Triiodothyronine Suppression Tests and TSH-Releasing Hormone Tests Before and After I-131 Therapy for Graves' Disease

Hajime Tamai, Tetsuya Nakagawa, Hideaki Takahashi, Noriyuki Ohsako, Osamu Fukino, Rishun Shinzato, Hiroyuki Suematsu, Fumio Matsuzuka, Kanji Kuma, and Shigenobu Nagataki

Khyshu University, Fukuoka; Kuma Hospital, Kobe; and University of Tokyo, Hongo, Tokyo, Japan

T_3-suppression and TRH tests were repeatedly performed in 63 patients with Graves' disease before, and 6, 12, 18, and 24 mo after I-131 therapy. These patients were selected from more than 200 I-131-treated patients; they satisfied the criteria of clinical euthyroidism, with normal serum T_4 concentrations at least during the period between 6 mo and 2 yr after the therapy. The numbers of T_3-suppressible patients increased, but only 27 of the 63 patients (43%) were suppressible at 2 yr after therapy. Those responding to TRH also increased, and 36 of 63 patients (57%) responded to TRH at 2 yr after therapy. Most of T_3-suppressible patients were TRH responsive. Although serum T_4 concentrations were within the normal range, serum T_3 levels were above normal in almost one third of these patients, and most of those with high serum T_3 levels were T_3-nonsuppressible and TRH-nonresponding. Investigation of changes in T_3-suppressibility and TRH-responsiveness in individual patients revealed that although incidence of T_3-suppression and TRH responsiveness increased, seven patients became T_3-nonsuppressible and ten patients TRH-nonresponding within 12 mo of the time when they had been T_3-suppressible or TRH-responsive. Among TRH-responders, the number with exaggerated response to TRH increased gradually and reached 28 of 36 patients (78%) at 2 hr after therapy.

These results suggest that in Graves' patients with normal serum T_4 concentrations after I-131 therapy: (a) incidence of T_3-suppressibility and TRH-responsiveness increases and reaches 50% even 2 yr after the therapy, and that serum T_3 levels are high in T_3-nonsuppressible and TRH-nonresponding patients; (b) the results of both tests at 6 mo after therapy are not prognostically reliable; (c) latent hypothyroidism begins within 2 yr after I-131 therapy even in patients with normal serum T_4 and T_3 concentrations; and (d) failure to respond to TRH, or to T_3-suppression, is not proof that a patient requires further treatment with I-131.

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Radioiodine, provided enough is given, can induce either hypothyroidism or remission of hyperthyroidism in all patients with toxic goiter. The advantages of radioiodine therapy are its great efficacy and the fact that organs other than the thyroid are not injured. The isotope currently used almost exclusively in therapy is I-131 (*1*). The clinical usefulness of triiodothyronine (T_3) suppression tests has been demonstrated in the diagnosis of Graves' disease and in the prediction of the outcome of thionamide therapy (*2–4*). The response of serum thyroid-stimulating hormone (TSH) to stimulation by thyrotropin-releasing hormone (TRH) is also useful to distinguish the thyrotoxic state from eumetabolic states (*5,6*). However, the relationship of both tests in the

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For reprints contact: S. Nagataki, MD, Third Dept. of Internal Medicine, Univ. of Tokyo, Hongo, Tokyo 113, Japan.

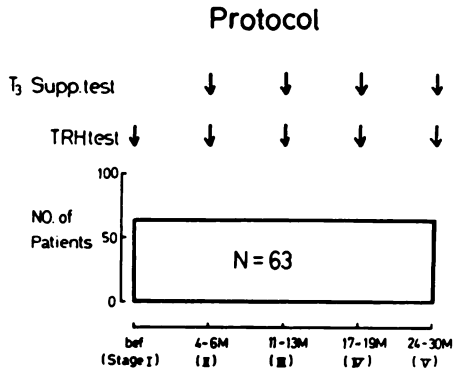

FIG. 1. General protocol of present study. Sixty-three untreated patients with Graves' disease were treated with I-131. Serum T_4, T_3, T_3-U, and TSH levels were determined at least once at 6 mo, and TRH and T_3-suppression tests were made before and at 6-mo intervals for 2 yr.

course of Graves' disease after I-131 therapy has not been clearly elucidated. In the present experiment, T_3-suppression and TRH tests were performed before and after I-131 therapy of Graves' disease to investigate (a) the correlation between T_3-suppressibility and TRH-responsivity, (b) the changes in the response to T_3 suppression and TRH tests, and (c) the relationship between the concentrations of serum thyroid hormone and T_3-suppression and TRH tests.

