



Total Thyroidectomy for the Treatment of Recurrent Graves' Disease With Ophthalmopathy

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OBJECTIVE: To determine the outcome of recurrent Graves' disease with ophthalmopathy (GO) following bilateral total thyroidectomy (TT) in patients with no history of anti-inflammatory treatment with steroids or radioactive iodine treatment.

METHODS: From May 2002 to August 2005, 35 patients (27 female, 8 male) with different stages of Graves' disease underwent TT. The degree of ophthalmopathy was assessed by the NOSPECS scoring system and thyrotropin receptor antibody (TRAb) levels were measured for the detection of thyroidal and retro-orbital inflammatory activity before and after surgery.

RESULTS: The mean duration of thyroid disease was 21.4 months and mean follow-up was 422 days. Significant improvement, which was defined as complete regression of periorbital oedema accompanied by a > 1 point decrease in NOSPECS, was observed in 30 (85%) patients. The remaining five patients had stable eye disease. The mean TRAb value and NOSPECS score before and after TT were 33.8 U/L versus 3.4 U/L and 3.0 versus 1.52, respectively, and the differences were statistically significant ($p < 0.0000$). A major reduction in TRAb values achieved after TT was clearly indicative of undetectable inflammatory activity and all the patients demonstrated negative TRAb values within 6 months of the operation. TT was accomplished with very low morbidity (3%) and provided a significant reduction in TRAb levels with attendant improvement in GO in the vast majority of patients in this study.

CONCLUSION: TT resulted in a significant reduction in TRAb levels with concomitant regression of recurrent GO in all patients. The operative morbidity was very low and mortality was nil. However, the long-term consequences of permanent hypothyroidism, which is the ultimate result of TT, are of major concern. [*Asian J Surg* 2008;31(3):115-8]

Key Words: Graves' disease, ophthalmopathy, thyroidectomy, TSH receptor antibody

Introduction

With rapidly progressing eye changes, the type and timing of surgery is still a matter of debate in Graves' disease, and the surgical gold standard for the remission of eye disease remains undetermined. Also, the impact of total thyroidectomy (TT) is questionable in terms of providing further regression of proptosis after its spontaneous

remission. It is claimed in some histological and serological studies that the thyroid follicles and preorbital adipose tissue fibroblasts have a common antigenic structure.¹⁻⁴ Thus, total removal of antigen, which is essentially comprised of a B-cell population in the basement membrane of thyroid follicles, would presumably stop the progression of ophthalmopathy with an abrupt remission of the disease. In view of the mechanisms mentioned above, we

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conducted a prospective study to evaluate the impact of TT on the clinical severity of recurrent Graves' disease with ophthalmopathy (GO), and to elucidate the factors related to remission and recurrence of the disease in the immediate and long-term follow-up.

Patients and methods

From May 2002 to August 2005, the data of 35 patients (27 female, 8 male) presenting with different stages of recurrent GO were collected before, at 6 months and annually following TT. Recurrent disease was defined as the onset of hyperthyroidism within 6 months of withdrawal of antithyroid medication. Antithyroid drugs were administered for at least 6 months and loading dosages were not tapered within 6–8 weeks after starting therapy, as per protocol. The ages of the patients ranged from 16 to 72 years, with a mean of 37 years. None of the patients received anti-inflammatory treatment with oral steroids or were pretreated with I¹³¹ before surgery. All patients had preoperative ultrasonographic examination of the thyroid to exclude nodular hyperplasia and had measurement of radioiodine uptake for diagnosis of diffuse toxic hyperplasia.

The unique treatment modality to achieve a euthyroid state was administration of propylthiouracil (PTU) or methimazol (MM) in this series. Thirty-two patients received PTU and three cases were treated with MM, with the average loading and maintenance doses being 360 mg/day and 22.3 mg/day for PTU and 289 mg/day and 10 mg/day for MM. Seven patients required a beta-blocking agent, propranolol, at a dose of 2–40 mg/day for hyperthyroidism-induced tachycardia. A 25–40% reduction in resting pulse

rate was intended with this treatment. The mean duration of antithyroid drug treatment was 15 months (range, 6–48 months).

The mean duration of thyroid disease, which was taken as the time between first diagnosis of GO and surgery, was 21.4 months. The choice of operation was bilateral TT for all patients with some degree of ophthalmopathy. Quantification of ophthalmopathy depended on a modified NOSPECS scoring as proposed by Wiersinga et al⁵ (Table). The severity of GO was estimated by the sum of scores obtained in each patient and qualified as mild, moderate or severe according to the scores 1–2, 3–8 and 9–14, respectively. The ophthalmological parameters were assessed by the same clinician using a Hertel exophthalmometer.

