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Three basic patterns of changes in serum thyroid hormone levels in Graves' disease during the one-year period after radioiodine therapy

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The purpose of this study was to clarify the characteristic patterns of the thyroid hormonal changes in Graves' disease during the one-year period after ^{131}I therapy considering that few serial hormonal data during this period are available in the literature. ***Methods:*** The levels of serum T_3, T_4 and FT_4 before and during one year were plotted as a function of time in 70 therapy courses of 58 patients without subsequent antithyroid or steroid therapy. ***Results:*** 35 euthyroid, 6 hypothyroid and 29 hyperthyroid states were obtained during one year after therapy. Although individual patients had individual hormonal changing patterns, 3 common basic patterns were observed from baseline to one month (early) and thereafter (late), respectively. The early patterns were a decrease in 54 (77%), a minimum change in 8 (11.5%) and an increase in 8 (11.5%). The late patterns were a stable state after an initial decrease with a bottom followed by an increase (valley pattern) in 47 (67%), a stable state after an initial increase with a peak followed by a decrease with a bottom and a subsequent re-increase (mountain pattern) in 12 (17%) and a late stable state after a gradual slow decrease without an obvious bottom near or till one year (downhill pattern) in 11 (16%). The bottom level and the degree of hormonal recovery from the bottom determined the stable euthyroid, hypothyroid or hyperthyroid state in 49 (86%) of 57 with the valley or mountain pattern. Most of the bottom levels (81%) and transient abnormal changes including transient hypothyroidism (93%, 13/14), peak or hyperthyroidism (85%, 11/13) and euthyroidism (67%, 10/15) appeared within 6 months. The post-therapeutic stable euthyroid, hypothyroid or hyperthyroid state could be judged from the hormonal patterns in 57% (39/68) from 2.5 to 6 months, in 18% (12/68) from 6 to 9 months and in 25% (17/68) thereafter. ***Conclusion:*** Although the changes in thyroid hormones are not constant in Graves' disease during one year after ^{131}I therapy, there are three basic patterns; valley, mountain and downhill patterns from one month after therapy. The post-therapeutic stable state can be judged by the hormonal level recovered from the bottom in most patients.

Key words: thyroid, Graves' disease, hyperthyroidism, ^{131}I, thyroid hormone

INTRODUCTION

THE EFFICACY AND SAFETY of radioiodine (^{131}I) therapy for Graves' disease have been confirmed during the past 60 years.[1] However, the time to judge the stable euthyroid, hypothyroid and hyperthyroid states after ^{131}I administration differs among institutions. For example, judgment as to the need for additional ^{131}I or replacement therapy has been made variously at 2,[2] 3,[3–5] 3–6,[6–8] 6,[9–15] 6–12,[16–20] 12[21–24] or more months.[9] The most important factor to decide the management of the patients after ^{131}I therapy may be the changes in serum thyroid hormone levels with time as well as clinical symptoms and signs. Although the changes in serum thyroid hormone levels within one month were analyzed by frequent measurements of thyroid hormones in relation to thyroid storm and effects of pre-^{131}I therapeutic use of antithyroid drugs,[25–30] few serial hormonal data are available on the changes for one

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year in the literature.[31–33] Therefore we retrospectively analyzed the serial hormonal changes to clarify the characteristic patterns of changes in thyroid hormones during the one-year period after ^{131}I therapy.

MATERIALS AND METHODS

Study population

We reviewed the clinical records of a total of 73 patients with Graves' disease treated by oral administration of ^{131}I from Aug 21, 1989 to May 7, 2002 at our Department. ^{131}I therapy was performed 91 times in these patients; once in 73 patients, twice in 15 patients and three times in 3 patients. We selected 58 patients {(F: 45 and M: 13, age range; 20–80 (mean ± SD, 52 ± 13) years old)}. The selection criteria were as follows: 1) measurements of serum thyroid hormones and TSH were serially made before and during at least one year after therapy including at least 3 times within 2 months-interval for 6 months (mean ± SD, 7 ± 2 measurements, range; 3–13) and at least twice thereafter to the next 6 months (mean ± SD, 4 ± 2 measurements, range; 2–7). 2) The patients who were administered antithyroid drugs or steroid after ^{131}I administration were excluded. ^{131}I therapy was performed 74 times in these patients, once in 45 patients, twice in 10 patients and three times in 3 patients. The hormonal data were inadequate after the first or second therapy in 4 of the 10 patients who received the therapy twice. Thus the hormonal data after 70 therapies of 58 patients were analyzed. Of these 58 patients, the initial ^{131}I therapy was done without previous antithyroid drugs (methimazole or propylthiouracil) or surgery in 12 (20.7%), due to side effects such as liver dysfunction, leukocytopenia and skin eruption in 34 (58.6%) and inadequate control by antithyroid drugs in 12 (20.7%).

Therapy methods

The therapy protocol was started after confirmation of elevated levels of thyroid hormones and suppression of serum TSH, because most of the patients (about 80%) received previous or ongoing therapy of antithyroid drugs at the time of visiting our Department. If the patients were taking antithyroid drugs, we instructed them to stop taking them. Eventually the drugs were stopped at least 13 days (13 days–one month; 9 patients, >one month; 37 patients) before ^{131}I therapy. When symptoms worsened, a β-blocker was used before and after administration of ^{131}I. After confirmation of elevated values of thyroid hormones, 3.7 MBq of ^{131}I was orally administered to obtain the thyroid image to confirm diffuse goiter, the 24 hr thyroid uptake ratio and the effective half life to calculate the therapeutic dose of ^{131}I to be administered. Thyroid volume was estimated by CT using the areas-summation technique.[34–36]

The therapeutic oral dose of ^{131}I was determined from the following Marinelli-Quimby modified formula: The oral dose (MBq) = desired Gy × 3.7 × W × 8 × 100/135 × U × Teff = 21.9 × desired Gy × W/U × Teff, where Gy; absorbed dose, W; thyroid weight (g), U; 24-hr thyroid uptake ratio (%) and Teff; effective half life (days). W was assumed to be the volume (m*l*) estimated by CT. U and Teff were obtained using a scintillation counter. Teff was calculated from three point counts (Days 1, 4 and 7). The dose concentration (MBq/g) could be also calculated as follows; oral dose (MBq) × U/100W. However, the 6 values of Teff and 5 values of W in the initial 4 patients treated before 1992 were lacking because the fixed dose or small dose method was employed. After 1993 the desired dose was determined according to patient choice. A small dose (~60 Gy) was given if the patient wanted not to become hypothyroid as long as possible and was willing to repeat therapy when symptomatic hyperthyroidism persisted. A medium dose (60–90 Gy) was given if the patient wanted to become euthyroid but avoid hypothyroidism, if possible. A large dose (>90 Gy) was given if the patient wanted to become quickly euthyroid and agreed to replacement therapy, if hypothyroidism occurred. Thus the administered dose and absorbed dose varied; the dose of ^{131}I ranged from 37 MBq (1 mCi) to 481 MBq (13 mCi) {159 MBq (4.3 mCi) ± 92.5 MBq (2.5 mCi), n = 70} and the absorbed dose ranged from 28 Gy to 162 Gy (75 ± 23 Gy, n = 64).

