

Evaluation of Thyroid Function after Bilateral Subtotal Thyroidectomy for Graves' Disease

—A long term follow up of 100 patients—

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One hundred patients who underwent bilateral subtotal thyroidectomy for Graves' disease between January 1980 and September 1984 have been evaluated. The observation period ranged from 5 to 9 years, the average being 6.2 years. Postoperative thyroid function was evaluated with T₃, T₄ and TSH and compared with their clinical manifestations. Eighty-two patients became euthyroid, 14 patients had recurrence and 4 patients developed hypothyroidism. The thyroid hormone level of euthyroid patients were in an unstable state up to 5 years after the operation.

Sixteen variables which might influence the postoperative recurrence and hypothyroidism were analyzed but no statistically significant factors were determined, although recurrences were found frequently in patients over 30 years, the patients with lower infiltration of lymphocytes and absent of fibrosis of thyroid tissue.

The results obtained in the present study suggest that mean 6.0gm of remnant thyroid is suitable for maintaining euthyroidism postoperatively in a majority of patients. In addition, patients should be followed closely for many years and should undergo hormonal determination periodically because recurrence and hypothyroidism can occur at 5 years or more after the operation.

Key Words: Graves' disease, subtotal thyroidectomy, prognostic factor

The goal of treatment in Graves' disease is to make the patient euthyroid with a minimum incidence of recurrence and hypothyroidism.

Although antithyroid drugs, radioactive iodine and surgery are available in the treatment of Graves' disease, none of them is completely satisfactory. Recently, postoperative complications have been considerably reduced

by the effective preoperative preparation and improvements in surgical techniques, and the fatality is now negligible (Behrns and Sakulsky. 1968; Cusick *et al.* 1987; Farneil *et al.* 1981; Heimann and Martinson. 1975; Olsen *et al.* 1970; Palestini *et al.* 1975). There are, however, considerable variations in outcome of the surgery depending on reporters. The incidence of recurrence ranges from one to eighteen percent and postoperative hypothyroidism from two to forty-nine percent (Cusick *et al.* 1987; Heimann and Martinson. 1975; Caswell and Maier. 1972; Harada *et al.* 1984; Maier *et al.* 1984; Ozoux *et al.* 1988; Palestini *et al.* 1985). The reasons for this widespread discrepancy is not clarified. Various factors have been speculated to predict the postoperative outcome, however, none of them appears to be decisive. In this series, we tried to evaluate

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the status more than 5 years after the surgery, and on the basis of these results, studied various factors which might affect the postoperative thyroid functions.

MATERIALS AND METHODS

One hundred patients who underwent operation for Graves' disease from January 1980 to September 1984 at Yonsei University College of Medicine were studied. There were 76 women and 24 men. Their ages ranged from 16 to 62, being 29 years old in average and 48 percent of them were in their thirties. The average follow-up period was 74 months ranging from 60 to 108 months. Serum triiodothyronine (T_3 ; normal value 80~220 ng/dl), throxine (T_4 ; normal value 5~13 ug/dl) and thyroid stimulating hormone (TSH; normal value 0~7 uIu/ml) were measured by radioimmunoassay (Abbott Lab). Titers of antithyroid antibody and antimicrosomal antibody were determined with the tanned red cell hemagglutination method, classifying the results into four groups: negative, low ($10^2 \sim 20^2$), middle ($40^2 \sim 80^2$), and high ($160^2 \sim 640^2$).

Chosen randomly, 67 cases were preoperatively prepared with propranolol and propylthiouracil (PTU), while 33 cases with propranolol, PTU and Lugol's solution. Bilateral subtotal thyroidectomies, leaving the upper poles in 59 cases and lower poles in 41 cases, were randomly performed. The weight of the remnant thyroid was 2~3 gm on each side and the overall weight was 6.0 gm in average. Histopathological findings by hematoxylin-eosin stain were classified into 4 grades according to the number of foci where lymphocytes had infiltrated in the area of a 1.5×2.0 cm: negative for no infiltration, mild for 1~3, moderate for 4~6 and severe for 7 or more. Germinal center and tissue fibrosis were also examined for pathological criteria. The evaluation of postoperative thyroid function was based on the value of serum T_3 , T_4 and TSH as well as on clinical findings; the first, third and sixth postoperative day and one month, six months and one year and then at annual

Table 1. Possible variables for outcome

Demography	Volume of gland
Age(year)	Specimen weight(gm)
Sex	Remnant weight(gm)
Symptom duration	% of remnant weight
Preoperative thyroid function	Immunology
Preoperative T_3 (ng/dl)	Antithyroglobulin antibody
Preoperative T_4 (ug/dl)	Antimicrosomal antibody
24-houriodine uptake(%)	
Treatment	Pathology
Preoperative preparation	Lymphocytic infiltration
Operation type	Germinal center
	Fibrosis

intervals. If more than 2 parameters were abnormal, the diagnosis of functional abnormality was established. However, if only one of them was abnormal, clinical findings were taken into consideration to determine the need for further therapy.

