

Analysis of the Factors Associated with Tc-99m Pertechnetate Uptake in Thyrotoxicosis and Graves' Disease

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Abstract

To determine the factors associated with 20 minute Tc-99m pertechnetate thyroid uptake, we examined all patients in whom thyrotoxicosis was diagnosed at Chiba-Hokusoh Hospital, Nippon Medical School from 2001 April through 2003 March. Patients with thyrotoxicosis diagnosed during this period were 57 with Graves' disease (76%), 11 with transient hyperthyroxinemia (TH) (14.7%), and 7 with subacute thyroiditis (SAT) (9.3%). The uptake of Tc-99m ranged from 0.97% to 40.1% in Graves' disease and from 0.15% to 0.8% in TH. Although TH may include spontaneous resolution of Graves' disease as well as painless thyroiditis, no treatment was necessary for these patients. Uptake in all patients with SAT was less than 0.5%. There were significant correlations between the level of Tc-99m uptake and the levels of free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH)-binding inhibitory immunoglobulin (TBII), and thyroid stimulating antibody (TSAb) in patients with Graves' disease. Older patients with Graves' disease showed lower uptake than did younger patients. Both Tc-99m pertechnetate uptake and TBII levels, but not fT3, fT4 or TSAb levels, at the beginning of antithyroid drug treatment correlated significantly with the duration of treatment until the daily dose of methimazole reached 5 mg. These data suggest that Tc-99m pertechnetate uptake reflects the severity of Graves' disease and its response to the medical treatment and that antithyroid drug therapy is not necessary when the uptake is less than 0.9%.

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Key words: Tc-99m pertechnetate, thyrotoxicosis, Graves' disease, painless thyroiditis, subacute thyroiditis

Introduction

Since the 1970s, the radionuclide Tc-99m pertechnetate has been used in thyroid-uptake studies and for thyroid imaging¹⁻⁵. Although the thyroid does not organify Tc-99m pertechnetate, the

uptake and imaging data provides important diagnostic information⁶.

The differentiation of Graves' disease from destructive thyroiditis is important because antithyroid drugs used to treat Graves' disease can have severe side effects, such as agranulocytosis and liver dysfunction. Although it has been generally

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acknowledged that Tc-99m pertechnetate uptake is a useful way to distinguish Graves' disease from destructive thyroiditis, there are no established absolute criteria for making such a diagnosis. It has been generally accepted that each clinical laboratory should establish its own criteria to define the normal range, because the degree of Tc-99m pertechnetate uptake depends on the technique used^{4,7}. However, Tc-99m pertechnetate uptake in patients with hyperthyroidism may be within the normal range⁷⁻¹⁰.

In the present study, we determined Tc-99m pertechnetate thyroid uptake in all patients with thyrotoxicosis who visited Chiba-Hokusoh Hospital, Nippon Medical School in Japan from 2001 April through 2003 March, to establish criteria for our laboratory and we analyzed various factors associated with Tc-99m pertechnetate thyroid uptake in Graves' disease.

Materials and Methods

Patients

From 2001 April through 2003 March, all patients who were found to have thyrotoxicosis at Chiba-Hokusoh Hospital, Nippon Medical School in Japan were examined with the Tc-99m thyroid uptake test. Patients with thyrotoxicosis diagnosed in this period were 57 with Graves' disease (76%) (45 women and 12 men ages 19 to 71 years, mean age, 42 years), 11 with transient hyperthyroxinemia (TH) (14.7%), and 7 with subacute thyroiditis (SAT) (9.3%). A diagnosis of Graves' disease was based on a positive thyroid-stimulating hormone (TSH)-binding inhibitory immunoglobulin (TBII) test or thyroid-stimulating antibody (TSAb), and/or clinically obvious Graves' ophthalmopathy. Patients with SAT exhibited the characteristic features of thyrotoxicosis, pain, tenderness, elevated C-reactive protein (CRP), and ultrasonographic findings. Patients with thyrotoxicosis but without any findings of Graves' disease were given a tentative diagnosis of possible TH including painless thyroiditis, pending confirmation by a self-limiting course without treatment of less than 3 months. The diagnosis of one patient was changed from TH to Graves' disease because of a gradual worsening of hyperthyroidism



Fig. 1 Tc-99m thyroid scintigram in a patient with Graves' disease. Procedure used for determining Tc-99m 20-minute thyroid uptake is described in the text.

