Changes in the thyroid function of Graves’ disease patients treated by subtotal thyroidectomy

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Abstract. The extent of thyroidectomy in Graves’ disease is still a matter of controversy. Subtotal thyroidectomy has been used as the standard surgical procedure for Graves’ disease in Japan, but high hyperthyroidism relapse rates have been reported. We retrospectively studied serial changes in the thyroid function Graves’ disease patients after they had been treated by subtotal thyroidectomy and assessed whether subtotal thyroidectomy should be recommended as the standard surgical procedure for the treatment of Graves’ disease. The subjects were 478 Graves’ disease patients who underwent subtotal thyroidectomy at our institution between 1994 and 1997 and were followed up on a regular basis, and their thyroid function 2-3 years after surgery (the early period) and 8-10 years after surgery (the late period) was evaluated and compared. The evaluations in the late period showed that 57% of the euthyroid patients in the early period remained euthyroid, 30% had developed a relapse of hyperthyroidism, and 13% had become hypothyroid. Approximately 80% of the patients who were overtly hyperthyroid or overtly hypothyroid in the early period remained so in the late period. During the entire periods 47 patients had subclinical hyperthyroidism and were followed up without any postoperative medication. Twenty (42.6%) of them developed overt hyperthyroidism, 11 (23.4%) experienced a spontaneous remission, and 16 (34%) continued to be subclinically hyperthyroid. Because thyroid function after subtotal thyroidectomy is unstable and reduces quality of life, subtotal thyroidectomy is concluded not to be suitable as a standard surgical procedure for the treatment of Graves’ disease.

Key words: Graves’ disease, Subtotal thyroidectomy

IN JAPAN, surgical treatment for Graves’ disease used to be more common, but now the first-line treatment for Graves’ disease is antithyroid drug (ATDs) or radioiodine (RI) therapy [1]. Fig. 1 shows the trends in the methods used to treat Graves’ disease at our hospital from 1955 to 2010. In the 1950s, most patients were treated surgically. However, the percentage of patients treated surgically has tended to gradually decrease since then. ATD therapy has become the mainstream treatment for Graves’ disease in recent years, and surgery has been used to treat about 5% of the patients. There are still several advantages of surgery and it has not been completely abandoned. Subtotal thyroidectomy is considered the optimal surgical procedure for achieving a permanent remission without the need for postoperative medication and has long been the standard surgical procedure used to treat Graves’ disease in our hospital. Factors related to postoperative thyroid dysfunction, especially recurrent hyperthyroidism, had to be elucidated to achieve a permanent remission without medication, and we have published several reports and concluded that thyroid remnant size is the only powerful factor related to postoperative thyroid dysfunction [2, 3]. We prospectively decreased thyroid remnant size as a strategy to reduce the postoperative hyperthyroidism relapse rate, but our strategy resulted in an increase in patients with hypothyroidism [4]. On the other hand, surgery for Graves’ disease is often indicated for young patients, especially for patients of child-bearing age. Since most cases of neonatal hyperthyroidism can be explained by transplacental passage of TSH binding inhibitory immunoglobulin (TBI), the ideal postoperative thyroid status is euthyroidism with a normal TBI.
thyroidectomy at our institution. The thyroid function of 474 of them was evaluated regularly and they were the subjects of this study. The 478 subjects consisted of 387 females and 91 males, and their median age at the time of surgery was 27 years old (range: 12 - 65). Their median resected thyroid weight, median estimated thyroid remnant weight, and median follow up periods were 59.6 g (range: 10.6 - 332), 3.8 g (range: 1.6 - 6.4) and 171 months (range: 154 - 200), respectively.

Evaluation of thyroid function

Thyroid function before surgery and during the postoperative course was assessed by measuring serum free triiodothyronine (FT3), free thyroxine (FT4), and TSH (thyrotropin). FT3, FT4, and TSH were determined by performing chemiluminescent enzyme immunoassays with commercially available kits. Postoperative thyroid status was evaluated mainly on the basis of the TSH levels. Patients with a suppressed TSH level for at least 6 months were classified as having recurrent hyperthyroidism, patients with a normal TSH level were classified as having euthyroidism and patients with an elevated TSH level were classified as having hypothyroidism. Patients with a combination of a suppressed TSH level and normal thyroid hormone were diagnosed with subclinical hyperthyroidism, and patients with a combination of a suppressed TSH level and elevated thyroid hormone level were diagnosed with overt hyperthyroidism. Patients diagnosed with subclinical hyperthyroidism were followed up without treatment, and patients with overt hyperthyroidism were treated with R1, ATD or inorganic iodine.

A postoperative follow-up examination was performed at 1 month, 3 months, 6 months, 12 months postoperatively and every 6 months thereafter. Thyroid function was evaluated in the early period (2-3 years after surgery) and in the late period (8-10 years after surgery) and the results were compared.

