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# Effect of Iodine Restriction on Thyroid Function in Patients with Primary Hypothyroidism

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Dietary iodine intake in Japan varies from as little as 0.1 mg/day to as much as 20 mg/day. The present study was undertaken to assess the frequency of iodine-induced reversible hypothyroidism in patients diagnosed as having primary hypothyroidism, and to clarify the clinical backgrounds responsible for the spontaneous recovery of thyroid functions. Thirty-three consecutive hypothyroid patients (25 women and eight men) with a median age of 52 years (range, 21–77 years) without a history of destructive thyroiditis within 1 year were asked to refrain from taking any iodine-containing drugs and foods such as seaweed products for 1–2 months. The median serum thyrotropin (TSH) level, which was initially 21.9 mU/L (range, 5.4–285 mU/L), was reduced to 5.3 mU/L (range, 0.9–52.3 mU/L) after iodine restriction. Twenty-one patients (63.6%) showed a decrease in serum TSH by >50% and to <10 mU/L. Eleven patients (33.3%) became euthyroid with TSH levels within the normal range (0.3–3.9 mU/L). The ratios of TSH after iodine restriction to TSH before iodine restriction (aTSH/bTSH) did not correlate significantly with titers of anti-thyroid peroxidase antibody and anti-thyroglobulin antibody or echogenicity on ultrasonography, but correlated inversely with $^{99m}$Tc uptake ($r = 0.600$, $p < 0.001$). Serum non-hormonal iodine levels, although not correlated significantly with aTSH/bTSH values, were significantly higher in the 21 patients with reversible hypothyroidism than in the remaining 12 patients. TSH binding inhibitor immunoglobulin was negative in all except one weakly positive case. In conclusion, (1) primary hypothyroidism was recovered following iodine restriction in more than half of the patients, and (2) the reversibility of hypothyroidism was not significantly associated with Hashimoto's thyroiditis but with increased $^{99m}$Tc uptake and elevated non-hormonal iodine levels.

## Introduction

IODINE-INDUCED HYPOTHYROIDISM is not rare, at least in Japan, where seaweed is habitually ingested (1–5). Dietary iodine intake varies from as little as 0.1 mg/day to as much as 20 mg/day. Young Japanese prefer to eat iodine-poor westernized dishes, whereas old or middle-aged Japanese often eat seaweed, presumably because of habit. Recently, intake of seaweed, a low-calorie food containing sufficient calcium, potassium, iron, and vegetable fibers, has been recommended for prevention of future development of arteriosclerotic diseases such as ischemic heart diseases, cerebrovascular diseases, disorders of lipid metabolism, diabetes mellitus, hypertension, and obesity, as well as the occurrence of osteoporosis and iron-deficiency anemia.

From the clinical point of view, it is important to differentiate hypothyroid patients who may recover spontaneously after iodine restriction from those who may not. Although Hashimoto's thyroiditis (6,7) is thought to be the underlying disease, anti-thyroid antibodies are not detected in some patients with reversible hypothyroidism (2–5,8). The present study was undertaken to assess the frequency of iodine-induced reversible hypothyroidism in patients diagnosed as having primary hypothyroidism, and to clarify the clinical backgrounds responsible for the spontaneous recovery of hypothyroidism. In this study, anti-thyroid antibodies such as anti-thyroglobulin antibody (TgAb), anti-thyroid peroxidase antibody (TPOAb), and TSH binding inhibitor immunoglobulin (TBII), sonographic findings, $^{99m}$Tc thyroidal uptake values, and serum non-hormonal iodine levels were determined in patients with reversible hypothyroidism and compared with those in patients with irreversible hypothyroidism.

## Patients and Methods

Thirty-three consecutive hypothyroid patients (25 women and eight men) who visited Kyoto University Hospital in Kyoto City ($n = 15$) and Obama Hospital ($n = 18$) in Obama City between 1998 and 2000 were studied. The city of Kyoto

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is located in the center of Kyoto Basin, while the city of Obama is on the Japan Sea. The median age was 52 years (range, 21–77 years). All 33 patients were diagnosed as having primary hypothyroidism based on an elevated serum thyrotropin (TSH) concentration (>3.9 mU/L). In this study, 12 subclinically hypothyroid patients with elevated TSH and normal free thyroxine (T4) levels were included. In addition to free T4 and TSH, TgAb, TPOAb, and TBII were determined in all patients. $^{99m}$Tc thyroid scintigraphy and ultrasonography (US) were also performed.

Hypothyroid patients with a history of neck surgery or irradiation and those with destructive thyrotoxicosis or pregnancy within a year were excluded. The diagnosis of renal dysfunction was given to two patients (9 and 14 in Table 1) who showed serum urea nitrogen and creatinine levels higher than 7.1 mmol/L and 106 $\mu$mol/L, respectively (3). One patient (20 in Table 1) had a history of treatment of hyperthyroidism by methimazole.