None of the patients had ultrasonography or computed tomography scan for the determination of the severity of eye disease. To find any existing mediating activity of thyroid stimulating hormone (TSH) receptor antibodies (TRAb) on the clinical severity of GO, TRAb levels were detected before the operation, during discharge and in the 6th month of follow-up. A conventional luminescence receptor bioassay (Brahms, TRAK Human D-16761 Hennigsdorf) was used for the quantitative determination of TRAb with the reference ranges of < 1 U/L, 1.0–1.5 U/L and > 1.5 U/L being considered negative, equivocal and positive antibody titres, respectively. The same procedure was applied to thyroid hormones, and serum samples were collected for the measurement of TSH, free thyroxine (fT4) and free triiodothyronine (fT3) by immunologic assay Immulite 2000 third generation for TSH, Immulite 200 for fT3, Immulite 200 for fT4 (DPC Los Angeles, CA 90045-6900 USA) with reference values for TSH of 0.4–4.0 mIU/mL, fT4 of 0.8–1.9 ng/mL and fT3 of 1.57–4.71 pg/mL.

Table. Modified NOSPECS score for the classification of the severity of Graves' ophthalmopathy

	NOSPECS score			
	0	1	2	3
Lid retraction	No	Yes		
Soft tissue inflammation*	0	1–4	5–8	> 8
Proptosis (mm)	< 17	17–8	19–22	> 22
Site difference (mm)	< 1	1–2	3–4	> 4
Extraocular muscle involvement	No	> 20° upgaze > 35° abduction		≤ 20° upgaze ≤ 35° abduction
Corneal defects	No	Yes		

*Upper lid oedema 0–2, lower lid oedema 0–2, conjunctival injection 1, conjunctival chemosis 1.

The standard surgical approach was that of capsular dissection high on the lateral surface of the thyroid gland, without dissection of the recurrent laryngeal nerve (RLN) from the tracheoesophageal groove up to the cricopharyngeal membrane, but with isthmectomy and pyramidal lobectomy in all patients. The RLN was encountered in every patient with this approach. The penetrating branches of the inferior thyroid artery were divided and ligated high on the surface of the gland. The vascular supply of the RLN was preserved by minimizing dissection and exposure of the nerve.

Follow-up ranged from 21 days to 1,309 days, with a mean of 422 days in this study. The difference between pre- and postoperative hormone and antibody values was investigated by means of the Wilcoxon signed rank test. The association between TRAb titres and NOSPECS scores was evaluated by Spearman's rank correlation analysis. The level of significance was accepted as $p < 0.05$.

Results

Permanent hypoparathyroidism and nerve injury was observed in only one of the 35 patients because of minimal dissection around the parathyroid glands and RLN. This was the first patient involved in this study group and TT was performed after the isolation of the RLN and parathyroid glands, which was a rather unsafe technique when compared to our standard capsular dissection.

Significant improvement in ophthalmopathy, which was qualified as completely regressed periorbital oedema with a ≥ 1 point decrease in NOSPECS score, was observed in 30 (85%) patients. The remaining five patients had no signs of worsening and had stable eye disease. Preoperative NOSPECS scores ranged from 1 to 7 with a mean of 2.84, indicating moderately active eye disease. This was successfully reduced to a mean of 1.52 after the operation. The difference in NOSPECS scores was significant between the two periods ($p < 0.0000$).

Preoperative TRAb values ranged from 0.71 U/L to 19.3 U/L, with a mean of 4.84 U/L. Five patients had negative or equivocal TRAb values ranging between 1.10 U/L and 1.34 U/L. However, the evaluation of TRAb specimens collected during the first 6 months after the operation revealed a significant reduction of antibody levels in almost all patients, with values ranging between 0.01 U/L and 3.57 U/L, with a mean of 0.61 U/L. These results were clearly indicative of undetectable inflammatory activity

and the difference between pre- and postoperative TRAb values was significantly different ($p < 0.0000$).

There was no apparent and direct correlation between preoperative TRAb levels and NOSPECS scores. Thus, the rank of elevation in TRAb levels did not necessarily translate into severity of ophthalmopathy in patients who already had high initial antibody levels ($p = 0.374$; $r = 0.178$). However, there was a significant difference between pre- and postoperative NOSPECS scores, indicating the efficacy of TT in improving GO ($p = 0.000$; $r = 0.75$).

