Thyrotropin Receptor Antibody Activities Significantly Correlate with the Outcome of Radioiodine (^{131}I) Therapy for Hyperthyroid Graves' Disease

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Abstract. The outcome of ^{131}I therapy for 109 patients with Graves' disease was analysed according to pretreatment laboratory data including thyrotropin receptor antibody (TRAb) activities. Forty-five percent of patients became euthyroid, and 13% of patients became hypothyroid within one year after ^{131}I therapy. Forty-two percent of patients remained hyperthyroid one year after ^{131}I therapy. Pretreatment values for serum T_4 , T_3 , and the estimated weight of the thyroid were significantly higher in the hyperthyroid group. The mean for the TRAb index of the hyperthyroid group was significantly higher than that of the euthyroid group. Life table analysis revealed a significant effect of the TRAb index on the rate of hyperthyroidism after 3 months or later. These results appear to suggest that the TRAb index is one of the factors which influence the outcome of ^{131}I therapy for Graves' disease.

Key words: Radioiodine therapy, TSH receptor antibody, Graves' disease, Hyperthyroidism.
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RADIOIODINE (^{131}I) is widely used for the treatment of hyperthyroid Graves' disease, although the high frequency of later development of hypothyroidism and delay in controlling hyperthyroidism are problems associated with its use. Some factors including the size of the gland, degree of hyperthyroidism and concurrent thionamide drugs affect the sensitivity of response to ^{131}I therapy [1]. Recent studies have clearly shown that hyperthyroid Graves' disease is an autoimmune thyroid disease due to anti-thyrotropin (TSH) receptor antibodies [2]. TSH receptor antibodies have frequently been investigated as a parameter for clinical prediction in Graves' disease treated

with thionamide drugs. Data concerning the use of TSH receptor antibodies to predict the outcome of ^{131}I therapy are scarce. In this paper we aimed to analyse the use of TSH receptor antibody index (TRAb index) measured with TSH radioreceptor assay in the prediction of clinical response to ^{131}I therapy for hyperthyroid Graves' disease. We found that the TRAb index before ^{131}I therapy was one of the factors which influenced the short term outcome of ^{131}I therapy of hyperthyroid Graves' disease.

Subjects and Methods

One hundred and eighty-nine patients with hyperthyroid Graves' disease were treated with radioiodine (^{131}I) in our clinic from January, 1984 to October, 1988. One hundred and nine patients

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were treated for the first time and followed up for one year or longer after ^{131}I therapy. The study population of 109 subjects consisted of 75 female and 34 male patients. The mean age was 50.5 years (range 31–77 years). Eighty patients were excluded from the study for the following reasons: 13 had had previous radioiodine therapy, 2 had had previous surgical therapy for Graves' disease, 9 had been treated with antithyroid drugs for more than one year just before radioiodine therapy, 18 had been lost from the follow-up study, and 38 had not been studied for the TRAb index before the treatment.

The therapeutic dose of ^{131}I was calculated from the following formula:

$$\frac{\text{Estimated thyroid weight(g)} \times 2.96 \text{ MBq} \times 100}{24 \text{ h } ^{131}\text{I uptake}(\%)}$$

$$= (\text{MBq})$$

The size of the gland was estimated by palpation. All doses were calculated and given by one doctor.

Of 109 patients, 36 patients received thionamide drugs for less than 2 months before ^{131}I therapy. These patients discontinued thionamide drugs 7 days before ^{131}I therapy. Forty-five patients started the treatment with thionamide drugs 7 to 10 days after ^{131}I therapy.

Thyroid function tests of the patients, including thyrotropin receptor antibody (TRAb) index and antithyroid antibodies, were measured before ^{131}I therapy. Thyroid functions of patients after ^{131}I therapy were evaluated at monthly intervals. The patients whose physical status and thyroid func-

tion tests were normal for two consecutive months without medications were diagnosed as euthyroid. Hypothyroidism was diagnosed on the basis of the physical status and thyroid function tests. Hypothyroid patients were observed for at least 3 months to confirm that it was not temporary. The time to the diagnosis was 28 months on average (range 3–70 months).

Serum T_4 , T_3 and TSH were measured with commercially available radioimmunoassay (RIA) kits. The TRAb index was measured with a commercial kit (Baxter, Japan) [3]. The normal range of the TRAb index was -10 – 10% . Anti-thyroglobulin antibodies (TGHA) and anti-microsomal antibodies (MCHA) were measured with heamagglutination kits.