The serum TSH concentration was measured at least twice with an interval of 2 weeks to 4 months before commencement of iodine restriction. All patients showed an increase or no more than a 30% decrease in serum TSH, or remained hypothyroid with a TSH level higher than 40 mU/L during the follow-up period, indicating that they had persistent hypothyroidism before iodine restriction. In nine patients who had a repeated test before iodine restriction with an interval of 2–3 weeks, persistent hypothyroidism was confirmed based on the evidence suggesting failure of serum TSH to decrease and of free T4 to increase during the follow-up period.

All patients were asked to refrain from taking any iodine-containing drugs or foods such as seaweed products. Blood was taken for the measurement of serum TSH and free T4 concentrations every 2–3 weeks up to 8 weeks following the commencement of iodine restriction. Reversible hypothyroidism was diagnosed when serum TSH decreased by more than 50% and when serum TSH after iodine restriction was below 10 mU/L; otherwise irreversible hypothyroidism was diagnosed. The serum total iodine levels were also measured before and 2 weeks to 3 months after the initiation of iodine restriction in all except four patients by a Technicon Autoanalyzer using the ceric arsenite methods. Serum non-hormonal iodine levels were calculated by subtracting iodine contained in serum T4 and triiodothyronine (T3) from total iodine levels. Hormonal iodine level ($\mu$g/L) were calculated according to the formula presented by Sato et al. (3) as serum T4 level (nmol/L) $\times$ ($127 \times 4 \times 10^{-3}$) + serum T3 level (nmol/L) $\times$ ($127 \times 3 \times 10^{-3}$).

### *Ultrasonography*

US was performed using a high-frequency (7.5-MHz) real-time scanner with a linear transducer (Hitachi EUB555, Yokogawa RT-2800, or LOGIQ 500 MD, Tokyo, Japan). The US findings was classified into (1) normal, (2) decreased, and (3) heterogeneous groups. The echogenicity was evaluated by comparing with that of the anterior neck muscles.

### *Thyroid* in vitro *tests*

Serum T4, T3, and free T4 concentrations were determined by radioimmunoassay using commercially available kits (T4 and T3, Dainabot Radioisotope Laboratories, Tokyo; free T4, Ortho-Clinical Diagnostics K.K., Tokyo). The normal range (mean $\pm$ 2 standard deviations) of free T4 was 12.7–24.7 pmol/L. Serum TSH concentrations were measured by immunoradiometric assay (hTSH kit, Riagnost, Tokyo; normal range, 0.3–3.9 mU/L). TgAb and TPOAb were determined using radioassay kits (RSR Ltd., Cardiff, Wales) (9). The undetectable range was <0.3 U/mL for both TgAb and TPOAb. TBII was assayed using a commercially available kit (Cosmic Corp., Tokyo). The normal range was between $-11.9\%$ and 11.0% (10). Thyroid-stimulating antibody (TSAb) and thyroid stimulation-blocking antibody (TSBAb) were assayed according to methods previously described. The normal ranges were between 55% and 145% and between $-37\%$ and 32%, respectively (11).

### *$^{99m}$Tc thyroidal uptake*

$^{99m}$Tc thyroidal uptake was measured 30 min after the intravenous injection of 148 MBq of $^{99m}$Tc-pertechnetate. The normal range was 0.4–3.0%.

### *Statistical analysis*

Comparisons were made by Wilcoxon's signed rank sum test.

## Results

Clinical data in all 33 patients with primary hypothyroidism are demonstrated in Table 1. Goiter was not palpable in eight patients. Goiter size was rather small in the remaining 25 patients, with a mean transverse diameter of 5.0 $\pm$ 0.7 cm ($\pm$ standard deviation). $^{99m}$Tc thyroid uptake was increased (>3.0%) in 15 patients (45.5%), and decreased (<0.4%) in two patients (4.4%). Both TgAb and TPOAb were detected in 17 patients (51.5%). TBII was negative in all except one patient (15 in Table 1), who showed a weakly positive result (15.7%). She showed slightly increased TSAb activity at 181.6% with negative TSBAb at 6.3%. TBII and TSAb activities of Patient 20, who had remained in remission, were both negative. US revealed normal, decreased, or heterogeneous echogenicity in 11, 17, or five patients, respectively.

The median serum TSH level, which was initially 21.9 mU/L (>10.0 mU/L in 23 patients), was reduced to 5.3 mU/L after iodine restriction. The median serum free T4 levels, which were initially 10.3 pmol/L, showed a 1.4-fold increase. Twenty-four of 33 patients (72.7%) displayed reduction of TSH to less than half of the initial levels. The median ratio of TSH after iodine restriction to TSH before iodine restriction (aTSH/bTSH) was 0.28. Serum TSH was normalized in 11 patients (33.3%). According to the criteria described previously, 21 (63.6%) patients were judged to have reversible hypothyroidism (group 1), and 12 (36.4%) were diagnosed as having irreversible hypothyroidism (group 2). This criterion separated the patients into the two groups: one with significant changes in thyroid functions either from overt hypothyroidism to subclinical hypothyroidism or euthyroidism, or from subclinical hypothyroidism to euthyroidism, and the other with maintenance of overt or subclinical hypothyroidism.

