INFLUENCE OF TOTAL THYROIDECTOMY ON ORBITAL
OPHTALMOPATHY AND LEVELS OF ANTITHYROID ANTIBODIES IN
PATIENTS WITH GRAVES’ DISEASE*

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Graves’ disease is an autoimmune disease. One of the most severe complications of Graves’ disease is
orbitopathy.

The aim of the study was to estimate the influence of total thyroidectomy on the postoperative course
of exophthalmus and determine the levels of thyroid antibodies after surgery.

Material and methods. During the period between 2002 and 2005, 1514 strumectomies were performed
at the I Chair and Department of General, Gastroenterological and Endocrine Surgery, Medical University in Wroclaw. The study included 69 (4.5%) patients, who were operated on because of Graves’
disease. Forty-two (60%) of these patients had progressive opthalmopathy and were subjected to total
thyroidectomy (35 women and 7 men, mean age was 31 years). The diagnosis of Graves’ disease was
established on the basis of the clinical evaluation, fT3, fT4 and TSH values, as well as the determination
of serum thyroid antibody levels. Every patient was subjected to an ophthalmological examination, with
measurements of the degree of exophthalmus, as compared to the ATA (American Thyroid Association)
scale. Above-mentioned parameters were measured before surgery and 6, 12 and 18 months after total
thyroidectomy.

Results. Considering patients after total thyroidectomy, exophthalmus did not proceed. In 17 (40%)
patients, 2-3 mm of eyeball retraction was noted, mainly during the initial six months. After surgery, a
statistically significant reduction of TSH-receptor and anti-TPO antibody values were observed.

Conclusions. Total thyroidectomy in patients with Graves’ disease and orbital opthalmopathy signifi-
cantly reduced the progression of orbitopathy. It also leads to the normalization of serum anti-receptor
(TRAb) and anti-peroxidase (anti-TPO) antibody levels.
Total thyroidectomy is a quick and effective procedure in the hands of an experienced surgeon and
should be performed in secondary or tertiary care centers.

Key words: Graves’ disease, orbitopathy, total thyroidectomy

Graves’ disease is an autoimmune condition, frequently caused by hyperthyroidism. It is due
to antibodies present in the blood, which bind to thyroid cell receptors, resulting in the exces-
sive production of thyroid hormones (1, 2). One of the severe complications of the disease is pro-
gressive ophthalmopathy, which may lead to vision loss. Considering medical practice and literature data, we could not find publications concerning the influence of total thyroidectomy on the outcome of thyroid ophthalmopathy (2, 3, 4).

The aim of our study was to estimate the influence of total thyroidectomy on the postoperative course of exophthalmus and determine the levels of thyroid antibodies after surgery.

**MATERIAL AND METHODS**

During the period between 2002 and 2005, 1514 thyroidectomies were performed at the I Chair and Department of General, Gastroenterological and Endocrine Surgery, University in Wrocław, including 69 (4.5%) patients with Graves’ disease. In this group, 42 (60%) patients with excessive exophthalmus qualified for a total thyroidectomy. There were 35 women and 7 men, between 19 and 57 years of age (average age: 31±6 years).

The diagnosis of disease was based on the clinical examination, elevated levels of thyroid hormones fT₃ and fT₄, and low levels of TSH, excessive exophthalmus, as well as thyroid antibody levels. The patients were treated pharmacologically before surgery for a period of 1-9.2 years (average – 4.3 years).

All patients were treated with antithyroid drugs in decreasing doses to obtain euthyreosis. Exophthalmus was observed in 18 patients at the beginning of the disease and in the remaining patients, it appeared during the course of the disease and gradually intensified. Exophthalmus persisted for 8 months to 4 years (average – 1.8 years). The progression of eye symptoms intensified, in spite of pharmacological treatment. Progressive orbitopathy was the main indication for total excision of the thyroid gland.

All patients were laryngologically examined and the movements of vocal cords were estimated. Considering the ophthalmological examination, before surgery and 6, 12 and 18 months after the operation, the degree of exophthalmus was estimated by means of a Hertel’s exophthalmometer. Protrusion of the eyeballs greater than 20 mm was estimated as a diagnostic index of ophthalmopathy, according to the ATA scale (American Thyroid Association).

