

Correlation between $^{99m}\text{TcO}_4^-$ Thyroid Scintigraphy and Blood Test in Primary Hyperthyroidism

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Abstract

Background: The $^{99m}\text{TcO}_4^-$ thyroid scintigraphy is commonly used for hyperthyroidism diagnosis. Uptake value of $^{99m}\text{TcO}_4^-$ on thyroid scintigraphy is an indicator of hyperthyroidism activity. Although, the correlation between free T3 value and free T4 value is not necessary clear in primary hyperthyroidism. **Introduction:** This study investigated the correlation between results of blood test and uptake of $^{99m}\text{TcO}_4^-$ on thyroid scintigraphy in primary hyperthyroidism. **Methodology:** In this retrospective study, uptake was calculated in patients diagnosed with primary hyperthyroidism (Graves' disease/Basedow's disease) based on clinical findings, blood tests, thyroid ultrasound, and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy (uptake $\geq 3\%$) at St. Marianna University School of Medicine Hospital between 1 January 2010 and 31 December 2019. This uptake of $^{99m}\text{TcO}_4^-$ was compared with results of blood tests. **Results:** Fifty-four consecutively arriving patients at the hospital (12 men, 42 women; mean age 43.0 ± 14.0 years) were selected. Free T3 ($n = 54$) was 14.6 ± 6.8 pg/mL, free T4 ($n = 53$) was 5.0 ± 2.3 ng/mL, and uptake on thyroid scintigraphy was $10.0\% \pm 7.1\%$. The correlation coefficients were 0.60 ($p < 0.01$) between free T4 (all case), 0.39 ($p < 0.01$) between free T4 (under 7 ng/mL), 0.12 ($p = 0.70$) between free T4 (above 7 ng/mL) and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy uptake. **Conclusion:** In primary hyperthyroidism (Graves' disease), there is a correlation between free T4 value and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy uptake, but there is no correlation in patients with high free T4 level.

Keywords

Graves' Disease/Basedow's Disease, $^{99m}\text{TcO}_4^-$ Thyroid Scintigraphy, Free T3,

1. Introduction

Hyperthyroidism is a disease characterized by abnormally high levels of thyroid hormone secretion. It is caused either by Graves' disease (Basedow's disease) or by overactive thyroid nodules. However, Graves' disease is responsible for the majority of cases. In Japan, Graves' disease is diagnosed using the "Guidelines for the diagnosis of thyroid disease, 2010," published by the Japan Thyroid Association [1]. As recommended in the guidelines, the measurement of thyroid uptake of radionuclide is used in the diagnosis of Graves' disease. In Japan, ^{123}I and $^{99\text{m}}\text{TcO}_4^-$ are currently used for thyroid scintigraphy. ^{123}I is an iodine radionuclide that is incorporated as a component of thyroid hormone after being absorbed into the thyroid gland, in the same way as non-radioactive iodine. $^{99\text{m}}\text{TcO}_4^-$ behaves in a similar way to iodine and is also absorbed into the thyroid gland [2]. However, unlike ^{123}I , it is not incorporated as a component of thyroid hormone [2], and therefore, does not reflect the organification of iodine. Although $^{99\text{m}}\text{TcO}_4^-$ does not reflect true iodine metabolism in the same way as ^{123}I , the use of $^{99\text{m}}\text{TcO}_4^-$ does not require the same preparatory procedures as ^{123}I , such as dietary iodine restriction [2]. A further advantage of $^{99\text{m}}\text{TcO}_4^-$ is that the patient can be scanned 30 minutes after administration, and the test can thus be completed shortly after administration, whereas imaging with ^{123}I is typically performed 24 hours after administration [2]. Thus, $^{99\text{m}}\text{TcO}_4^-$ thyroid scintigraphy is more convenient. The reference value for uptake of $^{99\text{m}}\text{TcO}_4^-$ is set at 0.4% to 3% [2]. In addition to its use in diagnosis, the usefulness of $^{99\text{m}}\text{TcO}_4^-$ uptake as a predictor of responsiveness to drug treatments [3] and of responsiveness to ^{123}I treatment [4] [5] has also been reported. $^{99\text{m}}\text{TcO}_4^-$ thyroid scintigraphy is, thus, useful when diagnosing, as well as, when treating thyroid disease. There are reports of $^{99\text{m}}\text{TcO}_4^-$ uptake correlating with free T3, free T4, and TSH receptor antibody [6].