There was a significant correlation between initial TSH levels and $^{99m}$Tc uptake values ($p < 0.01, r = 0.493$) (data not shown). The $^{99m}$Tc uptake values also showed significant in-

TABLE 1. CLINICAL DATA IN ALL 33 PATIENTS WITH PRIMARY HYPOTHYROIDISM

| Group, patient | Sex | Age (years) | Goiter size[a] | $^{99m}Tc$ uptake (%) | Week | TSH (mU/L) | | aTSH/bTSH | FT4 (pmol/L) | | TgAb (U/mL) | TPOAb (U/mL) | TBII (%) | US | Serum free iodine (μg/dL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | bTSH[b] | aTSH[c] | | Before[b] | After[c] | | | | | Before[b] | After[c] |
| Group 1 | | | | | | | | | | | | | | | | |
| 1 | F | 63 | 4.0 | 11.5 | 4 | 206.2 | 2.7 | 0.01 | 3.9 | 19.3 | <0.3 | <0.3 | 0 | Low | 72.8 | 4.7 |
| 2 | F | 66 | 4.2 | 10.5 | 6 | 284.0 | 5.3 | 0.02 | 2.6 | 14.1 | 7.0 | 4.0 | 4.4 | Heterogeneous | 5.4 | 0.7 |
| 3 | F | 68 | 3.8 | 3.6 | 8 | 21.9 | 0.9 | 0.04 | 5.1 | 14.1 | <0.3 | <0.3 | 4.3 | Normal | 108.1 | 4.0 |
| 4 | F | 72 | 4.3 | 2.6 | 4 | 86.2 | 6.3 | 0.08 | 5.1 | 12.9 | <0.3 | <0.3 | 10.9 | Heterogeneous | 7.7 | 0.1 |
| 5 | F | 38 | 3.6 | 8.0 | 8 | 24.7 | 2.6 | 0.11 | 12.9 | 16.7 | 3.7 | 3.9 | 1.7 | Normal | 10.6 | 8.7 |
| 6 | M | 40 | 5.0 | 5.1 | 4 | 58.0 | 6.2 | 0.11 | 9.0 | 16.7 | 20.1 | 41.8 | 0 | Low | 4.4 | 3.3 |
| 7 | M | 50 | NP | 8.4 | 8 | 24.8 | 3.2 | 0.13 | 9.0 | 15.4 | <0.3 | <0.3 | 2.6 | Normal | ND | ND |
| 8 | F | 44 | 4.7 | 2.5 | 4 | 285.0 | 9.7 | 0.14 | 2.6 | 14.1 | 2.8 | 41.3 | 2.2 | Low | 2.3 | 2.0 |
| 9 | F | 57 | 5.3 | 12.8 | 2 | 27.7 | 3.8 | 0.14 | 6.4 | 11.6 | 17.5 | 7.4 | −0.1 | Low | 5.1 | 2.5 |
| 10 | M | 74 | NP | 5.1 | 4 | 42.3 | 6.2 | 0.15 | 3.9 | 16.7 | <0.3 | <0.3 | 9.7 | Normal | 13.3 | 2.4 |
| 11 | F | 34 | 6.0 | 9.5 | 4 | 24.5 | 3.9 | 0.16 | 7.7 | 15.4 | 15.0 | 3 | 7.0 | Low | 6.7 | 0 |
| 12 | F | 49 | NP | 6.9 | 2 | 37.2 | 6.4 | 0.17 | 10.3 | 14.1 | <0.3 | 1.4 | 7.3 | Low | ND | ND |
| 13 | F | 27 | 5.0 | 2.7 | 2 | 5.4 | 1.4 | 0.26 | 9.0 | 10.3 | <0.3 | <0.3 | 3.1 | Heterogeneous | 6.8 | 2.5 |
| 14 | F | 46 | 4.3 | 1.5 | 6 | 20.1 | 5.5 | 0.26 | 11.6 | 12.9 | 4.6 | 856 | 4.2 | Low | 19.7 | 4.0 |
| 15 | F | 24 | 6.0 | 2.4 | 3 | 17.1 | 4.6 | 0.27 | 12.9 | 16.7 | 64.7 | 7.0 | 15.7 | Low | 2.6 | 1.5 |
| 16 | F | 52 | 5.0 | 2.2 | 8 | 15.1 | 4.2 | 0.28 | 11.6 | 14.1 | 5.2 | 0.5 | 4.2 | Normal | ND | ND |
| 17 | F | 69 | 5.8 | 3.4 | 6 | 8.1 | 2.4 | 0.29 | 10.3 | 15.4 | <0.3 | <0.3 | 0 | Low | 15.7 | 5.1 |
| 18 | F | 73 | NP | 1.3 | 4 | 7.4 | 2.2 | 0.30 | 14.1 | 15.4 | <0.3 | <0.3 | 0 | Low | 6.9 | 5.5 |
| 19 | F | 77 | 5.2 | 3.9 | 4 | 9.1 | 3.5 | 0.38 | 12.9 | 12.9 | <0.3 | <0.3 | 2.0 | Heterogeneous | 25.4 | 5.6 |
| 20 | M | 46 | 5.2 | 3.6 | 4 | 11.7 | 4.5 | 0.39 | 14.1 | 14.1 | 16.4 | 26.5 | 4.5 | Low | 4.2 | 3.5 |
| 21 | M | 72 | NP | 0.4 | 4 | 6.6 | 2.7 | 0.40 | 14.1 | 14.1 | <0.3 | <0.3 | 1.4 | Normal | 25.7 | 3.6 |
| Median | | 52* | | 3.6** | 4* | 24.5* | 3.9** | 0.16 | 9.0* | 14.1* | <0.3* | 0.5* | 3.1* | * | 7.3*** | 3.4* |
| Range | | 24–77 | | 0.4–12.8 | 2–8 | 5.4–285 | 0.9–9.7 | 0.01–0.4 | 2.6–14.1 | 10.3–19.3 | <0.3–64.7 | <0.3–856 | −0.1–15.7 | | 2.3–108.1 | 0–8.7 |