Hormonal measurements

The levels of serum triiodothyronine (T_3), thyroxine (T_4) and free T_4 (FT_4) and thyroid-stimulating hormone (TSH) were measured in the Clinical Laboratory of our University Hospital after referral of the patients to our Department. The levels of serum T_3, T_4, FT_4 and TSH were measured by enzyme immunoassay (EIA) from Aug., 1988 to Dec., 1992 (standard ranges: T_3; 0.70–1.80 ng/m*l*, T_4; 3.7–12.1 μg/d*l*, FT_4; 0.71–1.85 ng/d*l* and TSH; 0.40–4.44 μIU/m*l* with the detection limit, 0.01 μIU/m*l*), by chemical luminescent immunoassay (CLIA) from Dec., 1992 to May, 1995 (standard ranges: T_3; 0.60–1.81 ng/m*l*, T_4; 4.8–12.9 μg/d*l*, FT_4; 0.76–1.79 ng/d*l* and TSH; 0.35–5.50 μIU/m*l* with the detection limit, 0.01 μIU/m*l*), and by chemiluminescent EIA (CLEIA) thereafter (standard range: T_3; 0.70–1.80 ng/m*l*, T_4; 4.5–13.1 μg/d*l*, FT_4; 0.71–1.85 ng/d*l* and TSH; 0.35–5.50 μIU/m*l* with the detection limit, 0.10 μIU/m*l*). The upper detection limit of FT_4 was 8 ng/d*l*. The chronological standard range was employed as the normal range of each thyroid hormone. Suppression of serum TSH was less than the chronological detection limit (<0.01 μIU/m*l* or <0.1 μIU/m*l*).

Data analysis

Serum thyroid hormonal levels before and after the therapy were serially plotted as a function of time on graph papers for the individual therapeutic courses. The changes of serum T_3, T_4 and FT_4 were concordant in 79% of 647 changes between 2 measurements in 70 therapeutic

Table 1 Clinical data of the euthyroid (Eu), hypothyroid (Hypo) and hyperthyroid (Hyper) groups of patients with Graves' disease after ^{131}I therapy

Item	Group		
	Eu (n)	Hypo (n)	Hyper (n)
Sex (M : F)	5 : 30	4 : 2	6 : 23
Age (years)[a]	53 ± 14 (35)	60 ± 11 (6)	48 ± 10 (29)
Baseline			
Thyroid weight (g)[b]	27 ± 11 (33)	21 ± 8 (6)	57 ± 39 (26)
T_3 (ng/m*l*)[c]	3.36 ± 0.99 (34)	3.39 ± 1.06 (6)	4.98 ± 1.88 (29)
T_4 (μg/d*l*)[c]	18.7 ± 3.7 (34)	19.1 ± 4.8 (6)	24.4 ± 5.3 (25)
FT_4 (ng/d*l*)[c]	4.59 ± 1.65 (34)	4.46 ± 1.43 (6)	6.04 ± 1.65 (29)
TSH (μIU/m*l*)	< 0.01 or < 0.1	< 0.01 or < 0.1	< 0.01 or < 0.1
Oral dose (MBq)	141 ± 70 (35)	141 ± 70 (6)	181 ± 118 (29)
Dose concentration (MBq/g)[d]	2.89 ± 0.74 (33)	3.92 ± 1.33 (6)	2.55 ± 0.93 (26)
Absorbed dose (Gy)[e]	79 ± 18 (33)	99 ± 37 (6)	64 ± 20 (25)
Hormonal measurements			
Baseline day	−14 ± 9 (35)	−19 ± 11 (6)	−17 ± 8 (29)
Frequency after therapy			
≤ 6 months	6 ± 2 (35)	7 ± 3 (6)	7 ± 2 (29)
> 6 months	3 ± 1 (35)	4 ± 2 (6)	4 ± 2 (29)
Therapy course			
First	28	6	23
Second	4	0	6
Third	3	0	0

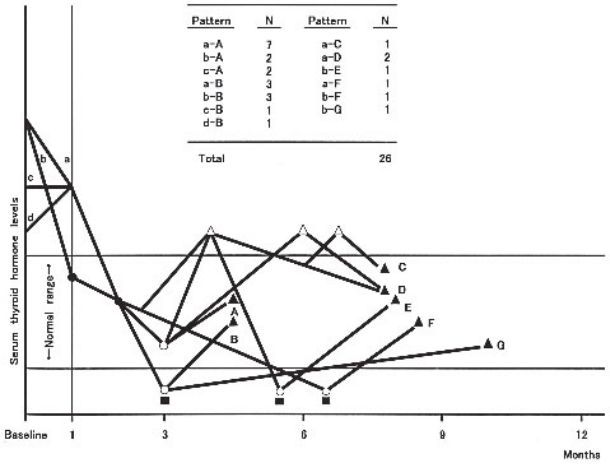
The values were expressed as mean ± SD. The level of $FT_4 > 8$ ng/d*l* was regarded as 8 ng/d*l*.
[a]Hypo vs. Hyper; $p < 0.05$, [b]Eu or Hypo vs. Hyper; $p < 0.01$, [c] Eu or Hypo vs. Hyper; $p < 0.01$ or $p < 0.05$, [d]Eu vs. Hypo; $p < 0.05$, Hypo vs. Hyper; $p < 0.01$, [e]Eu vs. Hypo or Hyper; $p < 0.05$, Hypo vs. Hyper; $p < 0.01$.

courses. When discordance was observed (21%), the change of two hormones was adopted as a hormonal change for the individual therapeutic course. We defined the levels of the 3 thyroid hormones or two of them within the normal ranges as euthyroid, beyond the normal ranges as hyperthyroid, and below the normal ranges as hypothyroid regardless of the levels of serum TSH. According to these criteria, we divided 70 treatment courses into three groups based on the thyroid hormonal states at the one-year or re-treatment time; the euthyroid group (35 therapies and 35 patients), hypothyroid group (6 therapies and 6 patients) and hyperthyroid group (29 therapies and 23 patients). Then, the time—hormonal concentration curves were analyzed in each group.