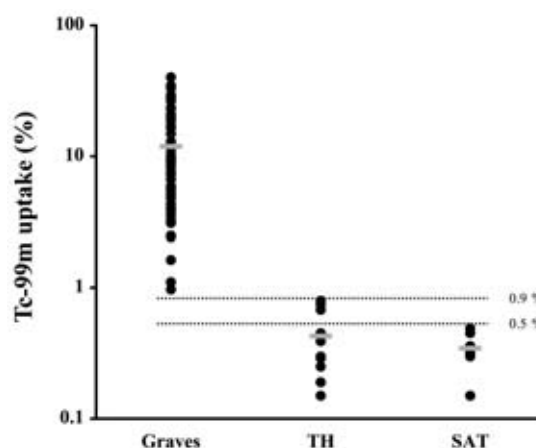


Fig. 2 Twenty minute distribution of Tc-99m thyroid uptake in subjects with Graves' disease (Graves), transient hyperthyroxinemia (TH), and subacute thyroiditis (SAT). Graves: range 0.97% ~ 40.1% (mean \pm SD; 11.87 ± 9.44), TH: 0.15% ~ 0.8% (0.42 ± 0.22), SAT: 0.15% ~ 0.5% (0.34 ± 0.11).

in the ensuing 3 months. The Tc-99m pertechnetate uptake in this patient was 0.97%.

Laboratory Assessment

The laboratory assessment of thyroid function was obtained by measuring serum levels of free thyroxine (fT4), free triiodothyronine (fT3), TSH, TBII, and TSAb before and during therapy. Levels of TSH, fT3 and fT4 were measured with automated chemiluminescence analysis (Kyowa Medex, Tokyo,

Table 1 Clinical data of three patients with transient hyperthyroxinemia and relatively high (more than 0.5%) TC-99m uptake

Case	Sex	Age	Date	Tc-99m uptake (%)	TSH (μ IU/ml)	fT3 (pg/ml)	fT4 (ng/dl)
					Normal 0.49 ~ 4.67	Normal 1.92 ~ 3.38	Normal 0.71 ~ 1.85
1	M	46	01.06.30	0.8	<0.10	4.9	1.9
			01.07.03				
			01.08.04		32.66	1.5	0.6
			01.09.22		7.57	1.8	1.2
			01.12.15		8.12	2.1	1.0
2	M	56	02.04.20	0.75	<0.10	4.7	1.9
			02.06.06		<0.10	2.5	0.9
			02.07.02		3.19	2.9	0.8
3	M	72	03.03.26	0.68	<0.10	4.1	1.3
			03.04.02		<0.10	3.6	1.5
			03.05.01		<0.10	3.5	1.3
			03.05.14		<0.10	3.0	1.1
			03.05.31		<0.10	2.6	1.0
			03.06.18		<0.10	1.9	0.8
			03.09.24		<0.10	2.3	1.1

Japan). TBII was measured as TSH-binding inhibitory activity in a radioreceptor assay system using porcine TSH receptors (Cosmic III kit; Cosmic Corporation, Tokyo, Japan) and TSAb titers were assessed with a TSAb assay kit (Yamasa Corporation, Tokyo, Japan) that measures cyclic adenosine monophosphate (cAMP) production by porcine thyroid cells¹¹.