Surgical procedure

All patients were euthyroid at the time of the thyroidectomy, and they were operated on by one of several experienced endocrine surgeons in our hospital. Bilateral subtotal thyroidectomy (i.e., resection of the bilateral thyroid lobes with isthmus, leaving a small amount of the posterior rim of each lobe) was performed in all patients. Remnant thyroid was left widely and thinly to protect the parathyroid glands and the recurrent laryngeal nerves. Thus, the recurrent laryn-
geal nerve was not identified essentially. An attempt was made to leave all parathyroid glands in situ, but whenever a parathyroid gland was resected, it was transplanted into the sternocleidomastoid muscle. The size of the remnant thyroid was estimated by weighing a portion of the resected gland of the same volume. We did not use different surgical strategy in patients with coexistent thyroid nodules or with ophthalmopathy. However, if patients had complications to antithyroid medications, less than 3g of the thyroid was left.

**Surgical complications**

The most common surgical complications of subtotal thyroidectomy for Graves’ disease are hypocalcemia (hypoparathyroidism), hoarseness (recurrent laryngeal nerve palsy), and bleeding requiring reoperation. The serum calcium, phosphate, and albumin levels of all patients were measured on the day after the thyroidectomy. Hypoparathyroidism was diagnosed and evaluated on the basis of a physical examination and serum calcium determination on the next morning after the thyroidectomy. Hoarseness was evaluated on the basis of objective and laryngoscopic findings. If symptoms of progressive compression were noted in patients with postoperative bleeding, reoperation was performed immediately.

The study was reviewed and approved by the Institution’s Ethics Board and performed in accordance with the Declaration of Helsinki.

**Results**

**Postoperative thyroid function**

Thyroid function was evaluated 2-3 years after surgery (the early period) and 8-10 years after surgery (the late period), and the results were compared (Table 1). In the early period, 100 patients were euthyroid, 62 patients were hyperthyroid and 316 patients were hypothyroid, and in the late period, 122 patients were euthyroid, 111 patients were hyperthyroid, and 245 patients were hypothyroid. Patients with overt hyperthyroidism in the early period were treated by ATD, inorganic iodine or RI therapy. All patients treated by RI therapy were classified as overt hyperthyroid group in the late period even if they were hypothyroid or euthyroid. The patients treated by ATD or inorganic iodine were classified as overt hyperthyroid group in the late period if the treatment continued. When the patients were diagnosed as overt hyperthyroidism in the early period, treated by ATD or inorganic iodine and discontinued the treatment during these periods, they were classified according to their thyroid status at the late period.

The evaluation in the late period showed that 57% of the euthyroid patients in the early period remained euthyroid, 30% had developed a relapse of hyperthyroidism, and 13% had become hypothyroid. The evaluation in the late period for 316 patients with hypothyroidism in the early period showed that 228 patients remained hypothyroid (72.1%), 52 patients improved to euthyroidism (16.5%), and 36 patients developed a relapse of hyperthyroidism (11.4%). Approximately 80% of the patients who were overtly hyperthyroid or overtly hypothyroid patients in the early period remained so in the late period.

**Outcome of patients with postoperative hyperthyroidism**

During all follow-up periods, 132 patients experienced relapse of hyperthyroidism regardless of thyroid function at the latest consultation day. Two patients had overt hyperthyroidism just after thyroidectomy.
and were treated by ATD and inorganic iodine. They achieved remission 1 year after operation. Excluding these patients, 130 patients were included in this analysis. They consisted of 108 females and 22 males, and their median age was 27 years. There were 103 patients with overt hyperthyroidism and 47 patients with subclinical hyperthyroidism (20 patients of these 47 patients with subclinical hyperthyroidism subsequently developed overt hyperthyroidism). Between the early period and the late period, 75 patients developed overt hyperthyroidism, whose thyroid function at the early period was subclinical hyperthyroidism in 20 patients, euthyroidism in 25 patients, subclinical hypothyroidism in 22 patients, and overt hypothyroidism in 8 patients. Two patients developed overt hyperthyroidism between the early and the late periods, and achieved remission by ATD therapy (one patient was euthyroid and the other was subclinical hypothyroid at the late period). These 2 patients were classified as euthyroidism at the early period and were classified as euthyroidism and subclinical hypothyroidism at the late period. Treatment of the overt hyperthyroidism consisted of ATD therapy in 53 patients (51.4%), RI therapy in 32 patients (31.1%), and inorganic iodine treatment therapy in 18 patients (17.5%). Remission of Graves’ disease was achieved in 6 (11.3%) of the 53 patients who received ATD therapy, 31 (96.6%) of the 32 patients who received RI therapy, and 2 (11.1%) of the 18 patients who received inorganic iodine therapy. Of 8 patients with overt hyperthyroidism who were treated by ATD or inorganic iodine and achieved remission, 6 patients were euthyroid without medication and 2 patients had overt hypothyroidism at the late period. The 47 patients with subclinical hyperthyroidism, on the other hand, were followed up without medication, and in the late period 20 (42.5%) of them developed overt hyperthyroidism, 3 (6.4%) continued to be subclinical hyperthyroidism, 13 (27.7%) developed subclinical hyperthyroidism, and 11 (23.4%) experienced a spontaneous remission.

