

# Results obtained after the surgical treatment of Graves' disease depending on the levels of anti-thyroid antibodies

S. L. Shliakhtych<sup>1, 2</sup>, V. R. Antoniv<sup>1</sup>

<sup>1</sup> Bogomolets National Medical University, Kyiv

<sup>2</sup> Kyiv City Clinical Hospital No 3

✉ Sergiy Shlyakhtych: [shlyakhtychserg@gmail.com](mailto:shlyakhtychserg@gmail.com)

S. L. Shliakhtych, <http://orcid.org/0000-0002-7784-8320>

V. R. Antoniv, <http://orcid.org/0000-0001-6053-8097>

Graves' disease (GD) is a hereditary autoimmune disease which is characterized by persistent abnormal hypersecretion of thyroid hormones and thyrotoxicosis syndrome development. GD affects from 0.5 % to 2.0 % of population in different regions. 46 % of these patients develop ophthalmopathy. GD is a common cause of disabilities in patients under 60 years of age. In recent years, the incidence of GD in Ukraine has increased by 9.9 % — from 106.2 to 117.9 per 100,000 individuals. This can be connected with the improved diagnostic possibilities and active disease detection as well as with the increased number of autoimmune thyroid disorders. The recent studies focus on prevention of specific complications and recurrences of GD after surgery.

**OBJECTIVE** — to compare the levels of antibodies to the thyroid-stimulating hormone receptors (TSHR-Ab) during different postoperative periods as well as the incidence of early and late complications depending on the surgical technique used for the treatment of GD.

**MATERIALS AND METHODS.** The results of surgical treatment of 130 patients, with GD were compared. 29 male patients and 101 female patients aged from 19 to 76 (average —  $44.1 \pm 3.2$  years), receiving their treatment for GD in Kyiv Center of Endocrine Surgery during 2010—2018, were randomly selected and divided into two groups. At the time of operation the duration of disease was from 1 to 30 years (average —  $4.6 \pm 1.2$  years). Group 1 included 65 patients that underwent total thyroidectomy (TT) and group 2 included 65 patients that underwent subtotal thyroidectomy (ST). The following parameters were compared: surgery duration, the incidence of early postoperative complications, including bleedings and damage to the recurrent laryngeal nerves, and late outcomes of surgical treatment (persistent hypoparathyroidism disorder and disorder recurrences) depending on the method of surgery (ST or TT). Furthermore, the patterns of the TSHR-Ab level reduction were studied for different postoperative periods.

**RESULTS.** The comparison of surgical outcomes following TT and ST didn't reveal any statistically significant differences in such evaluation criteria as the average surgery duration, the average volume of intraoperative blood loss and the average duration of the postoperative inpatient treatment. The comparative assessment of the thyroid stump volume and the average amount of drained discharge showed statistically significant differences for TT. It allows considering TT as a surgery which causes less complications than ST. The studied parameters of early postoperative complications had no significant differences for ST and TT. The long-term (5 years) postoperative level of TSHR-Ab was statistically significantly lower in patients after TT and made up  $1.15 \pm 0.13$  IU/L (thus corresponding to the normal level).

**CONCLUSIONS.** Total thyroidectomy is an optimal surgical technique and is more appropriate compared with subtotal thyroid gland resection. It should be noted that TT provides lower risk of complications due to significantly lower level of TSHR-Ab in late postoperative period.

## KEYWORDS

antibodies to the thyroid-stimulating hormone receptors, Graves' disease, subtotal thyroidectomy, thyroidectomy.

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The Graves' disease (GD) is a hereditary autoimmune disease, which is characterized by the persistent pathological hypersecretion of thyroid hormones with the thyrotoxicosis syndrome development. It develops due to the thyroid-stimulating globulins which begin to compete with thyrotrophin for its receptors and stimulate the production of thyroid hormones.

Other factors (inheritance, infectious and psychogenic effects) serve as drivers promoting autoimmune disorders. Infectious diseases (influenza, angina, chronic tonsillitis, scarlatina, pertussis, rheumatism, and encephalitis) precede, in 17–20% of cases, the development of the clinical picture typical for GD. Nowadays, GD is considered a classical autoimmune disease which induces synthesis of the thyro-stimulating hormone (TSH) antibodies and their binding to the  $\alpha$ -subunit of the TSH receptor on a thyrocyte membrane causes the activation of adenylate cyclase, increased levels of the intracellular cAMP (cyclic adenosine monophosphate) resulting in phosphorylation of protein kinase A and activation of transcription factors [7, 11, 17, 21]. These processes contribute to the increased iodine capture, synthesis of thyroid peroxidase and thyroglobulin, and, finally, to hyperthyroidism.

GD affects from 0.5% to 2.0% of population in different regions. 46% of these patients develop ophthalmopathy [5, 25]. GD is a common cause of disabilities in patients under 60 years of age. In recent years, the incidence of GD in Ukraine has increased by 9.9% — from 106.2 to 117.9 per 100,000 individuals. This can be connected with the improved diagnostic possibilities and active disease detection as well as with the increased number of autoimmune thyroid disorders.

Despite significant achievements in studying of GD pathogenesis, there are still many disputable issues on diagnostics and treatment strategies that need further research. Thus, the data on the levels of antibodies to the thyroid-stimulating hormone (TSHR-Ab) receptors in patients with GD during different stages of the disease and throughout early and late postoperative periods are not structured.

The treatment of GD mainly includes conservative, radioiodine and surgical therapy. However, surgery is the most frequent and preferable option since it ensures fast removal of thyrotoxicosis manifestations. The recent studies focus on prevention of specific complications and recurrences of GD after surgery.