Tc-99m Pertechnetate Uptake

Tc-99m pertechnetate uptake was examined on the day of or within 1 week of the diagnosis of thyrotoxicosis. All patients were allowed to eat a normal diet. Thyroid scintigraphy was performed 20 minutes after intravenous injection of 370 MBq (10 mCi) of Tc-99m pertechnetate using a scintillation camera equipped with a low-energy, high-resolution, parallel-hole collimator (PRISM 2000, Philips Electronics Japan, Tokyo, Japan). Images of the syringe were also obtained before and after radiopharmaceutical injection. The number of counts present in the thyroid was determined by outlining a manual region of interest (ROI) drawn around the borders of the gland. Another ROI was drawn on the right side of the chest for background subtraction (**Fig. 1**). Uptake was calculated with the

following equation on the basis of thyroid and syringe counts corrected for acquisition time and the decay of Tc-99m and is expressed as a percentage of the administered dose:

TC = counts in thyroid ROI,

TP = thyroid ROI pixels

BC = counts in background ROI,

BP = background ROI pixels

IC = corrected injection counts

$$\text{Tc-99m uptake (\%)} = (\text{TC} - \text{BC} \times \text{TP}/\text{BP}) \times 100 / \text{IC}$$

Statistical Analysis

Statistical comparisons were performed using StatView 4.5 software (Abacus Concepts, Inc., Berkeley, CA, USA). Correlation analyses were performed using Pearson's correlation. A P value of < 0.05 was considered to indicate significance.

Results

Fig. 2 shows the distribution of Tc-99m thyroid uptake after 20 minutes in subjects with Graves' disease, TH, and SAT. Uptake in patients with Graves' disease ranged from 0.97% to 40.1% (mean \pm SD, 11.87 \pm 9.44). Uptake in all patients with SAT was

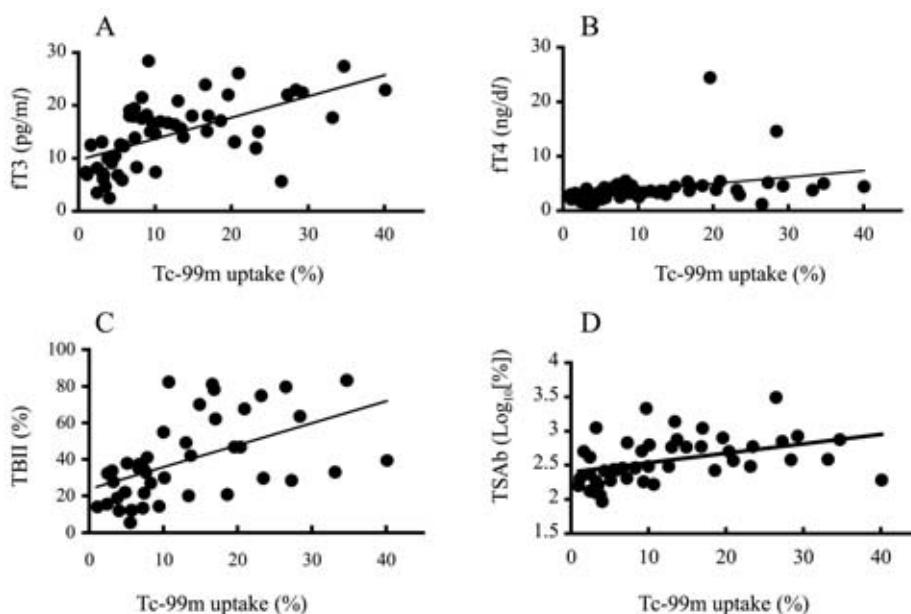


Fig. 3 Correlation of Tc-99m uptake with fT3 (A: $r=0.593$, $p<0.0001$, $n=55$), fT4 (B: $r=0.334$, $p<0.05$, $n=56$), TBII (C: $r=0.608$, $p<0.0001$, $n=42$), and TSAbs (D: $r=0.414$, $p<0.01$, $n=48$) in patients with Graves' disease.