We analyzed the hormonal changes from baseline to one month (early) and thereafter (late) separately. The early changes were divided into a decrease (<90% of the baseline levels), a minimum change (± 10% of them) and an increase (>110% of them) by drawing lines from baseline levels to one month levels in thyroid hormones. We noted the appearance time and duration (if necessary) after ^{131}I administration on the following changes in thyroid hormones and the time of the additional therapy; 1) the euthyroid group; normalization (initial hormonal fall into normal ranges), the bottom (the lowest hormonal levels during one year after the therapy), transient hypothyroidism (transient subnormal hormonal levels), transient hyperthyroidism (transient elevation of the hormonal levels beyond the normal upper levels after normalization), transient peak (transient hormonal elevation from one month after therapy) and stable euthyroid state (continuous euthyroid hormonal state). When the bottom was situated at 12 months, the bottom was regarded as the stable state. 2) the hypothyroid group; normalization, hypothyroidism (initial hormonal fall into the subnormal levels), the bottom, and stable hypothyroid state. 3) the hyperthyroid group; in this group, there were large fluctuating changes with two bottoms in some patients. The first and second bottoms, transient euthyroidism and hypothyroidism (transient hormonal fall into normal ranges and below the normal ranges), initial peak (hormonal peak from one month after therapy), late peak (peak of 150% or more of the stable state levels), and stable hyperthyroid state (continuous hormonal hyperthyroid state after the first bottom or transient euthyroidism). When the bottom situated at 12 months, the bottom was regarded as the stable state. Last, the changes of serum TSH were examined in each group.

Statistical analysis

Kruskal-Wallis-H-test with Student-Newman-Keuls test or Mann-Whitney U-test was used to examine the differences among three groups or between two groups, respectively, in mean age, ^{131}I oral dose, dose concentration, absorbed dose, thyroid weight, baseline day of hormonal measurement, frequency of hormonal measurements,



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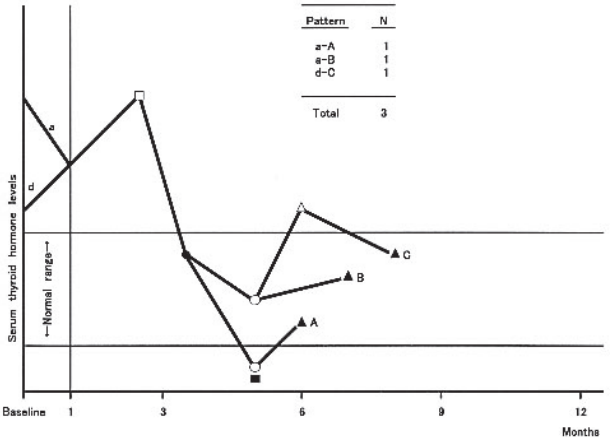

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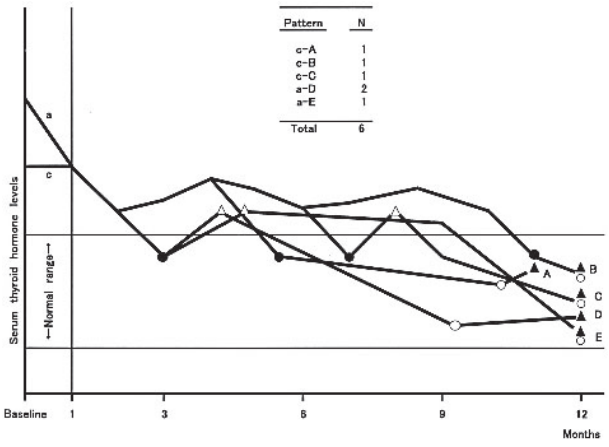

C

Fig. 1 Thyroid hormone changing patterns in the post-therapeutic euthyroid group. The small letters in the figures indicate the changes from baseline to one month after radioiodine therapy: a; a decrease above the normal range, b; a decrease into the normal range, c; minimum change, and d; an increase. The changes from one month after the therapy are A: Valley pattern (n = 26), B: Mountain pattern (n = 3), and C: Downhill pattern (n = 6). The marks in the figures indicate the important hormonal changes: ●; initial normalization, ○; bottom, ■; transient hypothyroidism, △; transient hyperthyroidism, □; initial peak and ▲; the beginning of the stable euthyroid state.

baseline hormonal levels, and time of bottom and stable states after the therapy. The distribution in sex, therapy courses, hormonal changes from baseline to one month and basic changing patterns thereafter were tested by 2 × 2 or m × n chi square test. $P < 0.05$ was considered significant. The mean values were expressed with standard deviation (SD).

RESULTS

Table 1 shows characteristics of the 3 post-^{131}I-therapeutic groups of 70 therapeutic courses of 58 patients with Graves' disease. Sex, ^{131}I oral dose, the day of baseline hormonal measurement, the frequency of hormonal measurements and the number of ^{131}I therapy courses showed no statistically significant differences between the 3 groups. The following showed statistically significant differences: Age was lower in the hyperthyroid group than in the hypothyroid group. Baseline thyroid volume was larger in the hyperthyroid group than in the euthyroid and hypothyroid groups. Baseline thyroid hormones were higher in the hyperthyroid group than the other 2 groups. Dose concentration was higher in the hypothyroid group than in the other 2 groups. Absorbed dose was higher in the hypothyroid group than in the other 2 groups and in the euthyroid group than in the hyperthyroid group.

The schematic patterns of changes in serum thyroid hormone levels with time in the euthyroid, hypothyroid and hyperthyroid groups are shown in Figures 1–3, respectively. These patterns were generated by plotting the hormonal levels at baseline, one month, and the times of the important hormonal changes mentioned above and the next therapy performed.

1. Early changes in thyroid hormones from baseline to one month after ^{131}I therapy

The hormonal levels at one month were available in 48 therapeutic courses. There were 36 (75%) decreased (17 euthyroid, 5 hypothyroid and 14 hyperthyroid), 6 (12.5%) minimum change (5 euthyroid and one hyperthyroid) and 6 (12.5%) increased (one euthyroid and 5 hyperthyroid) cases. In the other 22 therapeutic courses, the one month levels were regarded as the intersected levels between immediately before (baseline–3 weeks) and after one month (5–8 weeks). In these therapeutic courses, there were 18 (82%) decreased (10 euthyroid, one hypothyroid

and 7 hyperthyroid), 2 (9%) minimum change (one euthyroid and one hyperthyroid) and 2 (9%) increased (one euthyroid and one hyperthyroid) cases. As a total, there were 54 (77%) decreased, 8 (11.5%) minimum change and 8 (11.5%) increased cases. There were no statistically significant differences in the distribution of the changes between the 3 groups.