(*continued*)

Table 1. Clinical Data in All 33 Patients with Primary Hypothyroidism (Cont'd)

| Group, patient | Sex | Age (years) | Goiter size[a] | $^{99m}Tc$ uptake (%) | Week | TSH (mU/L) | | aTSH/bTSH | FT4 (pmol/L) | | TgAb (U/mL) | TPOAb (U/mL) | TBII (%) | US | Serum free iodine (μg/dL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | bTSH[b] | aTSH[c] | | Before[b] | After[c] | | | | | Before[b] | After[c] |
| Group 2 | | | | | | | | | | | | | | | | |
| 22 | M | 70 | NP | 10.3 | 4 | 146.0 | 21.7 | 0.15 | 1.9 | 7.7 | <0.3 | <0.3 | −1.9 | Normal | 70.6 | 23.4 |
| 23 | F | 63 | NP | 0.2 | 2 | 186.0 | 52.3 | 0.28 | 3.6 | 11.6 | 200 | 50.0 | 1.0 | Low | ND | ND |
| 24 | F | 51 | 7.6 | 1.6 | 6 | 75.1 | 32.9 | 0.44 | 5.7 | 11.6 | 25.8 | 0.3 | 0.6 | Low | 1.7 | 3.4 |
| 25 | M | 70 | NP | 0.4 | 4 | 11.2 | 5.9 | 0.52 | 6.7 | 12.9 | <0.3 | <0.3 | 0 | Normal | 3.7 | 3.1 |
| 26 | F | 54 | 5.7 | 5.8 | 6 | 54.7 | 29.9 | 0.53 | 6.8 | 14.1 | 3,710 | 47.3 | 1.4 | Low | 1.1 | 0.4 |
| 27 | M | 37 | 6.0 | 1.4 | 4 | 7.6 | 4.9 | 0.65 | 8.4 | 18.0 | <0.3 | <0.3 | 3.0 | Normal | 5.8 | 2.4 |
| 28 | F | 40 | 4.8 | 2.3 | 2 | 8.8 | 6.8 | 0.76 | 9.8 | 14.1 | 110 | 2.5 | 0 | Low | 4.5 | 4.1 |
| 29 | F | 51 | 4.4 | 0.6 | 5 | 10.0 | 8.6 | 0.86 | 11.1 | 12.9 | <0.3 | <0.3 | 4.9 | Low | 25.2 | 0.2 |
| 30 | F | 40 | 6.0 | 1.2 | 4 | 5.4 | 4.8 | 0.89 | 11.4 | 15.4 | 4.4 | 20.9 | 3.8 | Heterogeneous | 2.6 | 4.7 |
| 31 | F | 21 | 4.2 | 1.2 | 4 | 28.0 | 28.7 | 1.03 | 13.2 | 11.6 | <0.3 | <0.3 | 10.8 | Normal | 1.5 | 0.9 |
| 32 | F | 57 | 5.2 | 0.7 | 3 | 5.5 | 5.9 | 1.07 | 13.8 | 15.4 | 30.0 | 8.0 | 0 | Low | 3.0 | 5.7 |
| 33 | F | 76 | 4.7 | 0.2 | 5 | 6.1 | 6.4 | 1.20 | 15.4 | 12.9 | 1.9 | 1.4 | 2.2 | Low | 3.1 | 4.2 |
| Median | | 53* | | 1.2** | 4* | 10.6* | 7.7** | 0.71 | 12.9* | 12.9* | 6.1* | 1.8* | 1.2* | * | 3.1*** | 3.4* |
| Range | | 21–76 | | 0.2–10.3 | 2–6 | 5.4–186 | 4.8–52.3 | 0.15–1.2 | 2.6–16.7 | 7.7–18.0 | <0.3–3,710 | <0.3–50 | −1.9–10.8 | | 1.1–70.6 | 0.2–23.4 |
| Groups 1 and 2 | | | | | | | | | | | | | | | | |
| Median | | 52 | | 2.6 | 4 | 21.9 | 5.3 | 0.28 | 10.3 | 14.1 | 1.9 | 0.5 | 2.2 | | 6.7 | 3.5 |
| Range | | 21–77 | | 0.2–12.8 | 2–8 | 5.4–285 | 0.9–52.3 | 0.01–1.2 | 2.6–16.7 | 7.7–19.3 | <0.3–3,710 | <0.3–856 | −1.9–15.7 | | 1.1–108.1 | 0–23.4 |