Thyroid function was compared by means of the Student's *t*-test. Chi-square test was used to compare the distribution of variables in the groups. The life table method was used to analyse the results of ^{131}I therapy.

Results

Of 109 patients, 49 (45%) became euthyroid within one year after ^{131}I therapy. Fourteen (13%) patients developed permanent hypothyroidism within one year after ^{131}I therapy. Thirty (27%) patients were still hyperthyroid, and 16 (15%) patients were receiving thionamide drugs even at one year after ^{131}I therapy. These patients were assigned to the hyperthyroid group. Sixteen patients in the hyperthyroid group became euthyr-

Table 1. Characteristics of patients before ^{131}I therapy

	Clinical outcome		
	Euthyroid	Hyperthyroid	Hypothyroid
No of patients	49	46	14
Sex (Male/Female)	19/30	11/35	4/10
Age (years)	50±9.4	50±8.5	54±2.7
T_3 (ng/dl)	414±148	512±206*	376±39
T_4 (µg/dl)	22±6.3	25±6.7**	22±10
^{131}I -uptake at 24 h (%)	59±13	62±14	62±14
TRAb index (%)	34±24	50±28**	38±19
Gland size (g)	43±12	52±21*	41±12
Dose of ^{131}I (MBq)	211±52	237±93	222±56
(Dose, mCi)	(5.7±1.4)	(6.4±2.5)	(6.0±1.5)

Values are means±SD except where otherwise noted.

* $p < 0.05$ as compared with the euthyroid group.

** $p < 0.01$ as compared with the euthyroid group.

Fig. 1. Incidence of hyperthyroidism in patients with Graves' disease after ^{131}I therapy. (○) patients with a high TRAb index ($\geq 50\%$); (●) patients with a low TRAb index ($< 50\%$).

Fig. 2. Incidence of hyperthyroidism in patients with Graves' disease after ^{131}I therapy. (○) patients with the large glands ($\geq 50\text{g}$); (●) patients with the small glands ($< 50\text{g}$).

oid thereafter. The mean time to become euthyroid was 8 months (range 2–37 months).

Pretreatment serum T_4 , T_3 and the TRAb index were significantly higher in the hyperthyroid group than in the euthyroid group (Table 1). No statistically significant differences were observed among these groups in the male to female ratio, the mean age at the time of therapy, the mean of dose of ^{131}I used, or the proportion of positive anti-thyroid antibodies. The estimated weight of the gland of the hyperthyroid group was greater than that of the euthyroid group. No significant

differences between pretreatment parameters were observed in the euthyroid and hypothyroid groups.

Sixteen out of 49 euthyroid patients and 20 out of 46 hyperthyroid patients were pretreated with thionamide drugs. The prevalence of this pretreatment did not differ among the groups (chi-square=0.76, $p>0.05$).

The range of the TRAb index was 1–92% and TRAb were detected in 98 patients. Figure 1 shows the percentage of hyperthyroid patients after ^{131}I therapy among patients with a high TRAb index ($\geq 50\%$) and a low TRAb index ($< 50\%$). The TRAb index values in 45 patients were above 50%. At 3 months after ^{131}I therapy, 95% of high TRAb patients and 75% of low TRAb patients remained hyperthyroid. Twelve months after ^{131}I therapy, 78% of high TRAb patients and 40% of low TRAb patients remained hyperthyroid. These values were significantly different ($p<0.05$ at 3 months and $P<0.01$ at 12 months).

Figure 2 shows the percentage of hyperthyroid patients after ^{131}I therapy among patients with large ($\geq 50\text{g}$) and small ($< 50\text{g}$) glands. Large glands were detected in 33 patients. At 3 months after ^{131}I therapy, 93% of patients with large glands and 80% of patients with small glands remained hyperthyroid. Twelve months after ^{131}I therapy, 77% of patient with large glands and 47% of patients with small glands remained hyperthyroid ($p<0.01\%$). In our patients, a slight but significant correlation between the TRAb index and thyroid weight ($r=0.35$, $p<0.01$) was observed. The TRAb index also correlated with T_3 and T_4 values ($r=0.29$, $p<0.01$, and $r=0.23$, $p<0.05$, respectively), but thyroid weight did not correlate with T_3 or T_4 values ($r=0.12$ and $r=0.05$, respectively).