2. *Patterns of changes in serum thyroid hormone levels after one month*

1) The euthyroid group (n = 35)

Although variable patterns were noted, they could be divided into 3 basic patterns. A) the stable euthyroid state after an initial decrease with a bottom value (within or below the normal range) followed by an increase (n = 26) (Fig. 1A). B) the stable euthyroid state after an initial increase with a peak followed by a decrease with a bottom and a subsequent re-increase (n = 3) (Fig. 1B) and C) the late stable state after a gradual slow decrease without an obvious bottom near or until 12 months (n = 6) (Fig. 1C). Recovery from the bottom determined the euthyroid state in 25 (86%) of 29 patients with an A or B pattern.

2) The hypothyroid group (n = 6)

Two patterns were observed (Fig. 2); A) the stable hypothyroid state after an initial rapid decrease with a bottom followed by a slight increase (n = 5). Four of them received replacement therapy. The normal T_3 levels with low T_4 and FT_4 levels were noted after the bottom in the remaining patient who did not need replacement therapy. The other pattern (n = 1) was analogous to the C pattern in the euthyroid group and the bottom situated at 11 months. Recovery from the bottom determined the stable hypothyroid state in all 5 patients with an A pattern.

3) The hyperthyroid group (n = 29)

Many variable patterns were also observed from one month after the therapy. However the basic patterns were essentially the same as observed in the euthyroid group. A) the stable hyperthyroid state after an initial decrease with a bottom situated above the upper normal level (n = 9) (Fig. 3A), within the normal range or below the normal lower level (n = 7) (Fig. 3B) followed by an increase, B) the stable hyperthyroid state after an initial increase with a peak followed by a decrease with a bottom and a subsequent increase (n = 9) (Fig. 3C), and C) the stable hyperthyroid state with a slow continuous decrease with small fluctuations until 12 months (n = 4) (Fig. 3D). Recovery from the initial bottom determined the stable hyperthyroid state in 19 (83%) of 23 patients with an A or B pattern.

We named the A, B, and C patterns in the 3 groups valley, mountain and downhill patterns, respectively (Fig. 4). There were 47 patients with a valley pattern, 12 patients with a mountain pattern and 11 patients with a downhill pattern. There was no statistically significant difference in the distribution of these basic patterns among the euthyroid, hypothyroid and hyperthyroid groups. There

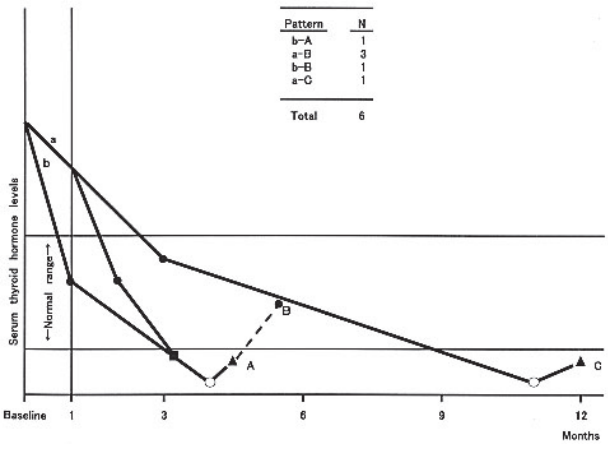

Fig. 2 Thyroid hormone changing patterns in the post-therapeutic hypothyroid group. The definitions of the small letters in the figure are shown in the Figure 1 legends. The changes from one month after the therapy are A and B (n = 5): Valley patterns; the stable hypothyroid state after an initial decrease with a bottom with an increase to the level under normal ranges (A) or to the normal ranges recovered by replacement therapy (------) (B), and C (n = 1): Downhill pattern; the late stable state after a gradual slow decrease without an obvious bottom near or till one year. The marks in the figures indicate the important hormonal changes; ●; initial normalization, ■; initial hypothyroidism, ○; bottom, and ▲; the beginning of the stable hypothyroid state.

were also no statistically significant differences in age, sex, thyroid weight, oral dose, dose concentration and absorbed dose among the valley, mountain and downhill patterns in the euthyroid and hyperthyroid groups, between the subgroups with and without transient hypothyroidism in the euthyroid group, or between the subgroups with and without transient euthyroidism and hypothyroidism in the hyperthyroid group, respectively.

3. *The time and duration of important changes in thyroid hormone levels*

Tables 2–4 show the number of patients for the appearance time and duration of changes in thyroid hormones after the therapy in the euthyroid, hypothyroid and hyperthyroid groups, respectively.

1) Euthyroid group (Table 2)

Hormonal normalization was achieved within 3 months in most (83%) patients. The hormonal bottom value appeared within 6 months after the therapy in 28 (80%) with the peak incidence of 18 (51%) from 2 to 4 months. Transient hypothyroidism appeared in 13 patients (37%) and in 12/13 (92%) within 6 months and recovered to the euthyroid state within 3 months in 11 patients. Transient hyperthyroidism occurred 10 times in 9 patients (26%) and 8 times within 6 months and recovered to the euthyroid state within 3 months on 8 occasions. One of them developed transient hyperthyroidism twice. Transient peak occurred in 3 patients (9%) at 1.5–3 months and recovered

