

Post-Operative Thyroid Status of Patients with Graves' Disease Is Determined by the Responsiveness of Thyrocyte to TSH under the Present Thyroid Gland Remnant

HIROTO YAMASHITA, SHIRO NOGUCHI*, NOBUO MURAKAMI*,
SHIN WATANABE*, AND HITOSHI KAWAMOTO*

Department of Pathology, Oita Medical University, Oita 879-5503, and

*Noguchi Thyroid Clinic and Hospital Foundation, Beppu 874, Japan

Abstract. In order to determine whether thyrocyte responsiveness to TSH is correlated with post-operative thyroid status, thyrocytes obtained from 51 patients with Graves' disease were cultured for 3 days. This was followed by culture with 10 mU/mL of TSH (TSH group) or without TSH (control group) for 3 additional days. On the 8th culture day, the amount of thyroglobulin (Tg) secreted into the culture medium was assayed and the Tg ratio (amount of Tg from the stimulated group/amount of Tg from the control group) was calculated. Log_{10} (the Tg ratio) was used for the statistic study. The post-operative status of the patient was determined based mainly on the serum concentration values of free T3 and T4 obtained between 5 and 16 months after surgery. Multivariate analysis revealed that among age, gender, TSH-binding inhibitory immunoglobulin (TBII) obtained before the surgery, estimated weight of the thyroid gland remnant, and Log_{10} (Tg ratio), only Log_{10} (Tg ratio) was statistically significant ($P=0.008$). When the Log_{10} (Tg ratio) value was small, most patients showed signs of as post-operative hypothyroidism, and as the value became larger as the number of euthyroid and/or hyperthyroid patients increased.

Key words: Graves' disease, Post-operative status, Cell culture, Thyroglobulin

(Endocrine Journal 45: 513–517, 1998)

AT PRESENT, surgery, antithyroid drugs and radioiodine therapy are employed for the treatment of Graves' disease. Each of these methods has advantages and disadvantages. Surgery is the most rapid method, and has a definite advantage over the other treatments.

After surgery, most patients become euthyroid; but in some patients, post-operative hypothyroidism or relapse of hyperthyroidism occurs.

Various factors are important in determining the

post-operative thyroid status. Among these, the size of the thyroid gland remnant is considered to be the main prognostic determinant and it is generally agreed that thyroid gland remnants that are too small or too large cause post-operative hypothyroidism and hyperthyroidism, respectively [1–3], but the optimum size of the thyroid gland remnant which causes all patients to be euthyroid after surgery has not yet been determined [4–7]. Noguchi *et al.* reported that the post-operative status could not be determined by the weight of the present thyroid gland remnant [8].

In a previous study, we reported that cultured thyroid cells obtained from patients with Graves' disease secreted thyroglobulin (Tg) into the culture medium with or without TSH and that the Tg ratio (amount of Tg secreted by the cells cultured with

Received: December 4, 1997

Accepted: April 6, 1998

Correspondence to: Dr. Hiroto YAMASHITA, Department of Pathology, Oita Medical University, 1-1 Idaigaoka, Hasamamachi, Oita-gun, Oita 879-5503, Japan

TSH/without TSH) differed from case to case [9].

In the present study, it was found that the Tg ratio, which has not been considered a post-operative prognostic determinant, was correlated with the post-operative thyroid status more closely than the size of the thyroid gland remnant.

Materials and Methods

Thyroid tissues obtained from patients with Graves' disease who underwent subtotal thyroidectomy at the Noguchi Thyroid Clinic and Hospital Foundation from 1992 to 1994 were used for the present study.

The surgical technique was strictly standardized and intended to leave a from 6 to 8 g thyroid gland remnant [10]. The weight of the thyroid remnant was estimated by weighing a plastic mass of almost the same size as the remnant.

The cell culture was done as reported previously [9]. In brief, for the first three culture days thyroid cells were cultured without TSH, then cultured with 10 mU/ml of TSH (stimulated group) or without TSH (control group) for an additional 3 days, in an atmosphere of 5% CO₂. The culture medium was changed once a day until the 6th culture day. On the 8th culture day, the amount of thyroglobulin and cyclic AMP secreted in the culture medium and the peroxidase (PO) activity of thyrocytes were measured as reported previously [9]. The Tg ratio of the TSH-stimulated to non-stimulated groups was calculated and Log₁₀ (the Tg ratio), which showed a normal distribution (Shapiro-Wilk W test $W=0.970582$, $\text{Prob}<W=0.38$), was used for statistical analysis. Ratios of cAMP and PO activity were calculated in the same manner.