TSH, thyrotropin; FT4, free thyroxine; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TBII, TSH binding inhibitorimmunoglobulin; US, ultrasonography; ND, not determined.

Group 1, reversible hypothyroidism (TSH after iodine restriction [aTSH]/TSH before iodine restriction [bTSH]) <0.5 and aTSH <10 mU/L); Group 2, irreversible hypothyroidism (aTSH/bTSH >0.5 and aTSH >10 mU/L). Normal ranges are: $^{99m}Tc$ uptake, 0.4–3.0%; TSH, 0.3–3.9 mU/L; FT4, 12.7–24.7 pmol/L; TgAb, <0.3 U/mL; TPOAb, <0.3 U/mL; TBII, <11%. TSH, FT4, and free iodine concentrations were measured two or three times every 2–3 weeks in most of the patients after iodine restriction.

[a]Transverse diameter (cm). NP, not palpable.

[b]Before iodine restriction (the initial level).

[c]After iodine restriction, when the patients' thyroid function was nearest to the euthyroid state.

*Not significant, **$p < 0.01$, ***$p < 0.05$.

verse correlation with aTSH/bTSH values ($p < 0.001$, $r = 0.600$, Fig. 1A). Furthermore, they were significantly greater in group 1 patients than in group 2 patients ($p < 0.01$).

The diagnosis of Hashimoto's thyroiditis, when determined based on the detection of either TgAb or TPOAb (9), was found for 11 patients in group 1 and seven patients in group 2. The frequencies were similar (11 of 21 [52.3%] vs. seven of 12 [58.3%]). There was no significant difference in TgAb, TPOAb, or echogenicity between group 1 and group 2 patients. The aTSH/bTSH values did not correlate with TgAb, TPOAb, or echogenicity on US.

Serum non-hormonal iodine levels inversely correlated with aTSH/bTSH values, but the correlation was not statistically significant ($r = 0.355$, $0.05 < p < 0.1$, Fig. 1B). However, they were significantly higher in group 1 than in group 2 ($p < 0.05$). Figure 2 demonstrates changes in serum non-hormonal iodine levels in two groups of patients selected according to the response to iodine restriction with marked (initial TSH >20 mU/L and aTSH/bTSH <0.2) or no (initial TSH >10 mU/L and aTSH/bTSH >0.8) improvement of thyroid function. In successfully treated cases, serum non-hormonal iodine concentrations all decreased irrespectively of the initial levels. There was a considerable decrease in serum iodine levels even in one case (patient 31) without improvement of thyroid functions.