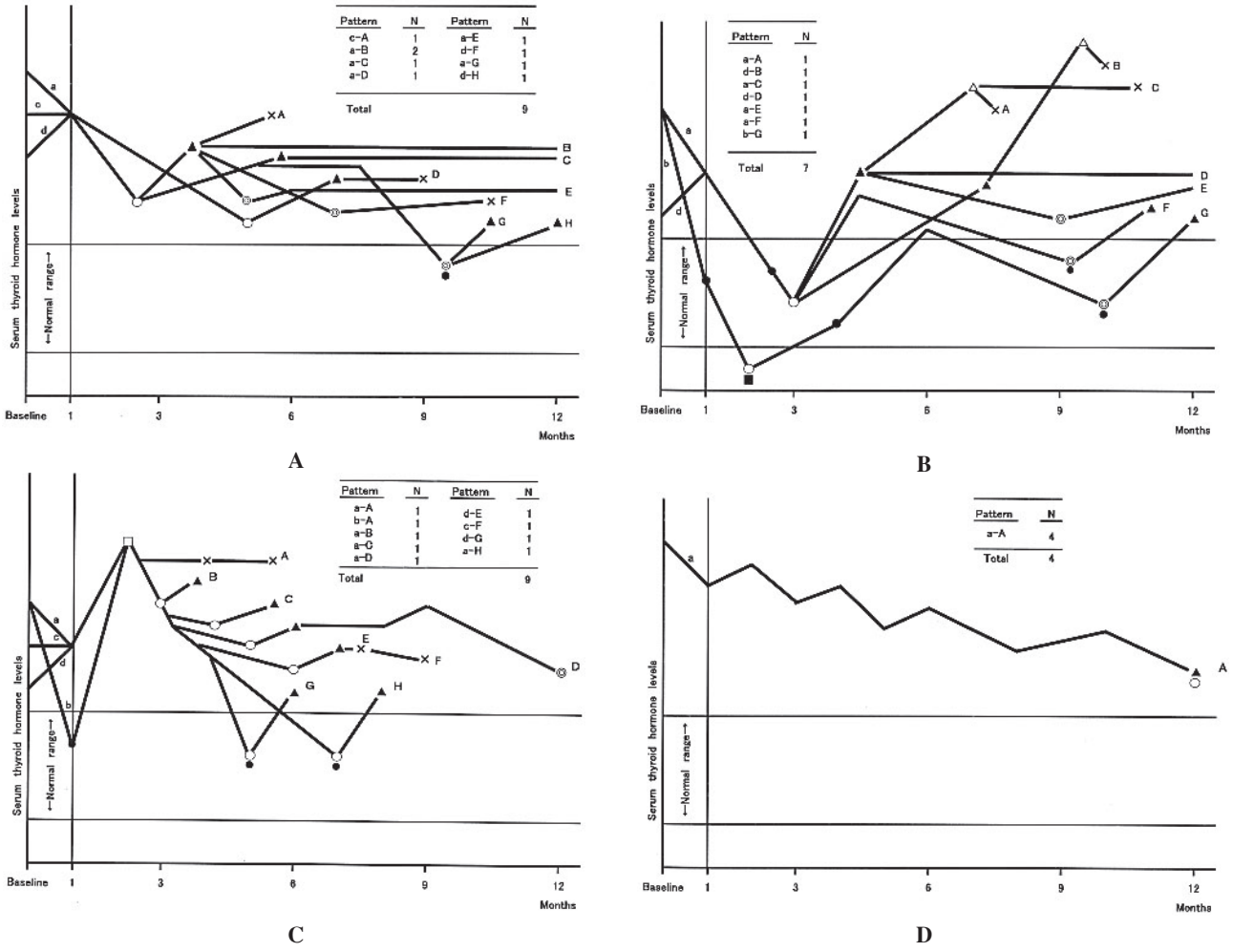

Fig. 3 Thyroid hormone changing patterns in the post-therapeutic hyperthyroid group. The definitions of the small letters in the figures are shown in the Figure 1 legends. The changes from one month after the therapy are A: Valley pattern in which the bottom situates above the upper normal level (n = 9), B: Valley pattern in which the bottom situates within the normal range (n = 6) or below the normal range (n = 1), C: Mountain pattern (n = 9), and D; Downhill pattern (n = 4). The marks in the figures indicate the important hormonal changes; ●; transient euthyroidism, ■; transient hypothyroidism, ○; the first bottom, ◎; the second bottom, ▲; the beginning of the stable state, □; initial peak, and △; late peak. The additional ^{131}I therapy is indicated by ×.

within 2 months. The stable euthyroid state was achieved from 2.5 to 6 months in 20 patients (57%) and thereafter in 15 patients (43%). The stable state occurred from the bottom within 6 months in all 32 patients and within 3 months in 84% (27/32) patients. Three patients had the bottom at 12 months.

2) Hypothyroid group (Table 3)

Hormonal normalization occurred from 0.5 to 3.25 months and within 4 months in all 6 patients. The duration was from 0.25 to 3 months in 5 patients and 7.75 months in one patient. Hypothyroidism appeared within 5 months in 5 and at 11 months in one. The bottom value appeared from one to 5 months in 5 patients and at 11 months in one patient. The stable hypothyroidism was obtained from 3 to 6 months in 5 patients (83%) and at 12 months in one patient. The duration from the bottom to the stable state was from 0 to 1.25 months. Replacement therapy was performed from 3.5 to 6 months in 4 patients.

3) Hyperthyroid group (Table 4)

The initial bottom value appeared from 1.75 months and within 6 months in 22 patients (82%) and in 5 patients thereafter. Two patients could not be evaluated because ^{131}I therapy was performed before the bottoms appeared. The second bottom appeared from 5 to 12 months in 8 patients. Transient euthyroid state was observed in 44% (12/27) patients and 15 times; once in 10 patients, twice in one patient and three times in one patient. It appeared 10 times within 6 months and 5 times thereafter. The euthyroid state changed to the hyperthyroid state within 2 months on 11 occasions and from 3 to 4 months on 3

occasions. In one patient, transient euthyroidism appeared three times at one, 4 and 10 months and transient hypothyroidism appeared at 2 months. In this patient, the transient euthyroid state at one month changed to transient hypothyroidism at 2 months. Initial peak was observed 9 times in 9 patients (31%) within 5 months. The duration was from one month to 4 months in 7 patients. Late peak was observed in 3 patients at 7, 7 and 9.5 months. The stable recurrent state occurred within 6 months in 52% (14/27) patients and thereafter in 13 patients. The duration from the initial bottom to the stable state was within 2 months in 74% (17/23). The bottom located at 12 months in 4 patients with a downhill pattern. Additional ^{131}I therapy was performed in 3 patients from 3.5 to 6 months and in 7 patients from 6 to 12 months.

There were no statistically significant differences in the appearance time of the bottom and stable state among the euthyroid, hypothyroid and hyperthyroid groups. Of the 68 patients, the cumulative stable state after the therapy was obtained in 10% at 3 months, 25% at 4 months, 41% at 5 months, 57% at 6 months, 63% at 7 months, 75% at 8 months, 75% at 9 months, 78% at 10 months, 82% at 11 months and 100% at 12 months.

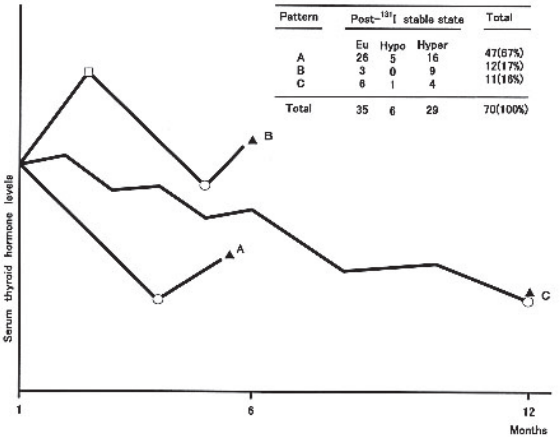

Fig. 4 Three basic thyroid hormone changing patterns from one month after ^{131}I therapy.
A; valley pattern (n = 47), B; mountain pattern (n = 12) and C; downhill pattern (n = 11). The marks in the figure indicate the important hormonal changes; □; the initial peak, ○; bottom and ▲; the beginning of the stable state.