less than 0.5% (0.34 ± 0.11). Uptake in patients with TH ranged from 0.15% to 0.8% (0.42 ± 0.22). TH may include painless thyroiditis, spontaneous resolution of Graves' disease, and other unknown mechanisms. **Table 1** shows the clinical data of three patients with TH in whom uptake was relatively high (more than 0.5%). Of these patients, patient 3 showed relapse of thyrotoxicosis with an uptake of 1.7% 2 years later (2005 January) and a gradual worsening of hyperthyroidism thereafter. Graves' disease was diagnosed in 2005, but it is unknown whether the mechanism of thyrotoxicosis in 2003 was hyperthyroidism or destructive thyroiditis.

To clarify which factors are correlated with Tc-99m uptake in Graves' disease, we examined the correlation between Tc-99m thyroid uptake and the levels of various factors obtained from in vitro thyroid function tests. **Fig. 3** shows the correlations between Tc-99m thyroid uptake and serum levels of fT3, fT4, TBII, and TSAbs at the time of diagnosis. Tc-99m uptake correlated significantly with each of these factors: fT3 ($r=0.593$, $p<0.0001$), fT4 ($r=0.334$, $p<0.05$), TBII ($r=0.608$, $p<0.0001$), and TSAbs ($r=0.414$, $p<0.01$). As for clinical factors not associated with thyroid function, age was found to correlate with Tc-99m thyroid uptake in patients with Graves'

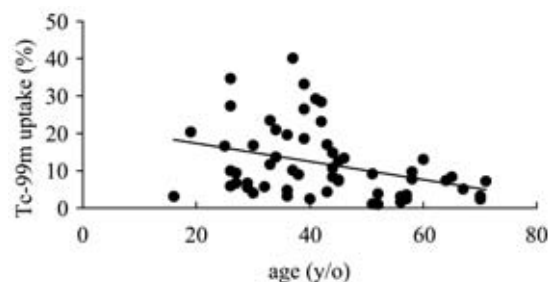


Fig. 4 Correlation between Tc-99m uptake and age in patients with Graves' disease ($r=-0.349$, $p<0.01$, $n=57$).

hyperthyroidism, as shown in **Fig. 4** ($r=-0.349$, $p<0.01$). Older patients showed lower uptake than did younger patients.

We examined whether Tc-99m uptake is a predictive factor for treatment outcome in patients with Graves' disease. Thirty-one patients were monitored for more than 2 years. Patients were initially treated with 30 mg of methimazole per day, then the doses were adjusted to achieve normal serum concentrations of fT3, fT4, and TSH; a similar protocol has been reported by Kashiwai et al.¹² of methimazole at the end of the two year treatment period. The patients were divided into three groups according to the daily dose of methimazole (none, 2.5

Table 2 The number of patients in each group after two year of treatment

	none	$2.5 \leq \text{MMI} \leq 5\text{mg}$	$5\text{mg} < \text{MMI}$	others
number of subjects	4	16	8	3

Patients were divided into four groups according to the dose of methimazole (MMI) they were taking at the end of their two year treatment. (others: converted to operation or radioiodine treatment)