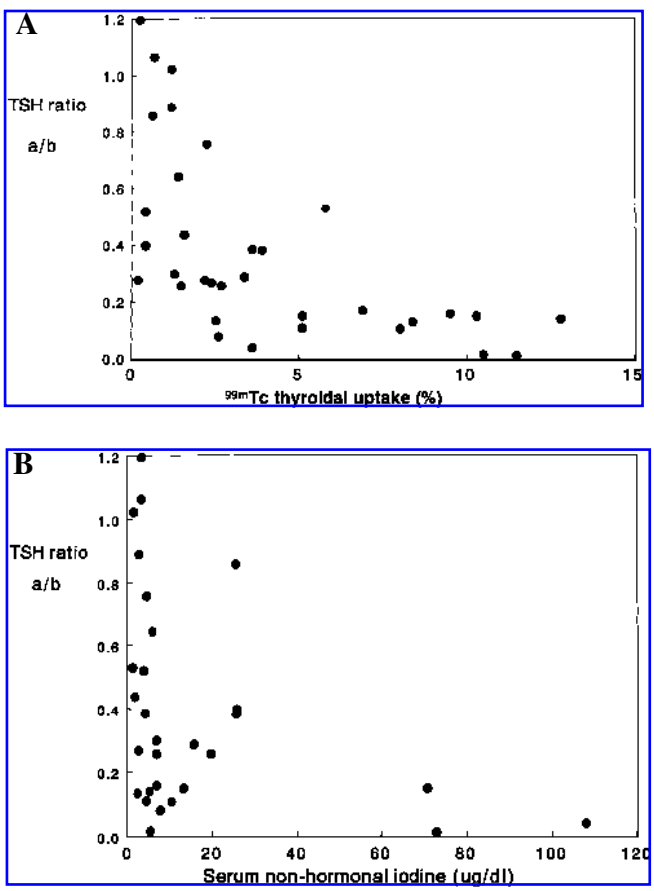


**FIG. 1.** Relation between $^{99m}$Tc thyroid uptake (**A**) or non-hormonal iodine levels (**B**) and changes in serum thyrotropin (TSH) compared with the initial levels after iodine restriction. a/b, TSH after iodine restriction/TSH before iodine restriction.

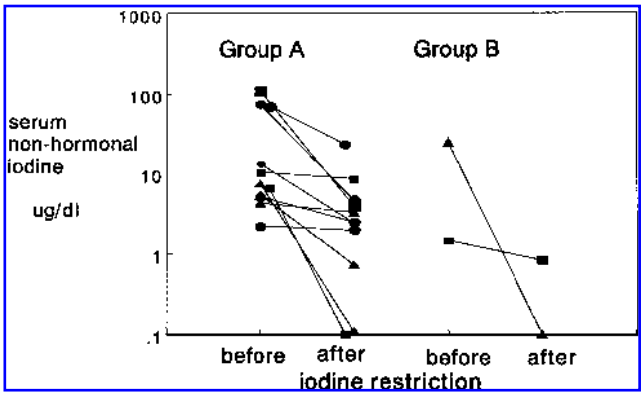


**FIG. 2.** Changes in serum non-hormonal iodine levels after iodine restriction in two groups of patients selected according to the response to iodine restriction with and without improvement of the thyroid dysfunction. Group A, successfully treated cases with the initial thyrotropin (TSH) level being >20 mU/L and the TSH after iodine restriction/TSH before iodine restriction (aTSH/bTSH) value being <0.2 (Patients 1–6 and 8–11). Group B, unsuccessfully treated cases with the initial TSH level being >10 mU/L and the aTSH/bTSH value being >0.8 (Patients 29 and 31).

In confirmation of the finding reported by Sato et al. (3), the iodine restriction caused 86% and 74% decreases of TSH concentrations in two patients (9 and 14, respectively, in Table 1) with renal dysfunction.

## Discussion

Iodine excess is a well-known exogenous factor that causes hypothyroidism. Iodine induces suppression of TSH-stimulated cyclic AMP production and protein iodination *in vitro* (12). Administration of excessive amounts of iodine induces thyroiditis in genetically susceptible animal strains (13,14). Sundick et al. (15) reported that highly iodinated thyroglobulin synthesized by animals fed a high iodine diet was more immunogenic than thyroglobulin containing fewer iodine atoms.

According to Braverman et al. (6), four of seven euthyroid patients with Hashimoto's thyroiditis who were given a solution of potassium iodide (180 mg of iodine) daily developed hypothyroidism after 4–8 weeks. Reinhardt et al. (7) reported that seven of 40 patients with underlying Hashimoto's thyroiditis living in an area of mild iodine deficiency given small amounts of iodine (250 $\mu$g daily) developed hypothyroidism.

The frequency of Hashimoto's thyroiditis in the reversible hypothyroidism group 1 (11 of 21, 52.3%) determined on the basis of TgAb or TPOAb detection is much higher than in healthy controls. Thus, patients with Hashimoto's thyroiditis appear susceptible to the development of iodine-induced hypothyroidism (6).

As to the effect of administration of excess iodine to euthyroid subjects, supplementary doses of 1,500 $\mu$g daily for 2 weeks caused a subtle but significant increase in TSH concentrations (16,17). In Japan, an area with high dietary iodine, serum TSH concentrations increased significantly in response to the administration of 27 mg of iodide for 28 days (18).

In 1965, endemic goiter due to excessive intake of iodine was reported to occur in coastal regions of Hokkaido, Japan (19). Recently, iodine-induced reversible hypothyroidism has been well documented mostly by Japanese investigators (1–5,8).

Reversible hypothyroidism occurs occasionally at the recovery phase of postpartum hypothyroidism, subacute thyroiditis, and painless thyroiditis. Such cases were excluded by the patients' history. Furthermore, in order to prove that the iodine restriction was responsible for the recovery of the thyroid function, we confirmed that all patients had persistent hypothyroidism by evaluating thyroid functions at least twice before iodine restriction.