4. Serial changes of serum TSH levels

1) The euthyroid group (n = 35)

At the time of hormonal normalization, TSH values were suppressed in 33 patients (91%), detectable but below normal in one (3%) and within the normal range in 2 (6%). On 13 occasions of transient hypothyroidism, TSH values increased to above normal (peak mean ± SD value and range; 78.10 ± 70.38, 24.5–255 μIU/m*l*) in 9 patients (69%), were detectable but below normal in one, within the normal range in one and were still suppressed in 2 (15%). Normalization of TSH values was delayed in 33 patients (91%) and occurred from one month to one year (1~3M; 6, ~6M; 2, 6M<; 9) in 17 patients with only 2 concordant changes and was still suppressed in 18 patients at 1 year. THS values were all suppressed throughout 1 year in 14 patients. At the time of 1 year, THS values were suppressed (<0.01 or <0.10 μIU/m*l*) in 18 patients, detectable but below normal in one, within the normal range (0.35–5.5 μIU/m*l*) in 8 patients, and increased to above upper normal values (>5.5 μIU/m*l*) in 8 patients.

2) The hypothyroid group (n = 6)

At the time of initial hormonal normalization before hypothyroidism, TSH values were suppressed in all 6 patients (100%). They increased to above normal in 4

Table 2 The number of patients for the appearance time and duration of changes in thyroid hormones in the euthyroid group of patients with Graves' disease after ^{131}I therapy

Hormonal changes	Time after ^{131}I-therapy or duration of hormonal changes (months)												N	Mean ± SD (months)
	~1	~2	~3	~4	~5	~6	~7	~8	~9	~10	~11	~12		
Normalization	7	11	11	1	1	2	1	0	0	0	1	0	35	2.7 ± 2.1
Bottom value	0	4	10	8	4	2	1	1	0	1	1	3	35	4.8 ± 3.0
Transient hypothyroidism	0	2	4	3	1	2	1	0	0	0	0	0	13	3.8 ± 1.6
Duration	4	5	2	1	0	0	1	0	0	0	0	0	13	2.2 ± 1.8
Transient hyperthyroidism	0	0	0	4	1	3	1	1	0	0	0	0	10	5.1 ± 1.6
Duration	4	2	2	0	1	0	1	0	0	0	0	0	10	2.5 ± 1.9
Transient peak	0	2	1	0	0	0	0	0	0	0	0	0	3	2.2 ± 0.6
Duration	1	2	0	0	0	0	0	0	0	0	0	0	3	1.4 ± 0.5
Stable state	0	0	2	5	7	6	1	6	0	2	1	5	35	6.8 ± 2.9
Bottom to stable state	9*	9	9	1	2	2	0	0	0	0	0	0	32	2.1 ± 1.4

*The bottom and stable states were situated at 12 months in 3 patients who were excluded.

Table 3 The number of patients for the appearance time and duration of changes in thyroid hormones and the time of replacement therapy in the hypothyroid group of patients with Graves' disease after ^{131}I therapy

Item	Time after ^{131}I-therapy or duration of hormonal changes (months)												N	Mean ± SD (months)
Hormonal changes	~1	~2	~3	~4	~5	~6	~7	~8	~9	~10	~11	~12		
Normalization	2	2	1	1	0	0	0	0	0	0	0	0	6	1.8 ± 1.0
Duration	1	3	1	0	0	0	0	1	0	0	0	0	6	2.7 ± 2.6
Hypothyroidism	1	0	2	0	2	0	0	0	0	0	1	0	6	4.5 ± 3.5
Bottom value	0	1	0	2	2	0	0	0	0	0	1	0	6	5.0 ± 3.1
Stable state	0	0	1	2	1	1	0	0	0	0	0	1	6	5.6 ± 3.3
Bottom to stable state	5	1	0	0	0	0	0	0	0	0	0	0	6	0.6 ± 0.5
Replacement therapy	0	0	0	2	1	1	0	0	0	0	0	0	4	4.6 ± 1.1

Table 4 The number of the patients for the appearance time and duration of changes in thyroid hormones and the time of the next ^{131}I therapy in the hyperthyroid group of patients with Graves' disease after ^{131}I therapy

Item	Time after ^{131}I-therapy or duration of hormonal changes (months)												N	Mean ± SD (months)
Hormonal changes	~1	~2	~3	~4	~5	~6	~7	~8	~9	~10	~11	~12		
Initial bottom value	0	6	6	4	4	2	1	0	0	0	0	4	27*	4.7 ± 3.4
Second bottom value	0	0	0	0	1	0	1	0	1	4	0	1	8	8.9 ± 4.2
Transient euthyroidism	1	3	2	3	1	0	1	0	0	4	0	0	15	4.8 ± 3.3
Duration	6	6	2	1	0	0	0	0	0	0	0	0	15	1.7 ± 0.9
Transient hypothyroidism	0	1	0	0	0	0	0	0	0	0	0	0	1	2
Duration	0	1	0	0	0	0	0	0	0	0	0	0	1	2
Initial peak	0	4	4	0	1	0	0	0	0	0	0	0	9	2.5 ± 0.9
Duration	4	1	1	1	0	0	0	0	0	0	0	0	7	1.8 ± 1.1
Late peak	0	0	0	0	0	0	2	0	0	1	0	0	3	7.8 ± 1.4
Duration	0	0	0	1	0	0	0	0	0	0	0	0	1	4
Stable state	0	0	4	3	3	4	3	2	0	0	2	6	27*	7.0 ± 3.4
Bottom to stable	13	4	1	1	0	0	0	1	2	1	0	0	23**	2.6 ± 3.1
Next ^{131}I-therapy	0	0	0	1	0	2	1	1	2	0	3	0	10	8.0 ± 2.6

* Of 29 patients, 2 received the next ^{131}I-therapy before the bottom levels appeared and showed the mountain patterns.
** The bottom and stable states were situated at 12 months in 4 patients who were excluded.

patients, were within normal range in one patient and were suppressed in one patient at the initial time when the thyroid hormones fell into the subnormal levels, and increased to above normal later in the latter 2 patients. The peak TSH values ranged from 56.3 to 153.8 (89.74 ± 36.22) μIU/m*l*. TSH values decreased after replacement therapy to variable degrees according to the administered dosage of thyroxine.