MATERIAL AND METHODS

Our subjects (eight males and 55 females, average age 43.6 yr) were selected from more than 200 I-131-treated patients with Graves' disease. They satisfied the criteria of euthyroidism, with normal serum T_4 concentrations and normal T_3 uptake (T_3-U) at least during the period between 6 mo and 2 yr after therapy. Before I-131 therapy, all patients were treated with antithyroid drugs for 1 to 2 mo. After the clinical euthyroid state had been achieved, the patients received I-131 therapy. Treatment with antithyroid drugs was continued for 2 to 3 mo to maintain T_3-U, serum T_4, T_3, and TSH concentrations within their respective normal ranges (T_3-U: 23–35%, T_4: 5.0–13.5 μg/dl, T_3: 80–180 ng/dl, TSH: <5 μU/ml). The mean dose of I-131 given to these patients was 5.9 mCi per patient or 80 μCi/g of thyroid tissue (*7*). As shown in Fig. 1, the T_3-suppression and TRH tests were repeatedly performed in 63 patients with Graves' disease. T_3-suppression tests were carried out at 6 mo (Stage II), 12 mo (Stage III), 18 mo (Stage IV), and 24 mo (Stage V) after treatment; TRH tests were performed at the first visit (Stage I) and also 6, 12, 18, and 24 mo after I-131 therapy. All of these patients were clinically euthyroid and their serum T_4 concentrations and T_3 uptakes were within the normal range at least during the period between 6 mo and 2 yr after the therapy. In regard to the T_3-suppression tests, suppressibility was defined as reduction of the 24-hr thyroidal uptake of I-131, to 50% or less of its previous level, by administration of 75 μg of T_3 daily for 8 days (*2*). TRH tests consisted of i.v. injection of 500 μg TRH,* with blood samples for TSH measurement collected before (0), and at 15, 30, 60, and 90 min after injection. TRH responsivity was considered positive when basal TSH levels were <2.0 μU/ml and the peak value >6.2 μU/ml, or when the difference between the two values was more than 5 μU/ml if the basal value was >2.0 μU/ml. Hyperresponsiveness to TRH was defined when the peak value of TSH was >35 μU/ml (*5,6,8,9*). Values for

TABLE 1. FREQUENCY OF TRH-RESPONSIVE AND T_3-SUPPRESSIBLE PATIENTS AFTER I-131 THERAPY

After therapy	T+, S+*	T+, S−	T−, S+	T−, S−	Total T+	Total S+
4–6 mo (Stage II)	8	11	3	41	19/63(30.5%)	11/63(17.4%)
11–13 mo (Stage III)	7	4	2	50	11/63(17.4%)	9/63(14.2%)
17–19 mo (Stage IV)	12	6	3	42	18/63(28.5%)	15/63(23.8%)
24–30 mo (Stage V)	26	10	1	26	36/63(57.1%)†	27/63(42.8%)†

* T+ = TRH-responsive, S+ = T_3-suppressible, T− = TRH-nonresponsive, S− = T_3-nonsuppressible. max TSH (mean ± s.e.) T+: 48.7 ± 4.7μU/ml (N = 84); T−: 0.94 ± 0.05μU/ml (N = 168)†; I-131 UPT (mean ± 2 s.d.). Before T_3: S+ = 33.6 ± 1.1%; S− = 42.8 ± 0.8%. After T_3 S+ = 13.6 ± 0.7% (N = 62)†; S− = 41.5 ± 0.8% (N = 190).

† Significant at P <0.01.

serum T_4 and T_3 concentrations, and T_3-U, were determined by commercial kits, and serum TSH concentrations were measured by a double-antibody technique (*10*). Statistical significance was assessed by t-tests and Cochran Q tests (*11*).

RESULTS

The frequencies for TRH-responders and T_3-suppressible patients after treatment are shown in Table 1. The percentages are based on the number of patients seen at the indicated times. Approximately 6 mo after the therapy, 19 out of 63 patients (31%) had responded to TRH. By 12 mo the TRH-responders had decreased. Thirty-six of 63 patients (57%) responded to TRH 2 yr after therapy. The percentage of T_3-suppressible patients was 17% at 6 mo, 14% at 12 mo, 24% at 18 mo, and 43% at 24–30 mo following treatment. The increased percentage was significant (by Cochran Q test) between the 18th and 24th month after treatment in TRH-responders, and between the 18th and 24th month after therapy in T_3-suppressible patients. The TRH-responsiveness and T_3-suppressibility were similar in more than 80% of the patients.