In an attempt to elucidate the factors associated with the postoperative prognosis, 16 variables were analyzed (Table I). All continuous variables were treated as categorical variables. Chi-square test was performed for univariate analysis and then stepwise multiple logistic analysis was carried out.

RESULTS

On histological examination, all of the resected specimens showed diffuse hyperplasia consistent with Graves' disease. The results of 100 patients followed up for a minimum of 5 years are shown in Fig. 1. In eighty-two euthyroid patients, 63 patients showed normal range of T_3 , T_4 and TSH. Thirteen patients exhibited an elevation of TSH with normal T_3 and T_4 , and 6 patients showed decreased T_4 with normal T_3 . However, none of these patients were aware of any symptoms of hypothyroidism. Of the fourteen recurrent cases of hyperthyroidism, 11 patients were

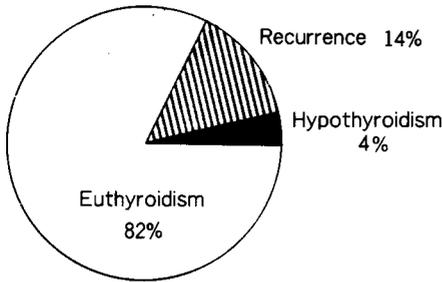


Fig. 1. Postoperative thyroid function.

found to have elevated T_3 and T_4 values. In two patients, T_3 values were normal showing 217 ng/dl and 203 ng/dl, but T_4 values increased to 15.4ug/dl and 16.3 ug/dl respectively and TSH values decreased to 0.01uIU/ml in both cases. One patient demonstrated elevation in T_3 (275 ng/dl) with normal T_4 (10.4 ug/dl) and TSH (0.4 uIU/ml). All of these 14 patients had clinical manifestations of recurrent thyrotoxicosis. Among four patients with thyroid failure, T_3 and T_4 in three patients were lower than the normal range and TSH increased. In one patient, T_4 (5.1 ug/dl) level was normal, in spite of subnormal T_3 (66 ng/dl) level and increased TSH (60 uIU/ml). These 4 patients had signs and symptoms of hypothyroidism.

Some of 82 euthyroid patients, the thyroid hormone was unstable for a certain period after operation. As shown in Table 2, thyroid hormone levels were still increased up to 5 years after the operation and decreased for 1 to 3 years after surgery. The timing of recurrence and hypothyroidism was 36.8 months and 39.5 months on average respectively after the operation. Of the 14 patients with recurrence, 4 developed the symptoms within two years after surgery, 5 in 2~5 years and 5 even after 5 years. Two cases (50%) of postoperative hypothyroidism were appeared 5 years or more after the operation (Table 3).

Factors which might influence the recurrence were analyzed. There were a higher prevalence of recurrences in patients aged over 30 compared with those under 30. But

Table 2. The change of postoperative serum T_3 and T_4 levels in euthyroid patients (N=82)

POD#	Increased		Decreased	
	T_3	T_4	T_3	T_4
1 D.	25%	39%	65	7%
3 D.	0	9%	17%	13%
6 D.	0	0	26%	24%
1 Mo.	8%	17%	17%	22%
6 Mo.	17%	16%	8%	14%
1 Yr.	16%	6%	12%	12%
2 Yr.	12%	13%	0	6%
3 Yr.	13%	8%	0	7%
4 Yr.	15%	3%	0	0
5 Yr.	5%		0	0

Table 3. Onset of recurrence and hypothyroidism

Postoperative year	Recurrence	Hypothyroidism
<2	4	1
2~5	5	1
>5	5	2
Total	14	4
Mean Duration: Recurrence		36.8 months
Hypothyroidism		39.5 months

the difference was not statistically significant ($X^2=0.43$, $P>0.05$). The examination result of histopathological factors such as lymphocytic infiltration, germinal center and fibrosis were available in only 52 cases. Recurrence was frequent in the cases with lower infiltration of lymphocytes and absent of fibrosis, although none were statistically significant ($X^2=3.68$, $P>0.05$, $X^2=1.34$, $P>0.05$). No relationship was demonstrated between recurrence and sex, type of preoperative regimen, weight of thyroid gland, percentage of gland resected, operation type, duration of symptoms, preoperative T_3 and T_4 level and titer of antithyroglobulin antibody and antimicrosomal antibody (Table 4). Stepwise multiple logistic analysis, eliminating the probable influence of each variable, resulted in no significance of any specific factors. A valid statistical analysis was unable to