Free T4 value is an indicator for initial methimazole (MMI) dose, and in patients with free T4 ≥ 7 ng/mL, 30 mg/day of MMI is recommended [7]. However, the association between free T4 value and activity of Graves' disease remains unclear. The aim of this study was to further investigate the correlation between blood test results and uptake of $^{99\text{m}}\text{TcO}_4^-$ on thyroid scintigraphy in primary hyperthyroidism.

2. Methods

2.1. Study Design and Sample Selection

This was a single-center, retrospective, observational study.

The study involved patients diagnosed with primary hyperthyroidism (Graves' disease) based on clinical findings, blood tests, thyroid ultrasound, and $^{99\text{m}}\text{TcO}_4^-$

thyroid scintigraphy (uptake $\geq 3\%$) at St. Marianna University School of Medicine Hospital between 1 January 2010 and 31 December 2019.

2.2. Blood Tests

The following laboratory parameters were measured at time of diagnosis and the results examined: WBC count, RBC count, hemoglobin, platelet count, TP, ALB, LDH, ALP, Na, K, Cl, Ca, blood glucose, HbA1c, neutral lipids, LDL-C, HDL-C, free T3, free T4, TSH, TSH receptor antibody, anti-thyroglobulin antibody, and thyroglobulin.

2.3. Ultrasound Scans

The thyroid volume was visually evaluated, and blood flow measured using thyroid ultrasound, at the time of diagnosis. The results were later examined and compared.

2.4. Thyroid Scintigraphy

Uptake and area on planar thyroid scintigraphy images were taken 10 to 20 minutes after intravenous administration of $^{99m}\text{TcO}_4^-$ at around 185 MBq (suitably adjusted using body weight $\times 3$ MBq as a guide) and results examined. The scintillation cameras used were ECAM and GX7200 (Canon/Toshiba Medical Systems Corporation, Nasu, Japan).

2.5. Statistical Analysis

The correlations between uptake on thyroid scintigraphy and blood test results were evaluated. Correlation coefficients were assessed using Spearman's rank correlation coefficient. We used EZR (Easy ZR), developed by Jichi Medical University, Saitama Medical center (Omiya Medical center) for statistical analysis, and the significance level was set at $p < 0.05$.

2.6. Ethical Considerations

This study was conducted with the approval of the Ethics Committee of St. Marianna University, School of Medicine (4779). The patients had the option to opt-out of the study using the "opt-out" facility on the hospital homepage and in the hospital.

3. Results

3.1. Patients

Fifty-four consecutively arriving patients at the hospital were selected; 12 were men, 42 were women, and their mean age was 43.0 ± 14.0 years (Table 1).

3.2. Blood Test Results

- Blood counts

The WBC count ($n = 51$) is $6156 \pm 3301/\mu\text{L}$, the RBC count ($n = 51$) is $4.4 \pm$

$0.6 \times 10^6/\mu\text{L}$, hemoglobin (n = 51) is 12.4 ± 1.8 g/dL, and the platelet count (n = 51) is $20.6 \pm 5.6 \times 10^4/\mu\text{L}$ (Table 1).

- Biochemistry

TP (n = 45) is 6.7 ± 0.6 g/dL, ALB (n = 37) is 3.8 ± 0.4 g/dL, LDH (n = 48) is 163 ± 28.1 IU/L, ALP (n = 48) is 385.6 ± 263 IU/L, Na (n = 51) is 140 ± 2.0 mEq/L, K (n = 51) is 4.1 ± 0.3 mEq/L, Cl (n = 51) is 105 ± 1.9 mEq/L, Ca (n = 26) is 8.9 ± 1.8 mg/dL, LDL-C (n = 38) is 66.0 ± 22 mg/dL, HDL-C (n = 38) is

Table 1. Patients' demographic characteristics.