All patients, who qualified for surgery, belonged to the IIIa group of orbitopathy intensification. The protrusion eye index ranged between 22-26 mm. The levels of TSH, fT₃, fT₄ and receptor antibodies (TRAb, TSH- receptor), thyroid peroxidase antibodies (TPO) and antithyroglobulin (TG) antibodies were estimated before surgery. The levels of thyroid hormones and TSH were detected by means of an immunoenzymatic test with the use of particles (Microparticle Enzyme Immunoassay MEIA). An immunoenzymatic test (DRG Diagnostics Instruments GmbH Germany) was also used to estimate antithyroid antibodies. The correct, doubtful, and positive levels are presented in tab. 1. The levels of thyroid hormones and antibodies were estimated before the operation and 6, 12 and 18 months after surgery.

All the above-mentioned total thyroidectomies were performed by one surgeon. The operation was performed under general anesthesia and Kocher’s arcuate incision on the neck was made. After identification of the parathyroid glands and recurrent laryngeal nerves, both thyroid lobes were removed. Localization of the parathyroid glands was established during each operation. The inferior thyroid artery was not ligated to assure blood supply to the parathyroid glands. Suction drainage was placed at the site of the operated thyroid lobes, which was removed after two days. Calcium levels were estimated in each patient after surgery. All patients underwent outpatient follow-up and re-

<table>
<thead>
<tr>
<th>Antibodies TRAb (U/l)</th>
<th>Before surgery</th>
<th>6 months after surgery</th>
<th>12 months after surgery</th>
<th>18 months after surgery</th>
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<tr>
<td></td>
<td>n=42</td>
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<tr>
<td>TRAb</td>
<td>13,3 (±13,1)</td>
<td>2,1 (±0,8) p &lt; 0,05</td>
<td>1,3 (±0,4) ns</td>
<td>1,1 (±0,3) ns</td>
</tr>
<tr>
<td>Antibodies anty- TPO (U/ml)</td>
<td>123,1 (±222)</td>
<td>19,1 (±14,2) p &lt; 0,05</td>
<td>16,3 (±4,7) ns</td>
<td>15,6 (±5,7) ns</td>
</tr>
<tr>
<td>Antibodies anty- TG (IU/ml)</td>
<td>40,9 (±57)</td>
<td>32,6 (±14,7) ns</td>
<td>27,7 (±12,5) ns</td>
<td>29,5 (±15,2) ns</td>
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received L-Thyroxine substitution at an initial dose of 75 μg, followed by 150-200 μg daily, depending on the TSH level (between 1-2 μIU/ml).

All mentioned parameters were statistically analyzed. Medium values and standard deviation were calculated (± SD). Statistical analysis was performed by means of the t-Student test. p<0.05 was considered statistically significant.

RESULTS

Study results are present in tab. 1 and fig. 1. Considering tab. 1, the levels of thyroid antibodies were detected in patients with Graves’ disease before surgery and 6, 12 and 18 months after the operation. Table 2 presented the range of norms, doubtful and positive values for each antibody.

The levels of TRAb were considerably elevated before surgery and decreased significantly 6 months after the operation. Medium values of TRAb approached normal levels 18 months after surgery. Statistically significant differences were observed between antibodies estimated before surgery and 6 months after the operation.

The levels of anti-TPO antibodies were considerably elevated before surgery. Six months after surgery these levels significantly decreased and returned to normal. The anti-TG antibodies were normal before surgery and did not change significantly after the operation. All patients, who were subjected to total thyroidectomy, qualified for the IIIa degree of ophthalmopathy group (ATA scale), and exophthalmus values were between 22-26 mm. With respect to postoperative examination, progressive orbitopathy was not observed in any of the patients.

Figure 1 presented the percentage of patients with diminished exophthalmus during the postoperative period, in comparison with the number of all operated patients. Among 13 patients (31%), orbitopathy diminished during the initial 6 months and after 12 months, the number of these patients increased to 17 (40%). After that time, this process was not observed. Orbitopathy diminished by 2-3 mm. The index of orbitopathy did not change in the remaining patients. There were no perioperative deaths and vocal cord palsy was not detected in any patient. One blood transfusion was necessary and one patient required reoperation, due to postoperative bleeding. One patient was diagnosed with postoperative hypoparathyroidism, which was corrected after 4 months of pharmacological treatment. This was the patient who was subjected to accidental removal of two parathyroid glands, which were during the same operation implanted to the sternocleidomastoid muscle.