3) The hyperthyroid group (29 therapies/25 patients)

TSH values were all suppressed when the hormonal values indicated hyperthyroidism. Transient euthyroidism occurred on 16 occasions in 29 therapeutic courses. Euthyroid hormonal values were obtained in 24 measurements on these occasions. THS values were suppressed in 21 (88%), within the normal ranges in 2 (8%) and detectable but below normal in one (4%) of these measurements. Transient hypothyroidism occurred on one occasion. The TSH values increased to above normal (34.4 and 35.28 μIU/m*l*) on this occasion.

DISCUSSION

The serial changes in thyroid hormone levels after radioiodine therapy are considered to reflect thyroidal damage from ^{131}I and recovery of thyroid tissues from it involving immunological reactions.[37–39] The primary effect of ^{131}I on thyroid cells is due to the beta rays from ^{131}I which is deposited in thyroid cells through the metabolic pathway of thyroid hormone synthesis.[40] Pathologically, ^{131}I initially causes cellular necrosis and acute inflammation and later induces atrophy, fibrosis and chronic inflammation in the thyroid tissues.[41] The degree of functional recovery may depend on the degrees of surviving thyroid cells and immunological reactions elicited by the damage from ^{131}I. However, the post-radioiodine therapeutic state cannot be precisely determined in advance, because it depends not only on the absorbed dose but also radiosensitivity of individual patients.[42]

Although a variety of patterns of changes in serum

thyroid hormone levels were noted after radioiodine therapy, they could be categorized into three basic patterns from baseline to one month and thereafter, respectively, in the present study. From baseline to one month after therapy, serum thyroid hormones showed a decrease in 77%, a minimum change in 11.5% and an increase in 11.5%. In this connection, the mean ± SD percentages of serum T_3, T_4 and FT_4 levels at one month after ^{131}I therapy to the baseline levels were 63 ± 17%, 77 ± 20%, and 66 ± 25% in the euthyroid group (n = 23), 60 ± 21%, 64 ± 21% and 45 ± 21% in the hypothyroid group (n = 5) and 80 ± 38%, 86 ± 26% and 83 ± 45% in the hyperthyroid group (n = 20) and 70 ± 29%, 79 ± 23% and 70 ± 35% as a whole (n = 48), respectively. These changes, however, do not always mean that they are linear or straightforward. Although most of the patients with Graves' disease would show a continuous decrease in serum thyroid hormones within one month after radioiodine therapy, a transient or continuous rise in them would also occur in some patients within this period.[25–30] The transient or continuous increase of the hormonal levels within one month may represent release of thyroid hormones from destroyed thyroid follicular cells.

A few papers described previously the changes in thyroid hormone levels from one month to one year after radioiodine therapy for Graves' disease. Daae et al. examined the hormonal changes until 14 weeks after the therapy in 10 therapeutic courses in 9 patients.[31] They separated these patients into three groups, based on case history and clinical examination. In the nonresponder group (2 patients), the hormonal levels did not change significantly during the investigation period. In group 2 (5 euthyroid patients), the T_4 and T_3 levels showed a plain fall in all patients to 41–74% and about half of the originals, respectively. In Group 3 (3 hypothyroid patients), the T_4 and T_3 values fell with fluctuations to 7–10% and 18–29% at 14 weeks, respectively. Bellabarba et al. studied the hormonal changes in a total of 62 patients with thyrotoxicosis (36; ^{131}I therapy, 20; antithyroid drug therapy and 6; thyroidectomy) by measuring thyroid hormones at 6 weeks, 3, 6, 9, 12 months and every 6 months thereafter.[32] Serum T_4 and T_3 showed a parallel and gradual decrease to normal levels in 44 (71%) of them with a period of 2–6 months after the therapy. However 5 measurements of thyroid hormones during one year did not reveal the detailed changes in thyroid hormones after radioiodine therapy for Graves' disease. Kusakabe et al. showed the mean changes in thyroid hormones measured at a one-month interval until 6 months of the patients who were euthyroid during 10 years after radioiodine therapy and the patients who developed hypothyroidism 4 years or later after radioiodine therapy[33]: The mean changes in thyroid hormones showed the valley pattern in which the bottom situated at 3 or 4 months.

In our study, from one month after ^{131}I therapy, 3 major changes in serum thyroid hormone levels were observed, the valley, mountain and downhill patterns. The valley pattern was observed most frequently (67%, 47/70) (Figs. 1A, 2 and, 3 A and B). The bottom was situated in three hormonal ranges; above, within and below the normal ranges. The bottom appeared at 3.3 ± 1.3 (range,1.75–7) months after therapy as a whole. The bottom levels may represent mainly an impaired function of thyroid cells which received the direct and maximum effect of ^{131}I. Then the recovery process ensues. This process may involve functional recovery of impaired but surviving follicular cells. The stable state as a whole in this pattern was obtained at 5.1 ± 1.7 months after therapy. Thus it requires usually 1–2 months to reach a stable state from a bottom.

The mountain pattern was observed in 17% (12/70) (Figs. 1B and 2C). The peak appeared from 1.5 to 4.5 (2.4 ± 0.8) months and decreased to the bottom at 5 ± 1 (range, 3–6) months and the bottom was also situated in three hormonal ranges as in the valley pattern. The stable state appeared at 6.5 ± 1.5 (range, 3.75–9.25) months and was also usually obtained 1–2 months after the bottom in this pattern. Although the release of thyroid hormones from the destroyed follicular cells usually may occur within one month,[25–30] the mechanism of producing the mountain pattern is considered to involve both the release of thyroid hormones from the follicular cells being destroyed continuously and the immunological stimulating reactions to the released antigens from the destroyed thyroid follicular cells as observed in 5% of the patients with nontoxic goiter who developed transient hyperthyroidism 3 months after ^{131}I treatment.[43] Recovery from the bottom determined the stable euthyroid or hyperthyroid state in this pattern as observed in the valley pattern.

The last pattern, downhill pattern, was observed in 16% (11/70) (Figs. 1C, 2 and 3D). This pattern may represent a gradual impairment of radio-resistant functioning thyroid cells during one year.[42] When this pattern is recognized, replacement or additional ^{131}I therapy can be delayed depending on the patient's symptoms and signs.