Discussion

In the present study, the outcome of ^{131}I therapy after one year was almost the same as reported earlier [1, 4–10]. Hypothyroidism has been a problem in ^{131}I therapy. In our previous study, the incidence of hypothyroidism was 20.7% after 10 years of ^{131}I therapy and 33% after 15 to 17 years after ^{131}I therapy [11]. Delay in controlling hyperthyroidism is another problem in patients who cannot be treated with thionamide

drugs because of adverse effects. Various dosimetries were proposed but proved not to provide uniform results. Early hypothyroidism can be reduced by giving a smaller ^{131}I dose to the thyroid. But a substantial proportion of patients will fail to achieve remission with a single smaller radiation dose [4–6, 12, 13].

Many factors such as age at therapy, the weight of the gland, thionamide drugs, antithyroid antibodies, and degree of hyperthyroidism are suspected to influence the outcome of ^{131}I therapy [1]. In our patients, those who did not achieve remission had significantly higher T_4 and T_3 levels indicative of severe disease as reported by Turner *et al.* [14] and Watson *et al.* [15]. An increase in T_4 and T_3 may correlate with the rate of iodine turnover in the thyroid and lead to a lower radiation dose [10].

In the present study, thionamide drugs did not affect the outcome of ^{131}I therapy. Early reports suggested that thionamide drugs before ^{131}I therapy increased the radioresistance of the thyroid to reduce the remission rate for ^{131}I therapy [8, 16, 17]. Our patients were treated with thionamide drugs for 2 months or less. Many factors, including the duration of thionamide drug and thyroid function at the time of therapy, may affect the radiosensitivity of the thyroid, but the precise reasons were not clear. Goolden and Fraser [18] reported that pretreatment with carbimazol for 4–8 weeks did not modify the response to ^{131}I therapy.

Graves' disease is thought to be an autoimmune disease in which anti-TSH receptor antibodies stimulate the thyroid and induce hyperthyroidism. In the present study, the TRAb index of patients without remission one year after ^{131}I therapy was significantly higher than that of the euthyroid group, and the TRAb index significantly correlated with the remission rate after ^{131}I therapy. These results suggest that the anti-TSH receptor antibody activity is a factor which influences the sensitivity to ^{131}I as well as factors already mentioned. Davies *et al.* [19] reported that TRAb endowed radioiodine with increased sensitivity. We cannot explain this discrepancy. However, a relationship between the serum TRAb concentration and the activity of the disease was observed,

since a gradual decrease in the TRAb index occurs after thionamide drug therapy [20] and a high TRAb index after the drug therapy indicates a high risk of relapse [21]. In euthyroid patients after ^{131}I therapy, TRAb values remained high [22]. These results suggest that functioning thyroid cells which remain after ^{131}I therapy continue to be stimulated by TSH receptor antibodies and the hypersecretion of thyroid hormones from these cells is maintained.

In our patients, thyroid weight was a factor which influenced the outcome of ^{131}I therapy as reported earlier. Our patients were treated with the same ^{131}I dose per gram of the thyroid. Some reports suggested that a larger gland requires a larger ^{131}I dose per gram of tissue than a smaller gland, and the ^{131}I dose should be graded according to gland size [6, 7]. But these methods were proved not efficient enough to reduce the late development of hypothyroidism. We adjusted the dose of ^{131}I administered to gland size which was estimated by palpation. A dose of ^{131}I based on the exact weight of the thyroid and the effective half life of ^{131}I in each patient may be necessary to obtain better results [9].

To date, no method of determining the precise dose of ^{131}I that will consistently achieve euthyroidism has been devised. Turner *et al.* [14] reported that no single or combination of pretreatment laboratory data was able to predict early outcome with sufficient accuracy. But data on the correlation of immunological activity of Graves' disease and the outcome of ^{131}I therapy in a large number of patients have not been reported. Residual thyroid cells after ^{131}I therapy are thought to be stimulated by anti-TSH receptor antibodies as mentioned above. The TRAb index, which can be measured in clinical laboratories with a TSH radioreceptor assay, may indicate the activity of Graves' disease. In the present study, the TRAb index before ^{131}I therapy and short term results of ^{131}I therapy in 109 patients with Graves' disease were significantly correlated. From these results, the anti-TSH receptor antibody activity of individual patients can be a useful parameter in predicting the outcome of ^{131}I therapy.

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