Based mainly on the follow-up data for serum free T₃ (FT₃) and free T₄ (FT₄), the post-operative thyroid status was classified into hypothyroid (low FT₃ and/or FT₄, or receiving thyroid hormone therapy), euthyroid (normal FT₃ and FT₄ without medication) or hyperthyroid (high FT₃ and/or FT₄, or receiving anti-thyroid hormone therapy). In the present study, latent hypothyroid and latent hyperthyroid status were included in the euthyroid category.

In total, 62 thyroid glands were cultured, although 11 of the 62 were followed up for fewer than 5 months after surgery. The data for these

patients were not used because post-operative transit hypothyroidism occurred shortly after surgery [11].

Therefore, the data from 51 patients were used for the present study. The post-operative follow-up period of these patients was 10.7 ± 2.8 months (mean \pm SD) after surgery.

Chi-square test and an ordinal logistic regression model were used for the statistic analysis. In the ordinal logistic regression analysis the probability of hypothyroid status ($\text{Pr}(\text{hypo})$) is calculated as $\text{Pr}(\text{hypo})=1/(1+\exp(-(a_1+\sum b_i \cdot x_i)))$, where a_1 is intercept 1 and b_i is the coefficient for variable x_i . Similarly, the sum of probabilities of hypothyroid and euthyroid status ($\text{Pr}(\text{hypo}+\text{eu})$) is calculated as $\text{Pr}(\text{hypo}+\text{eu})=1/(1+\exp(-(a_2+\sum b_i \cdot x_i)))$, where a_2 is intercept 2 and b_i is the common coefficient for variable x_i .

Informed consent relating to the risk of operation and the use of surgically removed material was obtained from all patients.

Results

Table 1 shows the post-operative thyroid status. During the follow up period, 18 (35%), 29 (57%) and 4 (8%) patients were diagnosed according to the status categories for hypothyroid, euthyroid and hyperthyroid, respectively. The age distribution and sex ratio of the patients were not significantly different among these 3 groups.

Fig. 1 shows the chronological changes in the mean serum TSH concentration in patients before and after surgery. All patients had low preoperative TSH values, but the postoperative TSH concentration was the highest in post-operative hypothyroid patients, high in euthyroid patients, and not increased in post-operative hyperthyroid patients.

Fig. 2 shows the chronological changes in the

Table 1. Thyroid status after subtotal thyroidectomy for Graves' disease

Status	No. of patients	Age (y)	M/F
Hypothyroid	18	30.3 ± 10.4	4/14
Euthyroid	29	30.8 ± 12.7	5/24
Hyperthyroid	4	29.8 ± 8.9	1/3

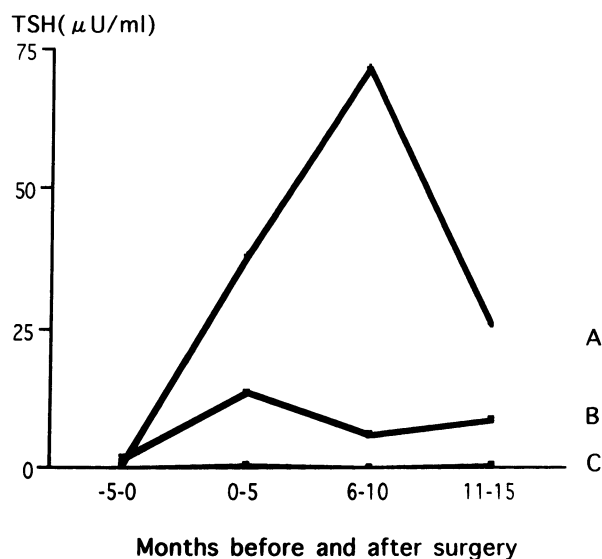


Fig. 1. Chronological change in the mean serum concentration of TSH before and after surgery in patients with post-operative hypothyroidism (A), euthyroidism (B) and hyperthyroidism (C).