Hypothyroidism occurred in all patients after TT. The mean pre- and postoperative serum TSH levels were 0.36 mIU/mL and 9.16 mIU/mL, respectively, and the difference between the means was statistically significant ($p = 0.000$). These patients received thyroid hormone replacement to keep TSH levels between 0.5 mIU/mL and 2.0 mIU/mL following the operation, and all achieved a euthyroid state with a mean maintenance thyroxine dose of 0.138 mg/day. The incidence of thyroid cancer was nil in our series.

Discussion

Strong evidence exists for autoimmune pathophysiology in Graves' disease. In his study in 1967, Heimann demonstrated lymphocyte infiltration with B-cell predominance in the basement membrane of thyroid follicles in patients with thyrotoxicosis.¹ The importance of this ultrastructure was further supported by the detection of higher levels of thyroid-stimulating antibody activity in thyroid vein blood samples but not in peripheral vein samples of patients with GO undergoing thyroid surgery. It was postulated in this study that the B cells infiltrating the thyroid follicles were the major source of these antibodies.² Common autoantibodies between the thyroid gland and the retro-orbital tissue have been demonstrated in patients with GO.³ Moreover, the identification of thyrotropin receptor and mRNA expression in fibroblasts located in retro-orbital adipose tissue of patients with Graves' disease supported the autoimmune nature and common antigenic structure of thyroid and retro-orbital adipocyte fibroblasts in this disease.^{3,4} In view of the mechanisms mentioned above, we conducted a prospective study to evaluate the impact of bilateral TT on the clinical activity of GO.

Evaluation of data on the treatment of Graves' disease reveals comparable efficacy of antithyroid drugs, radioiodine and various forms of surgery for inducing initial

remission.⁶ Antithyroid drugs and particularly the extended forms of surgery alleviate GO and achieve immediate regression when compared to radioiodine therapy.⁷ However, long-term remission is almost unexpected with antithyroid drugs and 25–50% relapse rates have been reported after the cessation of this therapy.^{8,9} Recurrence rates lower than with medical and radioiodine therapy have been reported with lesser forms of surgery. Among 340 patients who were prospectively randomized to bilateral subtotal thyroidectomy (BST) versus unilateral total and contralateral subtotal thyroidectomy (UTCST), recurrent hyperthyroidism was observed in 9% and 1.7% of the cases, respectively. The percentage of patients with GO was not definite and the thyroid remnant left after BST was twice that of the patients who underwent UTCST in that study.¹⁰ Similarly, a retrospective evaluation of 119 and 98 consecutive patients treated with BST and TT, respectively, for Graves' disease revealed comparable safety despite a significant relapse rate of 5.9% in the BST arm.¹¹ Concerning the patients with GO, lesser forms of surgery that were terminated with a small remnant left behind unavoidably resulted in aggravation of eye disease in 16–40% of the patients and necessitated the use of steroid therapy in some of those cases.^{12,13} In contrast, radioiodine or subtotal thyroidectomy resistant relapses of Graves' disease with progressive ophthalmopathy were satisfactorily treated by TT and resulted in the normalization of TRAb levels and improvement of eye signs in 86% and 96%, respectively, of patients.⁸ In another series, worsening of GO and persistent hyperthyroidism was observed in 8% of the patients in the subtotal thyroidectomy group and in none of the patients in the TT group, suggesting a favourable outcome after TT.¹⁴

The hyperthyroidic state of Graves' disease sometimes resembles the toxic phase of Hashimoto's thyroiditis. However, the disorder of Hashitoxicosis has been excluded in our study by the examination of pathological specimens to reliably confirm the features of Graves' disease in all patients. The incidence of thyroid cancer, most frequently the papillary type, varies from 5% to 10% in patients with Graves' disease, especially in those with a solid nodule in the parenchyma.¹⁵ The incidence of malignancy was nil in our study. This might be partially due to the inclusion criteria of this study, where the absence of nodularity in the ultrasound examination was a prerequisite.

Our patient cohort was quite homogeneous in terms of preoperative medical management and the applied surgery, and TT resulted in a significant reduction in TRAb levels with concomitant regression of recurrent GO in all patients. The operative morbidity was 3% and mortality was nil. The long-term consequences of permanent hypothyroidism, which is the ultimate result of TT, are of major concern.

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