroid function. In the year after radioiodine, 7 more patients developed TSHBAb, indicating a postradioiodine spreading of the autoimmune response to the TSH receptor (24) caused by the release of TSH receptor molecules from damaged follicular cells. The appearance of TSHBAb after radioiodine was suspected in early investigations (11, 12) and was demonstrated using specific bioassays in subsequent studies (13, 14). In the more recent one (14), TSHBAb were detected in 7 of 11 (63%) patients developing hypothyroidism 6 months after radioiodine, and in 54% of them, TSHBAb were found in the absence of TSAb. It was concluded that the appearance of TSHBAb and the disappearance of TSAb was a mechanism for the development of possibly transient postradioiodine hypothyroidism in patients given a relatively low dose of ^{131}I (240 ± 27 MBq). In our study, TSHBAb were observed in a minority (29% at 6 months; 20% at 12 months) of patients developing hypothyroidism after a medium-high dose of ^{131}I (518 ± 111 MBq), and with one exception, TSHBAb occurred in association with TSAb. Only one patient showed the appearance of TSHBAb and the disappearance of TSAb 3 months after radioiodine. He became hypothyroid, with a thyroid vol of 28 mL, suggesting that the change in biological activity of TRAb was the mechanism responsible for hypothyroidism. However, hypothyroidism at 3 months after ^{131}I was observed in another patient, who had a thyroid vol of 29 mL and circulating TSAb in the absence of TSHBAb. Postradioiodine inflammatory phenomena might explain the development of early hypothyroidism in patients with persistent TSAb and a still enlarged thyroid (8). Our data indicate that the appearance of TSHBAb in the absence of TSAb is not frequent after ^{131}I and is a potential, but unusual, mechanism of early postradioiodine hypothyroidism, at least when high, destructive doses of ^{131}I are given. Administration of prednisone at antiinflammatory doses, to some of the patients included in the present study, did not seem to significantly modify the results.

In conclusion: 1) the early outcome of thyroid function, after ^{131}I for GD, is mainly related to pretreatment thyroid volume and to the degree of its reduction after therapy; 2) high TSAb levels before ^{131}I are associated with persistent hyperthyroidism; 3) a postradioiodine increase in TSAb levels is related to the development of hypothyroidism; and 4) the concomitant appearance of TSHBAb and disappearance of TSAb are not frequent after ^{131}I and play a role in the development of early postradioiodine hypothyroidism only in a minority of patients.

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