DISCUSSION

Surgical thyroidectomy is one of the three alternative methods used in the treatment of Gra-
ves’ disease. The two other methods comprise oral anti-thyroid agents and radioactive iodine.

The best treatment method remains controversial and is widely debated in the literature. Obvious advantages of surgical treatment, especially total thyroidectomy, are as follows: permanent results with no late recurrences, relatively short duration of treatment and a relief of progressive exophthalmopathy (3, 5, 6). However, surgical treatment is not free from possible severe complications, which include recurrent laryngeal nerve damage, temporary or even permanent insufficiency of the parathyroid glands, and necessity for permanent substitution therapy with L-Thyroxine. One should also mention the economic factor (high costs of surgical therapy) and high level of patient stress, inevitably bound to the surgical intervention.

Surgical treatment of Graves’ disease is a rapid and radical method, but it offers the best possible results in a relatively short time. Overall, the costs of surgery are steadily decreasing, due to the permanent improvement of surgical techniques and surgeons’ experience resulting in lower postoperative complication rates and shorter hospitalization (3).

However, some authors continue to insist that surgery should not be the treatment of choice, considering Grave’s goiter (2).

There are several alternative techniques used in the surgical treatment of Graves’ disease including: bilateral subtotal thyroidectomy (ST), unilateral subtotal thyroidectomy with total thyroidectomy of the other side and finally bilateral total thyroidectomy (TT).

The choice of the proper surgical technique is widely discussed in the literature with bilateral total thyroidectomy having its supporters and adversaries (1-5, 7).

Shun-Yu et al. (6) compared the treatment results of Graves’ goiter following subtotal bilateral thyroidectomy and subtotal unilateral and total thyroidectomy of the other side. After analysis of postoperative complication rates including recurrence of hyperthyroidism and late hypothyroidism, they concluded that a more radical surgical approach offers better long-term results. Analysis of their clinical material revealed that total bilateral thyroidectomy (TT) is the best method of treating severe Graves’ disease connected with no late recurrences (3, 8). Other authors (9) suggested that TT should be performed in young patients (below the age of 20 years) with coexisting cold nodules or high serum levels of anti-thyroid antibodies. This approach is accepted in other centers, as well (4, 5). Other specialists (7) underlined the possibility of postoperative hypoparathyroidism and the lack of relationship between the extent of thyroidectomy and relief of exophthalmus. As a result, they did not recommend total thyroidectomy as the method of choice. They preferred subtotal thyroidectomy, which leaves 4 ml of glandular tissue. However, recently presented data confirmed the positive effect of total thyroidectomy with respect to the relief of progressive exophthalmus (9). Currently, progress in surgical techniques and postoperative care gradually makes surgical thyroidectomy the method of choice in the case of Graves’ disease (3).

Based on the authors’ own material, indications towards radical thyroidectomy included progressive orbitopathy. All operated patients underwent bilateral total thyroidectomy. No recurrence of hyperthyroidism was observed during postoperative follow-up. All patients received L-Thyroxine at a daily dose of 150-200 μg to maintain serum TSH levels between 1-2 μIU/ml. No permanent insufficiency of the parathyroid glands was observed with only one case of temporary postoperative hypoparathyroidism, which normalized after several months of substitution therapy. No vocal cord palsy was diagnosed during the postoperative examination. There were no fatal complications in the operated group with only one patient requiring a blood transfusion, due to significant intraoperative blood loss. One of the patients required emergency reoperation, due to massive postoperative hemorrhage.

The introduction of radioactive iodine into Graves’ disease therapy (Hertz and Roberts in 1946) made it the “golden standard” of treatment in some countries (10). Significant disadvantages of this method include the relatively long time necessary to achieve normal hormonal function after the administration of therapeutic doses of ¹³¹I, as well as the rather unpredictable effect of progressive exophthalmus, with some authors reporting worsening of orbitopathy after such treatment (11, 12). The long and gradual destruction of the gland tissue after ¹³¹I administration led to the prolonged release of thyroid antigens, which may stimulate and worsen symptoms of coexisting orbitopathy (13).
Many authors’ suggested that good economic results and patient safety during modern thyroid surgery times rendered surgical management superior to therapy with \(^{131}\text{I}\), considering subjects with Graves’ disease (3).

Endocrine orbitopathy is one of the most severe complications of Graves’ disease. It may be connected with various symptoms from only mild discomfort even up to serious damage, which may result in vision loss. Many studies comparing the results of radioactive iodine vs. surgical treatment on progressive orbitopathy showed that better long-term results were achieved following surgery (9, 11, 14).