Factor	Result
Patients	54
Sex	12 men, 42 women
White blood cell count	$6156 \pm 3301/\mu\text{L}$
Red blood cell count	$4.4 \pm 0.6 \times 10^6/\mu\text{L}$
Hemoglobin	12.4 ± 1.8 g/dL
Platelet count	$20.6 \pm 5.6 \times 10^4/\mu\text{L}$
TP	6.7 ± 0.6 g/dL
ALB	3.8 ± 0.4 g/dl
LDH	163 ± 28.1 IU/L
Na	140 ± 2.0 mEq/L
K	4.1 ± 0.3 mEq/L
Cl	105 ± 1.9 mEq/L
Ca	8.9 ± 1.8 mg/dL
LDL-C	66.0 ± 22 mg/dL
HDL-C	47.9 ± 16.0 mg/dL
TG	81.0 ± 45.2 mg/dL
BS	111.3 ± 16.9 mg/dL
HBA1c (NGSP)	$6.0\% \pm 0.9\%$
Free T3	14.6 ± 6.8 pg/mL
Free T4	5.0 ± 2.3 ng/mL
TSH	0.01 ± 0.0 $\mu\text{IU/mL}$
Thyroglobulin antibody	393.0 ± 256 IU/mL
Thyroglobulin	198.0 ± 256.0 ng/mL
TSH receptor antibody	14.2 ± 17.5 IU/L
Thyroid scintigraphy	Uptake $10.0\% \pm 7.1\%$ Area 43.8 ± 12.1 cm^2
Thyroid ultrasound (blood flow)	42 patients with increase 8 patients with no increase
Thyroid ultrasound (swelling)	39 patients with enlargement 10 patients with no enlargement

47.9 ± 16.0 mg/dL, TG (n = 37) is 81.0 ± 45.2 mg/dL, BS (n = 54) is 111.3 ± 18.7 mg/dL, and HbA1c (NGSP) (n = 24) is 6.0% ± 0.9% (**Table 1**).

- **Thyroid**

Free T3 (n = 54) is 14.6 ± 6.8 pg/mL (reference value 2.39 - 4.06 pg/mL), free T4 (n = 53) is 5.0 ± 2.3 ng/mL (reference value 0.76 - 1.65 ng/mL), and TSH receptor antibody (n = 54) is 14.2 ± 17.5 IU/L (reference value ≤ 2 IU/L). Thyroglobulin (n = 20) is 198.0 ± 256.0 ng/mL (reference value 0 - 33.7 ng/mL). Thyroglobulin antibody (n = 34) is 393.0 ± 256 IU/mL (reference value ≤ 4.11 IU/mL). TSH (n = 54) is 0.01 ± 0.0 μIU/mL (reference value 0.541 - 4.261 μIU/mL) (**Table 1**).

3.3. Ultrasound Scans

Blood flow was evaluated in 50 patients. The superior thyroid artery showed increased blood flow in 42 patients and no increase in 8 patients.

Thyroid size was evaluated in 49 patients. The thyroid was enlarged in 39 patients and not enlarged in 10 patients (**Table 1**).

3.4. Thyroid Scintigraphy

The uptake on $^{99m}\text{TcO}_4^-$ thyroid scintigraphy was 10.0% ± 7.1%. The uptake was 5.0% ± 3.6% in the right lobe and 5.2% ± 4.10% in the left lobe. The area is 43.8 ± 12.1 cm² (**Table 1**).

3.5. Correlation Coefficients

- **Uptake**

The correlation coefficient for TSH receptor antibody and uptake on $^{99m}\text{TcO}_4^-$ thyroid scintigraphy was 0.48 (p < 0.01). The correlation coefficient for free T3 and uptake on $^{99m}\text{TcO}_4^-$ thyroid scintigraphy was 0.53 (p < 0.01). The correlation coefficients were 0.60 (p < 0.01) between free T4 (all case), 0.39 (p < 0.01) between free T4 (under 7 ng/mL), 0.12 (p = 0.70) between free T4 (above 7 ng/mL) and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy uptake (**Table 2**).