It is well known that the thyroid function in hypothyroid patients with detectable TSH receptor antibodies, especially those with the blocking type, is changeable (11,20). There was one patient who was positive for TBII. She had detectable TSAb and undetectable TSBAb, indicating that TSH receptor antibodies do not appear to be involved in the manifestation of hypothyroidism.

In the present study, 21 of 33 patients (63.6%) with primary hypothyroidism showed recovery of thyroid function. The frequency was similar to that reported by other investigators: 12 of 22 (54.5%) (1); 49 of 116 (42.2%) (2); and 143 of 245 (58.4%) (3). It is very important for patients themselves to know whether they have irreversible hypothyroidism, requiring life-long thyroid hormone replacement therapy, or not. If they have permanent hypothyroidism, iodine restriction, which may not be beneficial for their health, is not necessary.

Thus, we have focused on the possible parameters that were predictive of the development of iodine-induced hypothyroidism. There was a good correlation between $^{99m}$Tc uptake values and aTSH/bTSH ratios. $^{99m}$Tc uptake values were significantly higher in group 1 (reversible) than in group 2 (irreversible). In accordance with the previous studies in which radioactive iodine uptake was measured (1,2), determination of $^{99m}$Tc uptake also predicted the patients' prognosis. The radioactive iodine uptake test is usually carried out after 1 week of restriction of iodine intake, when the thyroid function of the patients with iodine-induced hypothyroidism may be partially recovered. In contrast, the $^{99m}$Tc uptake test can be carried out even at the patients' first visit. The significant correlation of $^{99m}$Tc uptake with initial TSH values and with aTSH/bTSH values indicates that the responsiveness of the thyroid gland to endogenous TSH is preserved in spite of the impaired intrathyroidal synthesis of thyroid hormone in reversibly hypothyroid patients with increased $^{99m}$Tc uptake. In contrast, it is conceivable that autoimmune destruction of the thyroid is severe enough to cause an impaired response to TSH in irreversibly hypothyroid patients with decreased $^{99m}$Tc uptake (1). In the present study, seven of 12 (58.3%) patients in group 2 (irreversible hypothyroidism) had Hashimoto's thyroiditis as judged from TgAb and TPOAb titers. Although it is inexplicable why the remaining five patients, especially patients 29 and 31, had irreversible hypothyroidism, undetectable TgAb and TPOAb in serum do not appear to be predictive of favorable response to iodine restriction, in agreement and disagreement with the previous studies [Tajiri et al. (1) and Okamura et al. (2), respectively].

Hypoechogenicity of the thyroid is known to be a marker of autoimmune destruction (21), supporting the diagnosis of Hashimoto's thyroiditis in most patients with irreversible hypothyroidism. However, there was no significant difference between the reversible and irreversible hypothyroid groups, in disagreement with the previous study (5), since there were a considerable number of patients with hypoechogenicity in the reversible hypothyroid group, presumably due to hyperplastic epithelial changes (8). Thus, the echogenicity does not appear to predict the spontaneous recovery of thyroid functions.

The free iodine measurement may be helpful for prediction of prognosis of reversible hypothyroidism to some extent, since the free iodine levels roughly correlated with aTSH/bTSH values, and they were significantly higher in group 1 (reversible) than in group 2 (irreversible). However, the iodine measurement can be replaced by inquiring of the patients whether they habitually ingest seaweed products or not. What is important is that the thyroid function recovered spontaneously irrespectively of the initial free iodine levels, since the seaweed had been ingested occasionally or every day and was restricted strictly in patients with reversible hypothyroidism.

We assume that escape of the Wolff-Chaikoff effect (inhibition of organic binding of iodide in the thyroid by excess iodide intake) may not occur or the serum iodine levels to cause escape may be elevated, at 5–100 $\mu$g/dL in our cases, for unknown reasons. This phenomenon does not necessarily relate to Hashimoto's thyroiditis, since 10 of 21 (47.6%) patients in group 1 had no findings to support the clinical diagnosis of Hashimoto's thyroiditis. In this regard, Mizokami et al. (8) proposed a new type of hypothyroidism, which is pathophysiologically similar to adenomatous goiter.

In conclusion, hypothyroidism observed in patients with high $^{99m}$Tc uptake and non-hormonal iodine levels and undetectable or low titers of TgAb and TPOAb can be reversed, and we recommend starting thyroid hormone replacement therapy in those who are considered to have advanced Hashimoto's thyroiditis and history of infrequent ingestion of iodine-containing foods.