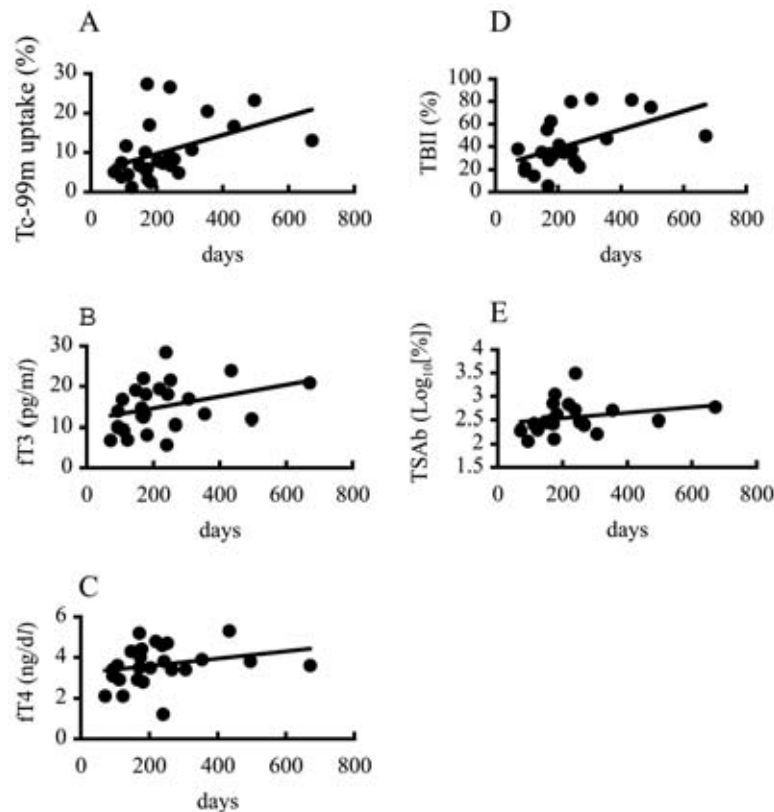


Fig. 5 Correlation between the duration (number of days) of treatment until the daily dose of methimazole reached 5 mg and Tc-99m uptake (A: $r=0.443$, $p<0.05$, $n=26$), fT3 (B: $r=0.349$, $p=0.088$, not significant, $n=25$), fT4 (C: $r=0.251$, $p=0.22$, not significant, $n=27$), TBII (D: $r=0.527$, $p<0.05$, $n=22$), and TSAb (E: $r=0.096$, $p=0.68$, not significant, $n=21$) at the beginning of treatment.

mg or 5 mg, more than 5 mg) at the end of the 2-year treatment period (Table 2). We compared the results of thyroid function test at the beginning of the treatment between the three groups. The levels of Tc-99m uptake, fT3, fT4, TBII, and TSAb at the beginning of the treatment period were not significantly different between the three groups (data not shown). We next examined the correlation between the duration of treatment until the daily dose of methimazole was reduced to 5 mg and thyroid functions, including Tc-99m uptake at the

beginning of the treatment period. As shown in Fig. 5, the duration of treatment until the dose reached 5 mg was correlated with the levels of Tc-99m uptake ($r=0.443$, $p<0.05$) and TBII ($r=0.527$, $p<0.05$) at the beginning of the treatment period, but was not correlated with the levels of fT3, fT4 or TSAb.

Discussion

It is not always easy to establish a definitive diagnosis of thyrotoxicosis, especially if the patient

does not exhibit ophthalmopathy. Furthermore, painless thyroiditis can occur in patients with Graves' disease^{13,14}. Radioactive iodine uptake measurements are used to differentiate transient painless thyroiditis from Graves' disease.

The pertechnetate ion is transported into thyroid tissue by the thyroid iodide-concentrating mechanism, presumably because it has the same charge and is the same size as iodide. Unlike iodide, however, it is not metabolized and, therefore, quickly diffuses out of thyrocytes. Tc-99m, which has been used worldwide to study thyroid function, has several advantages, including its short half-life (6 hours), short residence time in the gland, and absence of β -emission^{1-6,15}. Measurements of thyroid Tc-99m uptake coupled with scintigraphic images of the gland provides valuable diagnostic information in patients with hyperthyroidism¹⁶.