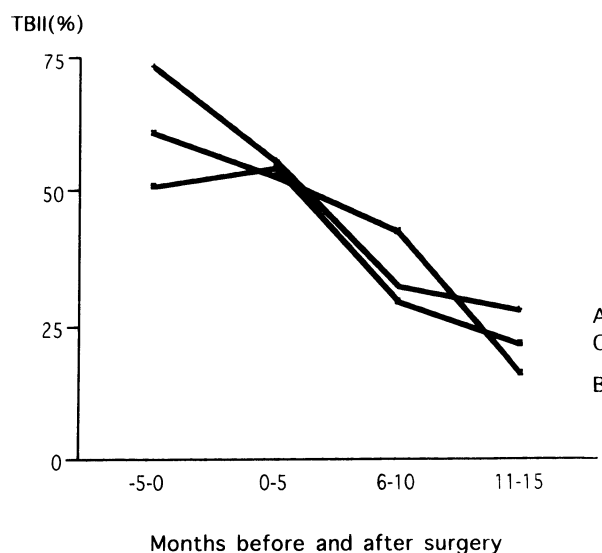


Fig. 2. Chronological change in the mean serum concentration of TBII before and after surgery in patients with post-operative hypothyroidism (A), euthyroidism (B) and hyperthyroidism (C).

mean serum TSH-binding inhibitory immunoglobulin (TBII) in patients before and after surgery. TBII did not seem to be useful in differentiating the post-operative thyroid status.

Fig. 3 shows the logistic regression for post-

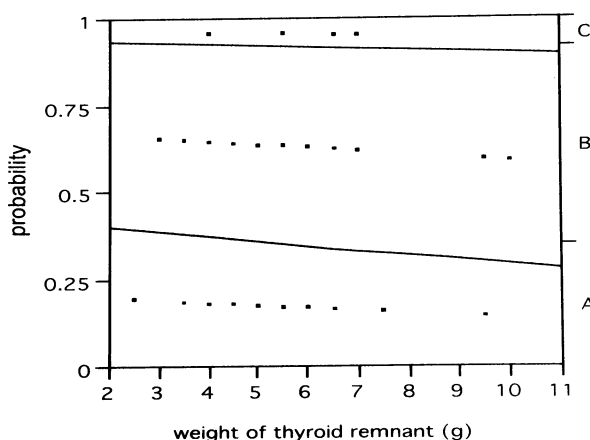


Fig. 3. Logistic regression for post-operative thyroid status (A=hypothyroid, B=euthyroid, C=hyperthyroid) and weight of thyroid remnant (g).

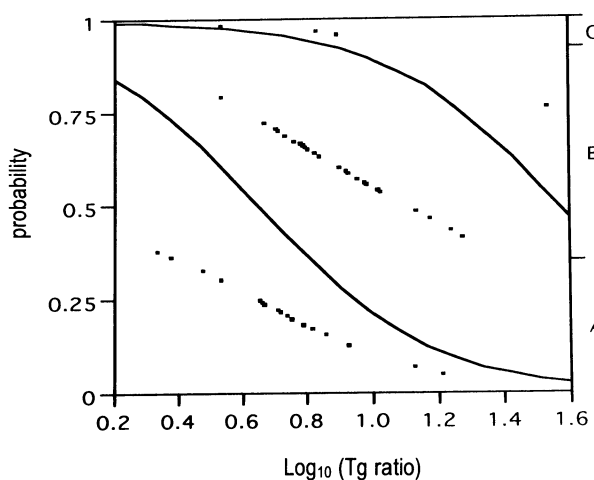


Fig. 4. Logistic regression for post-operative thyroid status (A=hypothyroid, B=euthyroid, C=hyperthyroid) and Log₁₀ (Tg ratio).

operative thyroid status and the estimated weight of the thyroid gland remnant (rem). When the rem was 2 g, the probability of the patient being hypothyroid was about 0.4. Statistically, there was no correlation between the post-operative thyroid status and the rem (probability of whole model test=0.7, values for estimated parameter a1, a2, and b1= -0.28, 2.80 and -0.06, respectively).