## References


1. Tajiri J, Higashi K, Morita M, Umeda T, Sato T 1986 Studies of hypothyroidism in patients with high iodine intake. J Clin Endocrinol Metab **63:**412–417.
2. Okamura K, Sato K, Ikenoue H, Yoshinari M, Nakagawa M, Kuroda T, Fujishima M 1988 Reevaluation of the thyroidal radioactive iodine uptake test, with special reference to reversible primary hypothyroidism with elevated thyroid radioiodine uptake. J Clin Endocrinol Metab **67:**720–726.
3. Sato K, Okamura K, Yoshinari M, Kuroda T, Ikenoue H, Okazawa K, Mizokami T, Onoyama K, Fujishima M 1992 Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. Acta Endocrinol (Copenh) **126:**253–259.
4. Konno N, Yuri K, Taguchi H, Miura K, Taguchi S, Hagiwara K, Murakami S 1993 Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations. Clin Endocrinol (Oxf) **38:**273–281.
5. Sato K, Okamura K, Hirata T, Yamasaki K, Ikenoue H, Kuroda T, Mizokami T, Inokuchi K, Fujishima M 1996 Im-

munological and chemical types of reversible hypothyroidism; clinical characteristics and long-term prognosis. Clin Endocrinol (Oxf) **45:**519–528.
6. Braverman LE, Ingbar SH, Vagenakis AG, Adams L, Maloof F 1971 Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. J Clin Endocrinol Metab **32:**515–521.
7. Reinhardt W, Luster M, Rudorff KH, Heckmann C, Petrasch S, Lederbogen S, Haase R, Saller B, Reiners C, Reinwein D, Mann K 1998 Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency. Eur J Endocrinol **139:**14–15.
8. Mizokami Y, Michigishi T, Nonomura A, Hashimoto T, Tonami N, Matsubara F, Takazakura E 1993 Iodine-induced hypothyroidism: A clinical and histological study of 28 patients. J Clin Endocrinol Metab **76:**466–471.
9. Kasagi K, Kousaka T, Higuchi K, Iida Y, Miyamoto S, Yamabe H, Konishi J 1996 Clinical significance of measurements of antithyroid antibodies in the diagnosis of Hashimoto's thyroiditis; comparison with histological findings. Thyroid **6:**445–450.
10. Southgate K, Creagh F, Teece M, Kingswood C, Rees Smith B 1984 A receptor assay for the measurement of TSH receptor antibodies in unextracted serum. Clin Endocrinol (Oxf) **20:**539–548.
11. Kasagi K, Hidaka A, Nakamura H, Takeuchi R, Misaki T, Iida Y, Konishi J 1993 Thyrotropin receptor antibodies in hypothyroid Grave's disease. J Clin Endocrinol Metab **75:**504–508.
12. Sherwin JR, Tong W 1975 Thyroidal autoregulation. Iodide-induced suppression of thyrotropin-stimulated cyclic AMP production and iodinating activity in thyroid cells. Biochim Biophys Acta **404:**30–39.
13. Bagchi N, Brown TR, Urdanivia E, Sundick RS 1985 Induction of autoimmune thyroiditis in chickens by dietary iodine. Science **230:**325–327.
14. Allen EM, Appel MC, Braverman LE 1986 The effect of iodide ingestion on the development of spontaneous lymphocytic thyroiditis in the diabetes-prone BB/W rat. Endocrinology **118:**1977–1981.
15. Sundick RS, Herdegen DM, Brown TR, Bagchi N 1987 The incorporation of dietary iodine into thyroglobulin increases its immunogenicity. Endocrinology **120:**2078–2084.
16. Gardner DF, Centor RM, Utiger RD 1988 Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol (Oxf) **28:**283–288.
17. Paul T, Meyers B, Witorsch RJ, Pino S, Chipkin S, Ingbar SH, Braverman LE 1988 The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism **37:**121–124.
18. Namba H, Yamashita S, Kimura H, Yokoyama N, Usa T, Otsuru A, Izumi M, Nagataki S 1993 Evidence of thyroid volume increase in normal subjects receiving excess iodide. J Clin Endocrinol Metab **76:**605–608.
19. Suzuki H, Higuchi T, Sawa K, Ohtaki S, Horiuchi Y 1965 Endemic goiter in Hokkaido, Japan. Acta Endocrinol (Copenh) **50:**161–176.
20. Kasagi K, Hidaka A, Endo K, Miyamoto S, Takeuchi R, Misaki T, Sakahara H, Konishi J 1993 Fluctuating thyroid function depending on the balance between stimulating and blocking types of TSH receptor antibodies: A case report. Thyroid **3:**315–318.
21. Torizuka T, Kasagi K, Hatabu H, Misaki T, Iida Y, Konishi J, Endo K 1993 Clinical diagnostic potentials of thyroid ultrasonography and scintigraphy: An evaluation. Endocr J **40:**329–336.

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2. Christos Zois, Ioanna Stavrou, Eugenia Svarna, Konstantinos Seferiadis, Agathocles Tsatsoulis. 2006. Natural Course of Autoimmune Thyroiditis After Elimination of Iodine Deficiency in Northwestern Greece. *Thyroid* **16**:3, 289-293. [Abstract] [PDF] [PDF Plus]