Effects of surgery on progressive exophthalmus remain to be fully understood. It is believed that there is a common antigen in the thyroid gland and retrobular tissue and its reaction with anti-thyroid antibodies plays a key role in the development of retrobular infiltration and development of orbitopathy (15). Remnants of thyroid tissue after non-radical treatment could be the source of this antigen and its gradual release may worsen symptoms of orbitopathy. On the other hand, total removal of thyroid tissue should (by lack of its antigens) lead to significant resolution of exophthalmus.

All our patients were subjected to total thyroidectomy. There were no signs of postoperative progression of orbitopathy. In 17 patients (40%), the degree of exophthalmus diminished by 2-3 mm within the first 12 months after the operation.

The presence of anti-thyroid antibodies (TRAb) is one of important features allowing the assessment of immune disturbances during the course of Graves’ disease. Elevation of serum levels of these antibodies after treatment with oral anti-thyroid drugs, radioactive iodine or surgical intervention seems to be an important prognostic factor of hyperthyroidism recurrence or progression of orbitopathy (14, 15). On the other hand, decreased levels of these antibodies are associated with successive treatment. The authors noticed a statistically significant (in comparison with preoperative values) reduction in serum levels of anti-receptor and anti-TPO antibodies in all operated patients.

CONCLUSIONS

Total thyroidectomy, after the identification of recurrent laryngeal nerves and parathyroid glands, is a quick and effective method of Graves’ disease treatment. Total thyroidectomy in patients with Graves’ disease and orbital opthalmopathy significantly reduces the progression of orbitopathy. It also leads towards normalization of serum anti-receptor (TRAb) and anti-peroxidase (anti-TPO) antibody levels.

Total thyroidectomy is a quick and effective procedure, in the hands of an experienced surgeon, and should be performed in secondary or tertiary care centers.

REFERENCES

The presented study is a valuable publication. The number of patients with autoimmune thyroid disorders increases, which is associated with a higher iodine supply. The increased number of patients with thyrotoxicosis is also connected with the uncontrolled intake of vitamin diet supplements by subjects, and also with the use of the so-called "iodine chambers."

Qualification towards surgical treatment of patients with orbital ophthalmopathy several years ago seemed doubtful.

Surgical treatment of patients with high antibody titers is technically very difficult. Bleeding control is difficult to obtain, surrounding tissues are swollen, which may lead to many complications, in comparison to thyroidectomy performed in the case of so-called "quiet" Graves’ disease. Non-operative treatment of orbital ophthalmopathy for many years was unsuccessful. In our Clinic patients with developing orbital ophthalmopathy are quickly qualified towards operative treatment. The only condition which must be fulfilled before the operation is the normalization of $fT_3$ and $fT_4$ concentrations. When the patient has elevated antibody titers the operation is performed with the addition of steroids and beta-blockers. In special cases, when the goiter is huge and vascular, the patient receives Lugol’s solution, 7-10 days preoperatively.

Without doubt in such cases total thyroidectomy must be performed. Routinely, we transplant one of the parathyroid glands, after dissection, into the omohyoid muscle. The above-mentioned decreases the number of postoperative hypoparathyroidism cases. Considering all patients after thyroidectomy, due to Graves’ disease there is a low concentration of PTH. The above implicates three months postoperative Calcium and Alfadiol supplementation treatment. In all cases, laryngeal recurrent nerves are identified intraoperatively with the help of neuromonitoring. Unfortunately, in 10% of cases transitory malfunction of laryngeal recurrent nerves occurs, due to laryngeal edema or vocal fold hematomas. I would like to congratulate the Authors’ results, in the absence of postoperative complications.

All patients must receive substitution doses of Thyroxine (125 mg daily) postoperatively, in order to maintain low TSH levels. In cases where the TSH level is high, orbital ophthalmopathy enlarges. Routinely, we check the antibody titer, and if elevated, administer steroids.

During the past months, isolated papers were published concerning monoclonal antibodies in orbital ophthalmopathy treatment. We have our own experience with the use of antibody anti-CD20 considering orbital ophthalmopathy treatment in Graves’ disease. The study concerning this problem will be published in the next issue of “The European Journal of Endocrinology”.

The presented study is a valuable clinical report and I would like to congratulate the Authors’ on their results.

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