Changes of responsiveness to TRH and T_3-suppression tests in patients after I-131 therapy are summarized in Fig. 2, A and B. The numbers of patients whose TRH-responsivness and T_3-suppressibility changed from negative to positive, and from positive to negative, are shown for the 2 yr of observation. Regarding the TRH test (Fig. 2A), between 0 and 6 mo and between 18 and 24 mo, TRH-responders increased. Conversely, between 6 and 12 mo, 10 of 19 responders became TRH-nonresponsive. In regard to the T_3-suppression test (Fig. 2B), between 0 and 6 mo, 11 patients became suppressible.

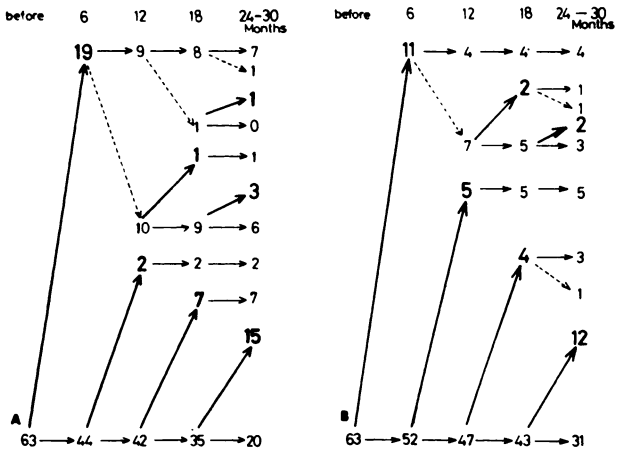

FIG. 2. Reactions to TRH and T_3-suppression tests. (A) Changes of responsiveness to TRH test in each stage; (B) Changes of T_3-suppression tests in each stage; →: from nonresponders to responders, or from T_3-nonsuppressible to T_3-suppressible patients. ⇢: from responders to nonresponders, or from T_3-nonsuppressible to T_3-suppressible patients.

TABLE 2. CHANGES IN SERUM T_3 AND T_4 CONCENTRATIONS AND THYROIDAL I-131 UPTAKES WITH CHANGES IN THE TRH AND T_3-SUPPRESSION TESTS*

	TRH-nonresponders	TRH-responders
Serum T_3 (ng/ml)	1.5 ± 0.1†	1.2 ± 0.1 ($P < 0.05$)
Serum T_4 (μg/dl)	10.1 ± 0.4	9.5 ± 0.3 (N.S.)
Thyroidal I-131 uptakes (%)	38.9 ± 2.0	33.6 ± 1.9 (N.S.)
	T_3-nonsuppressible	T_3-suppressible
Serum T_3 (ng/ml)	1.4 ± 0.1	1.2 ± 0.1 (N.S.)
Serum T_4 (μg/dl)	9.3 ± 0.3	9.5 ± 0.4 (N.S.)
Thyroidal I-131 uptake (%)	36.9 ± 2.3	33.4 ± 2.2 (N.S.)

* Values are obtained from those in Stages II → III, III → IV, IV → V.

† Means ± s.e.

In 6 to 12 mo, the patients who became suppressible and those who became nonsuppressible were almost equally numerous. However, among those whose responses changed between 18 and 24 mo, the patients who became suppressible greatly outnumbered the total who became nonsuppressible. Table 2 summarizes the changes in serum T_3 and T_4 concentrations, and in thyroidal I-131 uptakes, with changes in the TRH and T_3-suppression tests. Serum T_3 concentrations decreased significantly with changes in the TRH tests. However, serum T_4 levels and thyroidal I-131 uptakes were not changed with changes in the TRH tests. Changes in T_3-suppressibility were not accompanied by changes in serum T_4, T_3 concentration, or thyroidal I-131 uptake. Figure 3 shows the

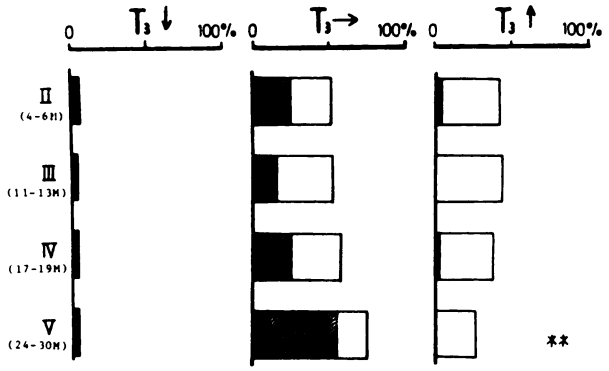

FIG. 3. Relationship between serum T_3 level and ratio of positive response to TRH test. ■: positive response to TRH, □: no response to TRH. **: $P < 0.01$.