Table 4. Analysis of prognostic factors

Variable	Subgroup	Euthyroid	Recurrence	Hypothyroid.	P-value
Age	Below 30	52(84%)	7(11%)	3(5%)	NS
	Above 31	30(79%)	7(18%)	1(3%)	
Sex	Male	20(83%)	3(13%)	1(4%)	NS
	Female	62(82%)	11(14%)	3(4%)	
Duration of symptom(year)	<1	47(87%)	6(11%)	1(2%)	NS
	1~3	20(77%)	5(19%)	1(4%)	
	3~5	11(69%)	3(19%)	2(12%)	
	>5	4(100%)	0	0	
Preoperative T3 level(ng/ml)	<250	6(75%)	2(25%)	0	NS
	251~500	27(77%)	6(17%)	2(6%)	
	501~700	26(90%)	3(12%)	2(8%)	
	>751		3(10%)	0	
Preoperative T4 level(ug/dl)	<16	12(86%)	2(14%)	0	NS
	16.1~20	16(76%)	5(24%)	0	
	20.1~24	11(65%)	4(23%)	2(12%)	
	>24	43(90%)	3(6%)	2(4%)	
24hour ¹³¹ I uptake(%)	<70	14(78%)	3(17%)	1(5%)	NS
	71~80	19(83%)	3(13%)	1(4%)	
	81~90	19(95%)	1(5%)	0	
	>90	16(80%)	4(20%)	0	
Preoperative regimens	Inderal+PTU	55(82%)	9(13.5%)	3(4.5%)	NS
	Inderal+PTU +Lugol's sol.	27(82%)	5(15%)	1(3%)	
Operation method (preserved)	lower pole	33(80%)	6(15%)	2(5%)	NS
	upper pole	49(83%)	8(14%)	2(3%)	
Antithyroglobulin antibody	Negative	37(81%)	8(17%)	2(20%)	NS
	Low	7(70%)	1(10%)	0	
	Middle	10(83%)	2(17%)	0	
	High	7(88%)	1(12%)	0	
Antimicrosomal antibody	Negative	10(83%)	2(17%)	2(17%)	NS
	Low	9(75%)	1(8%)	0	
	Middle	9(82%)	2(18%)	1(3%)	
	High	33(80%)	7(17%)	0	
Specimen weight (Gm)	below 25	10(91%)	1(9%)	0	NS
	26~50	40(78%)	9(18%)	2(4%)	
	51~75	16(76%)	3(14%)	2(10%)	
	above 76	16(94%)	1(6%)	0	
Remnant weight (Gm)	below 5	32(84%)	5(13%)	1(3%)	NS
	5~7	33(82%)	5(13%)	2(5%)	
	above 7	17(77%)	4(18%)	1(5%)	

Table 4. Continued

Variable	Subgroup	Euthyroid	Recurrence	Hypothyroid.	P-value
% of remnant weight	below 10	30(91%)	2(6%)	1(3%)	NS
	10.1~15	19(73%)	6(23%)	1(4%)	
	15.1~20	18(78%)	4(17%)	1(5%)	
	above 20.1	15(83%)	2(11%)	1(6%)	
Lymphocytic infiltration	mild	9(69%)	4(31%)	0	NS
	moderate	5(83%)	1(17%)	0	
	severe	9(82%)	1(9%)	1(9%)	
Germinal center	present	14(84%)	4(21%)	1(5%)	NS
	absent	9(82%)	2(18%)	0	
Fibrosis	present	17(81%)	3(14%)	1(5%)	NS
	absent	6(67%)	3(33%)	0	

be performed in 4 cases of hypothyroidism, because of small number of patients.

DISCUSSION

The assessment of postoperative thyroid function is not difficult when clinical manifestations and biochemical parameters such as T_3 , T_4 and TSH show unequivocal findings. However, subjective determination is often required when one or two of these do not coincide. In this study, clinical findings and biochemical parameters of the 77 patients (euthyroidism 63, recurrence 11 and hypothyroidism 3) showed constant figures. Therefore, no difficulty was recognized in determining the postoperative status. Another 23 patients showed inconsistent values between serum T_3 , T_4 and TSH. It is generally accepted that T_3 is more important than T_4 in the assessment of thyroid status when values of these hormones are inconsistent, because T_3 possesses three to five times higher metabolic activity than T_4 (Weatherall *et al.* 1987). Six cases of euthyroidism, 1 recurrence and 1 hypothyroidism were determined on the basis of such criteria, including presence or absence of clinical symptoms. But, two patients with normal levels of T_3 and increased T_4 were determined

as having recurrence because they had a typical clinical manifestations of thyrotoxicosis.