- **Area**

There were no significant correlations with blood test results.

Table 2. The correlation coefficient between $^{99m}\text{TcO}_4^-$ thyroid scintigraphy and blood test.

Factors correlating with $^{99m}\text{TcO}_4^-$ uptake	Correlation coefficients	P value
TSH receptor antibody	0.48	<0.01
Free T3	0.53	<0.01
Free T4 (all case)	0.60	<0.01
Free T4 (under 7 ng/ml)	0.39	<0.01
Free T4 (above 7 ng/ml)	0.12	0.70

4. Discussion

Thyroid scintigraphy in Japan can currently be performed using $^{99m}\text{TcO}_4^-$ and ^{123}I or ^{131}I . A correlation coefficient of 0.88 has previously been reported for test values 20 minutes after $^{99m}\text{TcO}_4^-$ and 24 hours after ^{131}I administration, indicating a strong positive correlation between the two [8]. Recently, the potential of $^{99m}\text{TcO}_4^-$ in predicting ^{131}I uptake in ^{131}I therapy has also been reported [9]. In a study of the correlations between $^{99m}\text{TcO}_4^-$ uptake and free T3, free T4, and TSH receptor antibody, the correlation coefficient was 0.593 ($p < 0.01$) with free T3, 0.334 ($p < 0.01$) with free T4, and 0.414 ($p < 0.01$) with TSH receptor antibody [7]. In a study using SPECT-CT, the correlation coefficient in 17 patients with Graves' disease was 0.492 (but $p > 0.05$) for uptake and free T3 and 0.564 ($p < 0.01$) for uptake and free T4 [10]. In this study, the correlation coefficients were 0.60 ($p < 0.01$) between free T4 (all case), 0.39 ($p < 0.01$) between free T4 (under 7 ng/mL), 0.12 ($p = 0.70$) between free T4 (above 7 ng/mL), and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy uptake. Free T4 value is an indicator for determining MMI dose. For patients with free T4 < 7 ng/mL, 15 mg/day of MMI is recommended, and for those with free T4 ≥ 7 ng/mL, 30 mg/day MMI is recommended [6]. However, in this study, there were no significant value between $^{99m}\text{TcO}_4^-$ uptake and free T4 in T4 ≥ 7 ng/mL group. Moreover, there were statistically significant collation between $^{99m}\text{TcO}_4^-$ uptake and free T4 in T4 < 7 ng/mL group, but the correlation coefficients were small. From these results, we think that T4 value is not necessary reflect the disease activity, and there is a problem about uniform MMI dose setting for patients based on T4 value.

The present study has several limitations. It was a single-center study and thus included a limited number of patients. Recently, a study of standard uptake value (SUV) using SPECT-CT reported that SUVmax and SUV were elevated in Graves' disease, but there were no correlations with free T3 or with free T4 [10]. It has been suggested that this could be because the accumulation of $^{99m}\text{TcO}_4^-$ in tissues, such as in the salivary glands, affects the measurement of uptake on planar imaging that fails to accurately reflect thyroid function [10]. There is, however, a probability that it is not appropriate to evaluate Graves' disease activity using free T4 value. It is therefore possible that studies with SPECT imaging would yield different results to those with planar imaging. There is a need to further investigate $^{99m}\text{TcO}_4^-$ uptake under established imaging conditions in multi-center, prospective clinical studies with a larger number of patients.

5. Conclusion

In primary hyperthyroidism (Graves' disease), there is a correlation between free T4 value and $^{99m}\text{TcO}_4^-$ thyroid scintigraphy uptake, but, there is no correlation in patients with high free T4 level.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

WBC: White Blood Cells

RBC: Red Blood Cells

TP: Total Protein

ALB: Albumin

LDH: Lactate Dehydrogenase

LDL-C: Low-Density Lipoprotein Cholesterol

HDL-C: High-Density Lipoprotein Cholesterol

TG: Triglyceride

BS: Blood Sugar

HBA1c (NGSP): Hemoglobin A1c

T3: Triiodothyronine

T4: Thyroxine

ALP: Alkaline Phosphatase