Fig. 4 shows the logistic regression for the post-operative state and Log₁₀ (the Tg ratio). When the Tg ratio was 2.0 (Log₁₀ (Tg ratio) =0.3), the probability of the patient being hypothyroid was

75%. As the Log_{10} value (Tg ratio) increased, the probability of being hypothyroid decreased rapidly, but the probability of being euthyroid and/or hyperthyroid increased. A significant relationship existed between the post-operative thyroid status and the Log_{10} value (Tg ratio) (probability of whole mode test=0.005, values for estimated parameter a_1 , a_2 and b_1 were 2.42, 5.8 and -3.76 , respectively).

The ratio of c-AMP or peroxidase activity showed the same tendency as that of the Tg ratio but no statistically significant correlation was found between these ratios and the post-operative thyroid status.

Table 2 shows the result of multivariate analysis with the ordinal logistic regression model. Among the factors for log_{10} (TG ratio), rem, TBII obtained before the operation, gender and age of the patients, only Log_{10} (Tg ratio) was statistically significant ($P=0.008$, 95% confidential interval= $-6.950 \sim -1.136$).

Discussion

In the present study, only 57% (95% confidence interval 42%–71%) of the patients became euthyroid after surgery. This incidence was lower than that reported by Toft *et al.*, who found that 80% were euthyroid 12 months after surgery [11]. In another series reported by the Noguchi Thyroid Clinic and Hospital Foundation, however, 90.6% became euthyroid after surgery [12]. This figure does not differ from data reported by other hospitals [13, 14]. Therefore, the low euthyroid rate observed in the present study might have been due to sampling errors independent of the current hypothesis. The presence of 11 censored cases (most of them were considered to be euthyroid), selection of enlarged thyroid glands to obtain enough amount of thyroid tissue for culture study, and the shortness of the observation periods after the surgery [11] might be related to the higher incidence of post-operative hypothyroidism.

In the present study, the nearly horizontal regression line in Fig. 3 shows that no relationship was found between the estimated weight of the remnant thyroid gland and post-operative thyroid status. Accordingly, within the weight range of the thyroid gland remnants employed in this study,

Table 2. Multivariate analysis (logistic regression model) for post-operative thyroid status

Variable	Chi-square	P value	b	95%CI
Log_{10} (X)	7.02	0.0081	-3.8076	$-6.950 \sim -1.136$
REM	0.00	0.9673	-0.0079	$-0.389 \sim 0.370$
TBII	0.59	0.4430	0.0090	$-0.014 \sim 0.033$
Gender	0.00	0.9463	-0.0259	$-0.790 \sim 0.723$
Age	0.04	0.8489	-0.0051	$-0.058 \sim 0.046$

X, TG ratio; CI, confidential interval. REM, weight of the thyroid gland remnant; TBII, TSH-binding inhibitory immunoglobulin.

the post-operative status could not be determined by the weight of the remnant. This result was identical with that of the previous study [8], although the methods of analysis and the subjects used were different in these two studies.

In contrast, the Tg ratio correlated well with the post-operative thyroid status as shown in Fig. 4. Under the present culture conditions, thyroid cells did not increase [9]. Therefore, the Tg ratio indicates the response of thyrocytes to TSH en masse and the conclusion of the present study is that patients with low-response thyrocytes tended to be hypothyroid. As the response became higher, the patients tended to be euthyroid and/or hyperthyroid. This conclusion clearly explains the post-operative change in the serum TSH concentration. After surgery, not only thyroid tissue but also thyroid stimulating immunoglobulin decreased [13, 15], both causing a decrease in the thyroid hormone level. Therefore, endogenous TSH increases to produce thyroid hormones. If thyrocytes do not respond to TSH, the thyroid hormone level does not increase (hypothyroid state). This results in increasing TSH. Conversely, highly responsive thyrocytes produce an excessive level of thyroid hormones even at subnormal levels of TSH (hyperthyroid state). In this instance, TSH does not increase. In the case of post-operative hyperthyroidism, the presence of other thyroid stimulating factors might be considered [16], but no clear relationship was seen between thyroid stimulating factors and relapse of hyperthyroidism [17, 18].

In the present study, no statistically significant relationship was found between the histology of the thyroid gland and the post-operative status (data not shown). Therefore, only the

responsiveness of thyrocytes to TSH is related to the short-term post-operative thyroid status.