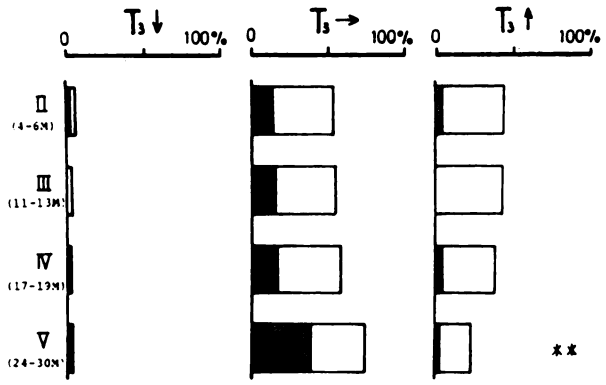

FIG. 4. Relationship between serum T_3 level and ratio of suppressed patients. ▨: suppressed patients, □: nonsuppressed patients. **: $P < 0.01$.

relationship between serum T_3 level and TRH responsiveness. Each column represents the number of patients as a percentage of the total patients in each stage. For example, in the Stage II patients, the number whose T_3 levels were below the normal range was only 3% of the number of patients in Stage II. Fifty-three percent of patients had normal serum T_3 concentrations, and approximately 50% of them were TRH responders. The percentage of Stage II patients with supranormal serum T_3 levels was 44%, but only 2% of them were TRH-responders. In patients whose serum T_3 concentrations were within the normal range, the proportion of TRH-responders increased significantly between Stages IV and V. Figure 4 shows the relationship between serum T_3 level and T_3-suppressibility. As in the TRH test, T_3-suppressible patients were noticeably increased in Stage V, after the therapy. Although serum T_4 concentrations and T_3-U were within the normal range, serum T_3 levels were higher than normal in almost one third of these patients, and most of the patients with high serum T_3 levels were T_3-nonsuppressible. Table 3 shows the correlation coefficients among basal TSH concentrations, thyroidal I-131 uptakes, and serum T_3 and T_4 concentrations in 252 determinations after I-131 therapy (Stages II–V). Serum T_4 and T_3 concentrations correlated significantly with thyroidal I-131 uptakes but correlated inversely with basal serum TSH concentrations. The incidence of exaggerated response to TRH by those who responded in each stage is shown in Fig. 5. The number of exaggerated responders to TRH was 42% (eight of 19) at 6 mo, 45% (five of 11) at 12 mo, 44% (eight of 18) at 18 mo, and 78% (28 of 36) at 24–30 mo after I-131 therapy. There were no significant differences in the percentages of exaggerated responses among Stages II, III, and IV. The proportion of TRH hyperresponders, however, increased significantly in Stage V. Averages of serum T_4 and T_3 concentrations in 49 hyperresponders were 8.2 ± 0.9 μg/dl and 1.2 ± 0.1 ng/ml, respectively, and those of 35 normal responders were 9.4

TABLE 3. CORRELATION COEFFICIENTS AMONG BASAL SERUM TSH CONCENTRATIONS, THYROIDAL I-131 UPTAKES, AND SERUM T_4 AND T_3 CONCENTRATIONS*

	Serum TSH	Thyroidal I-131 uptake
Serum T_4	−0.49 ($P < 0.01$)	0.23 ($P < 0.05$)
Serum T_3	−0.39 ($P < 0.01$)	0.40 ($P < 0.01$)

* Values were obtained from 252 determinations after I-131 therapy (Stages II–V).

± 0.3 μg/dl, 1.2 ± 0.1 ng/ml. Serum T_4 concentrations were significantly lower in hyperresponders than in normal responders ($P < 0.05$). In order to investigate whether the baseline TSH was better than the TRH responsiveness at predicting the outcome for these patients, values for baseline TSH, numbers of normal and hyperresponders, and number of patients whose basal TSH levels were greater than 5 μU/ml are shown in Table 4. All patients who had serum TSH levels greater than 5 μU/ml showed hyperresponse to TRH. However, more than 50% of hyperresponders showed basal serum TSH levels less than 5 μU/ml.