It is apparent that the hypothalamic-pituitary-thyroid axis is suppressed in the patients with Graves' disease. The level of circulating thyroid hormones decreased from six days to one month after the operation and returned to normal within one year (Bradley *et al.* 1980; Bradley *et al.* 1983; Harada *et al.* 1984; Lee *et al.* 1986; Makiuchi *et al.* 1981; Ozoux *et al.* 1988; Toft *et al.* 1978). In our results, the eighty-two cases who were determined as euthyroidism in the final assessment showed unstable values of thyroid hormone for a certain period. Twelve percent were found to have decreased hormone levels until one year after operation and 4 percent had increased values of thyroid hormone up to 5 years after the operation. This finding may support the theory that the remnant thyroid gland still is in an unstable state up to 5 years after the operation. More than 90% of patients who develop postoperative hyperthyroidism do so within two years and the recurrence gradually increase yearly up to 5 years after the operation (Olsen *et al.* 1970; Caswell and Maier. 1972; Lundstorm and Gillquist. 1981; Maier *et al.* 1984; Makiuchi *et al.* 1981; Ozoux *et al.* 1988). Hamburger *et al.* (1976) analyzed 53 recurrent cases and found that the recurrences occurred from 6 months up to 50 years (average 12.4 ± 11.9 years) after

the operation. For this reason, they recommended a lifelong follow up study. Our results were similar with others concerning recurrence. Therefore, we emphasize that the duration of follow up of less than 5 years may not provide an accurate assessment of postoperative thyroid functions.

Because of the large variations in the incidence of postoperative results between the reports, postoperative factors have been studied by many authors. Until recently, the factors which may influence the thyroid status after surgical treatment of Graves' diseases have included these: weight of the remnant thyroid, degree of lymphocytes infiltration and fibrosis of the thyroid tissue, autoantibody status, age, sex, amount and duration of preoperative preparation, total gland weight and length of follow-up duration. And also, there were some evidence that TBII (TSH binding inhibition immunoglobulin) activity after subtotal thyroidectomy and a positive TsAb (TSH stimulating antibody) index at the end of the drug treatment might be important factors in determining the outcome of surgery (Kasagi *et al.* 1988; Teng and Yeung. 1980; Teng *et al.* 1980). Out of these, many authors (Kaplan. 1984; Bradley and DiGirolamo. 1975; Bradley *et al.* 1980; Bradley and Liechty. 1983; Hedly *et al.* 1978; Lee *et al.* 1986; Michie *et al.* 1972; Pegg *et al.* 1973) agree that a correlation exists between the postoperative thyroid function (especially hypothyroidism) and weight of the remnant thyroid. Kaplan (1984) and Bradley *et al.* (1980), in their collective reviews, found an inverse relationship between the remnant size and the development of hypothyroidism, and insisted that the size of the thyroid remnant was the most important factor predicting postoperative hypothyroidism. In the present study, the average weight of the remnant thyroid is 6.0 gm which is smaller than recommended size. We have rarely seen postoperative hypothyroidism, but higher recurrence, than anticipated. The reason for this contrast to other reports is not clear, although further logical evidence shall be needed for the final speculation. As for the recurrence, 16 factors, which may be valid as variables, were subjected to univariate analysis and

stepwise multiple logistic analysis, but not a single factor was proven to be significant.

There have been a number of reports on the relationship of iodine intake and the incidence of thyrotoxicosis (Blum *et al.* 1974; Dickstein *et al.* 1984; Martino *et al.* 1984; Vidor *et al.* 1973). Thjodleifsson *et al.* (1977) reported that in Iceland, an area with a high dietary iodine level, the prevalence of postoperative hypothyroidism was one-fifth of that in north-east Scotland (an area of much lower dietary iodine intake). But, the prevalence of thyrotoxicosis was five times greater in Iceland. Such reports indicate that studies on the epidemiology of thyroid disease in Korea, where abundant iodine resources are available, will be needed. For this reason, further studies should include the environmental situation and racial differences as probable factors in searching for the causes of recurrence and hypothyroidism after surgical treatment for Graves' disease.

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