An important factor that determines Tc-99m uptake, as with radioiodine, is iodine intake. Reinhardt et al. have reported that pertechnetate uptake is reduced to basal levels independent of the TSH concentration, when iodine excretion exceeds 500 $\mu\text{g/g}$ creatinine¹⁷. According to a recent study, the median levels of urinary iodine in Japanese schoolchildren and adults are 362.6 $\mu\text{g/l}$ and 612 $\mu\text{g/l}$, respectively^{18,19}. In the present study, we examined Tc-99m uptake in patients who were not subject to iodine restriction. In such patients, pertechnetate uptake should be reduced. Furthermore, Tc-99m uptake in patients with Graves' disease may be within the normal range^{9,10}. Nevertheless, Graves' disease could be distinguished from TH on the basis of Tc-99m uptake in our study. On the other hand, as shown by patient 3 (**Table 1**), it is difficult to differentiate spontaneous resolution of Graves' disease from painless thyroiditis. We believe immediate medical treatment is not necessary for such a patient. Therefore, our results suggest that iodine restriction and the establishment of a normal range are not necessary, at least for treatment decision. We have demonstrated that Tc-99m thyroid uptake can be examined without iodine intake restriction immediately after diagnosis of thyrotoxicosis and that differential diagnosis can be performed in 20 minutes. Tc-99m is readily available

in most hospitals and has clear advantages over I-123.

For reasons that are unclear, all patients with SAT showed Tc-99m uptake of less than 0.5%, whereas some patients with TH showed Tc-99m uptake of more than 0.5%. The Tc-99m uptake did not correlate with levels of fT3 or fT4 in patients with TH, and in patients with SAT the levels of fT3 and fT4 were not significantly different from those in patients with TH or SAT. It has been reported that Tc-99m uptake in painless thyroiditis, which is included in TH and SAT, is usually markedly reduced^{9,20}, but in the case of SAT uptake is not always suppressed²¹. The reason for this apparent discrepancy is unknown. Further studies including larger numbers of patients may be needed.

Age is a factor influencing radioiodine uptake in patients with Graves' hyperthyroidism. In one study, 24-hour uptake fell within the normal range in 15% of patients younger than 65 years and in 27% of those older than 65 years²². In a study of 18 patients older than 75 years, 24-hour uptake was normal in 5 patients²³. In the present study, we showed that Tc-99m uptake correlates with age in Graves' hyperthyroidism, i.e., uptake was lower in older subjects with Graves' disease. Although there is a possibility that thyroid weight²⁴ could be a factor in the effect of age, this is, to our knowledge, the first report demonstrating a significant correlation of the uptake with age.

In the present study, the factors associated with Tc-99m uptake in patients with Graves' disease were analyzed. We found significant correlations between Tc-99m uptake and serum levels of fT3, fT4, TBII, and TSAb at the beginning of the treatment period. These findings indicate that Tc-99m uptake reflects the severity of disease at this time to a degree similar to that seen with iodine uptake²⁵. Why Tc-99m thyroid uptake TBII correlates more strongly with TBII than TSAb is unknown, but this phenomenon is compatible with other reports^{9,24,26}. We have also demonstrated that uptake is correlated with a patient's response to methimazole. The time (number of days) required to taper the daily dose of methimazole to 5 mg was correlated significantly with Tc-99m uptake at the beginning of

treatment. It has been suggested that radioiodide or Tc-99m uptake could be used to predict a patient's responsiveness to antithyroid medication^{9,27}, although there have not been any reports to date which have demonstrated this, as we have done in this study. Pretreatment levels of fT3 and fT4 did not correlate with the time required to reduce the daily dose of methimazole to 5 mg. TBII levels were found to correlate with the number of days needed for patients to reach a methimazole dose of 5 mg, whereas TSAb levels did not. It has generally been acknowledged that it is unclear whether there is a correlation between pretreatment serum TSH receptor antibody values and treatment outcome^{12,28}.

Our data suggest that the determination of Tc-99m thyroid uptake is useful for the differential diagnosis of thyrotoxicosis and that neither establishing a normal range of Tc-99m uptake nor iodine intake restriction are necessary for this determination. The measurement of Tc-99m uptake has a lot of advantages over the use of iodide for the diagnosis of Graves' disease; it can be determined immediately after the diagnosis of thyrotoxicosis, and can indicate both the severity of disease and the effect of treatment.

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