DISCUSSION

The advantages of radioiodine therapy are its great efficacy and the fact that the parathyroid, recurrent laryngeal nerves, and organs other than thyroid are not injured, although there are also important disadvantages to I-131 therapy. There is an interesting incidence of hypothyroidism in the years following therapy, despite initial induction of euthyroidism. Between 30 and 70% of patients followed have become hypothyroid after 10–20 yr (*12*). Even within 2 yr, radioiodine hypothyroidism had occurred in 5 to 25% of patients (*13,14*). However, the purpose of this study is not to observe

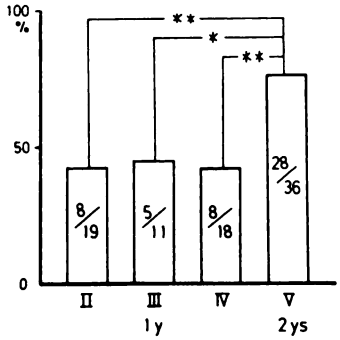

FIG. 5. Percentage of TRH-hyperresponders in each stage. Values shown represent percentage of hyperresponders: (number of hyperresponders to TRH)/(number of positive responders to TRH) in each stage.

TABLE 4. RELATION OF BASELINE SERUM TSH CONCENTRATIONS AND TRH-TESTS

Stage	II	III	IV	V
Averages of basal TSH of all patients (μU/ml)	3.7 ± 1.6	1.5 ± 0.5	3.0 ± 1.3	3.7 ± 1.3
Number of patients with TSH > 5μU/ml	4	3	5	8
Number of patients with normal response	11	6	10	8
Number of patients with hyperresponse	8	5	8	28

merely the frequency of hyper- or hypothyroidism after I-131 therapy, but to investigate various thyroid functions in clinically euthyroid posttherapy patients with normal serum T_4 concentrations. In this study, the number of TRH-responsive and T_3-suppressible patients increased, reaching 57 and 43%, respectively, after 24–30 mo. Most of the T_3-suppressible patients were TRH-responsive. Although the frequencies of TRH-responders and T_3-suppressible patients increased, 10 of 19 TRH-responders and seven of 11 T_3-suppressible patients changed from positive to negative response between 6 and 12 mo. These undesirable changes may be due to temporal effects of I-131 therapy (*15*) or due to the effects of antithyroid drugs given for 1–2 mo after the therapy.

Regarding the serum T_3, patients with supranormal serum T_3 levels were about 40% in Stages II, III, and IV, although their serum T_4 and T_3-U concentrations were within the normal range. All patients with subnormal serum T_3 levels were TRH-responsive regardless of stage, whereas almost all patients with supranormal T_3 levels were TRH-nonresponders, and most of the patients with high serum T_3 levels were T_3-nonsuppressible. Serum T_3 concentration appears to be very important in the diagnosis of subclinical thyrotoxicosis.

However, even among patients whose serum T_4 and T_3 levels were within normal limits, many showed hyperresponse to TRH: 42% of those who responded at 6 mo, 45% similarly at 12 mo, 44% at 18 mo, and 78% at 24–30 mo after I-131 therapy. Serum T_4 concentrations were significantly lower in hyperresponders than in normal responders. Exaggerated responses appeared to be the initial signs of hypothyroidism (*16–18*). As shown in Table 4, 50% of hyperresponders showed basal serum TSH levels less than 5 μU/ml, and we therefore believe that the TRH test is important in predicting the outcome of I-131-treated patients.

In the present study, approximately 50% of patients, despite their clinical euthyroidism, did not respond to TRH and did not become T_3-suppressible by the end of 2 yr. Therefore, TRH-nonresponsiveness or T_3-nonsuppressibility may not be the indication for retreatment with I-131. From the present study on the course of Graves' disease in patients before and during a 2-yr period after I-131 therapy, we have found that (a) the incidence of T_3-suppressibility and TRH-responsiveness increased to include about 50% of the cases even 2 yr after I-131 therapy, and serum T_3 levels are high in T_3-nonsuppressibles and TRH-nonresponders; (b) the results of both tests at 6 mo after the I-131 therapy are not reliable indicators of prognosis; (c) even though serum T_4 and T_3 concentrations are within normal range, latent hypothyroidism begins within 2 yr after I-131 therapy; and (d) failure to respond to TRH, or resistance to T_3 suppression, is not proof that a patient requires retreatment with I-131.

FOOTNOTES

* Synthetic TRH was obtained from Tanabe Seiyaku, Ltd., Osaka, Japan.

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