The present study showed that under thyroid surgery conditions today, to estimate the responsiveness of thyrocytes to TSH was necessary to predict the post operative status of patients with hyperthyroidism. But there is no method by which

to know the degree of responsiveness before surgery, which means that we must develop a new laboratory method to predict the post operative status. The mechanism underlying the responsiveness of thyrocytes to TSH requires further study.

References

1. Michie W, Pegg CAS, Bewsher PD (1972) Prediction of hypothyroidism after partial thyroidectomy for thyrotoxicosis. *Br Med J* 1: 13-17.
2. Crile G Jr, McCulleagh EP (1951) The treatment of hyperthyroidism. *Ann Surg* 134: 18-28.
3. Painter NS (1960) The results of surgery in the treatment of toxic goitre. A review of 172 cases. *Br J Surg* 48: 291-297.
4. Feliciano DV (1992) Everything you wanted to know about Graves' disease. *Am J Surg* 164: 404-411.
5. Okamoto T, Fujimoto Y, Obara T, Ito Y, Aiba M (1992) Retrospective analysis of prognostic factors affecting the thyroid functional status after subtotal thyroidectomy for Graves' disease. *World J Surg* 16: 690-696.
6. Takai Y (1995) Clinical evaluations of subtotal thyroidectomy for Graves' disease. *Folia Endocrinol Japon* 71: 27-38 (In Japanese).
7. Chen R, Kurihara H, Masuda T, Takamatsu M (1995) Changes in TSH-receptor antibody (TRAb) levels after thyroidectomy in Graves' disease. *Touhokudaigaku Iryoutankidaigaku Kiyou* 4: 147-152 (In Japanese).
8. Noguchi S, Murakami N, Noguchi A (1981) Surgical treatment for Graves' disease: A long term follow-up of 325 patients. *Br J Surg* 68: 105-108.
9. Yamashita H, Noguchi S, Murakami N, Adachi M, Yasuoka Y, Wakiya S, Kitamura H (1994) Effect of thyroid-stimulating hormone on cultured thyrocytes obtained from patients with Graves' disease and inhibitive effect by sodium iodide: A functional study. *Pathol Int* 44: 827-831.
10. Noguchi S (1985) Operative technique. Subtotal thyroidectomy for Graves' disease (1). *Endocrine Surgery* 1: 321-324 (In Japanese).
11. Toft AD, Irvine WJ, Sinclair I, McIntosh D, Seth J, Cameron EHD (1978) Thyroid function after surgical treatment of thyrotoxicosis. *New Engl J Med* 298: 643-647.
12. Noguchi A, Murakami J, Ito J (1974) Late results after thyroidectomy for hyperthyroidism. *Saisin Igaku* 29: 313-316 (In Japanese).
13. Ito K, Nishikawa Y, Harada T, Suzuki T, Momotani N (1974) A comparative evaluation of the treatment of hyperthyroidism. *Endocrinol Japon* 21: 131-139.
14. Kuma K (1974) Results of surgical treatment for hyperthyroidism. *Gekasyunryou* 31: 154-159 (In Japanese).
15. Mukhtar ED, Smith BE, Pyle SG, Hall R, Vice P (1975) Relation of thyroid-stimulating immunoglobulin to thyroid function and effects of surgery, radioiodine, and antithyroid drug. *Lancet* 1: 713-715.
16. Hedley AJ, Ross IP, Beck JS, Donald D, Albert-Recht F, Michie W, Crooks J (1971) Recurrent thyrotoxicosis after subtotal thyroidectomy. *Br Med J* 4: 258-261.
17. Kuma K, Matsuzaka F, Kobayashi A, Hirai K, Fukata S, Tamai H, Miyauchi A, Sugawara M (1991) Natural course of Graves' disease after subtotal thyroidectomy and management of patients with postoperative thyroid dysfunction. *Am J Med Sci* 302: 8-12.
18. Sugino K, Mimura T, Toshima K, Ozaki O, Ito K (1993) Outcome of surgical treatment for Graves' disease and a correlation between its clinical course and values of TSH receptor antibody (TRAb). *Nippon Geka Gakkai Zasshi* 94: 611-614 (In Japanese).