**Discussion**

The treatment policy for Graves’ disease varies from country to country and from institution to institution [1, 6-8]. Most endocrinologists in Japan treat Graves’ disease with ATD therapy rather than with RI therapy or by surgery. Thyroidectomy is often performed in patients with a large goiter, as a secondary treatment when antithyroid medication fails, in younger patients, and in patients who hope for an immediate remission. There is much controversy as to whether subtotal thyroidectomy or total thyroidectomy should be selected to treat patients with Graves’ disease [9-15]. We think that long-term euthyroidism without medication, not euthyroidism with thyroxin replacement therapy, is the ideal goal and that it can only be achieved by subtotal thyroidectomy. However, in our previous study, 18% of the Graves’ disease patients treated by subtotal thyroidectomy developed recurrent hyperthyroidism after 8 years postoperatively [16] and that was an unacceptably high rate. Factors related to postoperative thyroid dysfunction, especially recurrent hyperthyroidism, had to be elucidated to achieve the ideal goal, and we have published several reports [2, 3] and concluded that thyroid remnant size is the only powerful factor associated with postoperative thyroid dysfunction. Although thyroid remnant size is a significant factor related to postoperative thyroid dysfunction, patients with almost the same size thyroid remnant do not always have the same postoperative clinical course. Thus, there must be other factors associated with postoperative thyroid dysfunction, and an ideal outcome can be hoped for when these factors are identified. In our previous studies, preoperative TSH receptor antibody levels have a significant effect on the short-term results of subtotal thyroidectomy for Graves’ disease but not on the long-term results. Long-term surgical outcomes could not be predicted on the basis of the preoperative TSH receptor antibody level [2, 3].

Furthermore, an immunological remission does not occur in every patient who undergoes subtotal thyroidectomy. Graves’ disease sometimes has a significant impact on pregnancy, and most cases of neonatal hyper-
thyroidism can be explained by transplacental passage of thyroid stimulating antibodies. We previously reported finding that subtotal thyroidectomy resulted in an immunological remission in most patients, however, immunological remission was not achieved when hyperthyroidism relapsed after subtotal thyroidectomy [4]. Takamura et al., on the other hand, reported finding that total thyroidectomy was superior to subtotal thyroidectomy in normalization rate and decreasing speed of TSH receptor antibody [15].

We have been performing subtotal thyroidectomy for patients with Graves’ disease and reported risk factor for postoperative relapse of hyperthyroidism. Though RI therapy for postoperative hyperthyroidism was the definite therapy, postoperative relapse rate of hyperthyroidism was unacceptably high as in our previous reports. No definite factor except thyroid remnant size has been clarified and the ideal goal of surgical treatment could not be easily achieved by subtotal thyroidectomy. In addition, the results of the present study showed that thyroid function changed over time after subtotal thyroidectomy and that the physical condition of many patients changed with the change in the thyroid function, which reduce the quality of life. The patients should be followed up regularly for a long time though their thyroid functions have been stable for several years after surgery. High risk of relapse rate and unstable thyroid function after subtotal thyroidectomy led us to change the surgical strategy for Graves’ disease. Recently, we employed total thyroidectomy as our standard surgical procedure for Graves’ disease. Total thyroidectomy results in permanent hypothyroidism, which necessitates life-long thyroxine replacement, but the stable hormonal status endures stability of the patient’s physical condition. Several papers have reported that recommended total thyroidectomy as the standard surgical procedure for Graves’ disease, however, surgical complication, especially hypoparathyroidism was reported to increase. The prerequisite for the surgical treatment is low morbidity [12, 13, 18-22]. Thus, some authors recommend near total thyroidectomy, leaving a small thyroid remnant. The same as in our previous studies, no patients with remnant thyroid less than 2g developed recurrent hyperthyroidism [4, 23].

In conclusion, because of the unstable thyroid function and unacceptably high rate of recurrent hyperthyroidism after subtotal thyroidectomy, we do not consider subtotal thyroidectomy to be suitable as the standard procedure for the treatment of Graves’ disease.

Disclosure Statement

The authors declare that no competing financial interests exist.

References