In the euthyroid group, hormonal normalization was obtained in 29 of 35 patients (83%) within 3 months. Thereafter, the hormonal levels decreased further to a bottom in most of the patients. Then the hormonal levels elevated to the stable euthyroid or transiently hyperthyroid states. The bottom levels situated below or within normal ranges. When the bottom level is situated below the normal ranges, it is a well known phenomenon and called transient hypothyroidism[44–49] and it appeared in 13 (37%) of 35 euthyroid patients (mean oral dose, 3.8 ± 1.9 mCi), 3.8 ± 1.6 months after therapy and recovered in 2.2 ± 1.8 months and in 14 (21%) of the 68 patients in our study (mean oral dose, 4.3 ± 2.5 mCi). Although there were no statistically significant differences in oral dose, absorbed dose, ^{131}I concentration and thyroid weight between the transient hypothyroid positive and negative euthyroid subgroups in our relatively small oral dose

study, larger oral doses would decrease the frequency of transient hypothyroidism and increase that of permanent hypothyroidism: Dorfman et al. reported that 27 of 36 patients who had received 10 mCi of sodium ^{131}I for Graves' disease became hypothyroid within 4 months and observed transient hypothyroidism in 4 (11%) and permanent hypothyroidism in 23.[44] Sawers et al. treated 30 consecutive patients with thyrotoxicosis with a median dose of 8 (range, 5–24) mCi of ^{131}I.[46] They noted 5 (17%) transient hypothyroid patients 2–4 months after therapy which recovered during the ensuing 2 months. Connell et al. treated 55 patients with 100 μCi/g thyroid tissue and observed transient hypothyroidism which appeared 6–12 weeks and persisted 4–8 weeks after therapy in 5 patients (9%).[47] Gomez et al.[48] reviewed 355 patients with Graves' disease who received ^{131}I therapy; 333 received a dose <10 (6.6 ± 1.9) mCi and 22 received a dose >10 (12.8 ± 2.9) mCi and found transient hypothyroidism in 40 (12%) of 333 with a smaller dose and none of the 22 with a larger dose. It appeared 2.1 ± 1 (range, 1–6) months and recovery of thyroid function was delayed 3 ± 1.1 (range, 1–5) months. Aizawa et al. found transient hypothyroidism in 39 (15%) of 260 patients who had received a maximum dose of 10 mCi or less doses.[49] It is suggested that transient hypothyroidism may be due to transient impaired organification of iodide.[47]

Transient hyperthyroidism appeared on 10 occasions (29%) in 9 patients (26%); after hormonal normalization in 5 patients and after a bottom in 4 patients at 5.1 ± 1.6 (range, 4.3–7.8) months and returned to stable euthyroidism during 2.5 ± 1.9 (range, 1–7) months. This phenomenon has attracted little attention previously probably because of little symptomatic worsening. Transient peak from one month after therapy (the mountain pattern) was observed in 3 patients; the peak appeared at 1.5, 2 and 3 months after therapy, respectively. Thereafter, the hormonal levels decreased to the bottom at 4.5, 4.5 and 5 months. The bottom was situated within normal ranges in 2 and below normal ranges in one. Then, the hormonal levels recovered to the stable euthyroid states at 7, 5.75 and 8 months after therapy, respectively. Therefore, if the hormonal levels increase from one month after therapy, further observation is needed to confirm the bottom and stable state. The stable euthyroid state was achieved from 2.5 months after therapy. It situated from 2.5 to 6 months in 20, from 6 to 9 months in 7 and from 9 to 12 months in 8. The distribution of the periods of stable euthyroid state after therapy is related to the hormonal changing patterns. A valley pattern was observed in 19 of 20 early (≤6 months) stable state patients and a mountain pattern was observed in one of them. Of 7 middle (6–9 months) stable patients, 5 showed valley patterns with transient hypothyroidism or hyperthyroidism and 2 showed mountain patterns. Of 8 late (9–12 months) stable patients, 6 showed downhill patterns and 2 showed valley patterns with transient hypothyroidism.

In the hypothyroid group consisting of 6 patients, 5 patients showed valley patterns and one patient showed a downhill pattern. In 5 (83%) of 6 patients, the thyroid hormones showed subnormal levels followed by bottom levels within 5 months and stable hypothyroid states were judged to be present from 3 to 6 months based on clinical symptoms in addition to hormonal changes. Replacement therapy was discontinued temporarily in 4 patients to confirm the permanence of the hypothyroidism. When an ablation dose is administered, most of the patients appear to show the valley pattern and develop permanent hypothyroidism as early as 3 months and within 6 months.[3–15] In our study, one patient showed the serum hormonal levels of normal T_3 with low T_4 and FT_4 from one month to one year and did not need replacement therapy. Such cases have also been reported previously.[32]

In the hyperthyroid group, the distribution of basic valley, mountain and downhill patterns was similar to that of the euthyroid group. The initial bottom situated above, within and below the normal ranges in the valley and mountain patterns. When the initial bottom level is situated above normal, it may imply treatment failure because all 14 patients whose initial bottom was situated above the normal ranges in the valley and mountain patterns belonged finally to the stable hyperthyroid group. However, the bottom levels below or within the normal ranges cannot predict the post-therapeutic thyroid state because it situated within or below normal ranges in 9 (39%) of 23 patients with a valley or mountain pattern in the hyperthyroid group. Transient euthyroidism was observed in 12 of 27 patients and 15 times and appeared from one month to 6 months for a total of 10 times. Transient hypothyroidism was observed in one patient at two months. The appearance time and duration of these transient changes are analogous to those of transient hypothyroidism in the euthyroid group.

In the present study, the changes in serum TSH after radioiodine therapy for Graves' disease had two distinct features: One was an insensitive or blunted response to normalization of thyroid hormones. The other was a sensitive or quick response to hypothyroidism. Suppression of serum TSH was observed at the time of hormonal normalization from the hyperthyroid state in 96% (54/56) and concordant changes of serum TSH and thyroid hormones was observed in only 2 patients (4%). Recovery of serum TSH occurred variable periods after normalization of thyroid hormones. However, on 20 occasions of the initial time when thyroid hormones became subnormal, TSH increased concordantly to above normal in 14 (70%), to the normal range in 2 (10%), to detectable but below normal in 1 (5%) and was still suppressed in only 3 (15%). Such phenomena were previously reported.[50] Thus measurements of serum TSH levels alone after radioiodine therapy for Graves' disease are inadequate for biochemical assessment of the thyroid state.[50–52]

In conclusion, although the changes in the levels of

serum thyroid hormones were varied, 3 basic changing patterns were observed; the valley, mountain and downhill patterns after radioiodine therapy for Graves' disease. In the former two patterns, the bottom levels and the degree of the recovery determined the post-therapeutic stable state in most patients. About 80% of the bottom levels and transiently abnormal changes appeared within 6 months. There was no fixed time for reaching the stable euthyroid, hypothyroid and hyperthyroid states after radioiodine therapy: they were obtained from 2.5 to 6 months in 57%, from 6 to 9 months in 18% and thereafter in 25%. Measurements of thyroid hormones at a one-month interval until 6 months and a two or three-months interval thereafter until one year will clarify which one of the three hormonal basic patterns is present and the important hormonal changes which are useful for the correct judgment of the subsequent management including replacement or additional radioiodine therapy.

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