It is believed that the amount of the remaining thyroid tissue is one of the most important factors that can be controlled by a surgeon. However, surgical operation cannot always recover the euthyroid state of a patient. Hypothyreosis or thyrotoxicosis recurrence can appear during different

postoperative periods. Surgery indications and outcomes of surgical treatment are still being discussed.

**Aims:** The study aimed to compare the levels of antibodies to the thyroid-stimulating hormone (TSHR-Ab) receptors during different postoperative periods as well as the incidence of early and late complications depending on the surgical technique used for the treatment of GD.

## Materials and methods

130 patients (29 men and 101 women aged between 19 and 76 (mean age  $44.1 \pm 3.2$  years)), receiving their treatment for GD in Kyiv Center of Endocrine Surgery, were randomly selected and divided into two groups: group 1 included 65 patients that underwent total thyroidectomy (TT) and group 2 included 65 patients that underwent subtotal thyroidectomy (ST).

The following parameters were compared: surgery duration, the incidence of early postoperative complications, including bleedings and damage to the recurrent laryngeal nerves, and late outcomes of surgical treatment (persistent hypoparathyroid disorder, hypothyroidism (hypoPTH), and thyrotoxicosis recurrences) depending on the method of surgery (ST or TT). Furthermore, the patterns of the TSHR-Ab level reduction were studied for different postoperative periods.

TSHR-Ab were studied in a commercial laboratory, using a Siemens Architect 2000 analyzer for the chemiluminescent analysis. Reference values for TSHR-Ab were  $>0.55$  IU/ml for positive results and  $<0.55$  IU/mL for negative results. The parathormone level was determined immunochemically, using a Cobas 6000 analyzer for the electrochemiluminescence detection; reference values for a positive result were 15–65 pg/mL.

The obtained results were statistically processed by means of IBM SPSS Statistics Base (version 22), using various statistical methods. Student's t-test was used for the determination of the probability of average value difference. Data are provided as  $M \pm m$ . The difference was considered to be statistically significant in  $p < 0.05$ . The inter-series correlation analysis of parameters was calculated using the  $\chi^2$  criterion (Pearson's criterion).

## Results and discussion

According to the sex and age distribution, there were no statistically significant differences in groups (Table 1). The disease duration as of the moment of the surgery was from 1 to 30 years, on average  $4.6 \pm 1.2$  years. These patients had coexisting

**Table 1. Patient demographics, patient distribution depending on the size of thyroid nodules in groups**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Male	8	5
Female	57	60
Age, years	45.3 ± 2.24	41.7 ± 2.08
Disease duration before operation, years	2.85 ± 0.22	3.1 ± 0.31
Volume of the thyroid gland, cm <sup>3</sup>	38.53 ± 0.62	37.01 ± 0.75

All  $p > 0.05$ .

**Table 2. Comparative analysis of surgery parameters depending on a surgical technique**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Average surgery duration, min	110.83 ± 6.4	108.79 ± 2.39
Average volume of intraoperative blood loss, mL	84.8 ± 1.39	85.4 ± 1.46
Thyroid stump volume, cm <sup>3</sup>	0	2.2 ± 0.06*
Average volume of drained discharge, mL	46.6 ± 0.93	65.86 ± 1.33*
Average hyperthermia duration, h	20.12 ± 0.68	20.62 ± 0.67
Average duration of postoperative inpatient treatment, days	6.77 ± 0.06	6.59 ± 0.07

\* The difference between the groups is statistically significant ( $p < 0.05$ ).

**Table 3. Comparative analysis of the incidence of early postoperative complications depending on a surgical technique**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Postoperative bleeding	2 (3.1%)	3 (4.6%)
Transient hypoparathyroidism	5 (7.7%)	6 (9.2%)
Vocal fold paresis	5 (7.7%)	6 (9.2%)

All  $p > 0.05$ .

surgery indications, including multinodular goiter in 79 (60.8%) patients, recurrent disease – in 80 (61.5%) patients, cardiovascular complications – in 38 (29.2%) patients, among which the heart valvular insufficiency with heart insufficiency (degree III) was observed in 25 (19.2%) patients, atrial fibrillation – in 10 (7.69%) patients; thyrotoxic ophthalmopathy was diagnosed in 38 (29.2%) patients, presence of thyroid lesions – in 33 (25.38%) patients, and a drug allergy – in 3 (2.3%) patients.

The analysis of the outcomes of surgical treatment is given in Table 2.

The comparison of surgical outcomes following TT and ST didn't reveal any statistically significant differences in such evaluation criteria as the average surgery duration, the average volume of intraoperative blood loss and the average duration of the postoperative inpatient treatment.

The comparative assessment of the thyroid stump volume and the average amount of drained discharge showed statistically significant differences for TT. Thus, both surgeries have the same risk of causing complications under equal initial conditions.

Early postoperative complications are given in Table 3. There were no statistically significant differences in postoperative states of patients after ST and TT (see Table 2).

The analysis of each clinical case revealed that the early postoperative period was complicated with subcutaneous vessel bleeding in 1 patient, bleeding from the right superior artery in 2 patients, bleeding from the right vascular pedicle in 1 patient, and bleeding from the thyroid stump in 1 patient.

The symptoms of transient hypoparathyroidism were observed on the 3th-5th day in 6 (9.25%) patients after TT and in 5 (7.7%) patients after ST.

It is commonly known that in most cases the vocal fold mobility is impaired due to the damage to the recurrent laryngeal nerves during surgeries [4, 6]. The recurrent laryngeal nerves can be damaged due to the deformation and anatomical mapping relationships caused by significant thyroid enlargement, anatomical proximity of the recurrent laryngeal nerve to the inferior thyroid artery, excessive use of electric coagulation, postoperative edemas, hematoma or nerve involvement into a cicatrization [20, 22].

Based on the course and duration, injuries of the recurrent laryngeal nerves are divided into two categories: transient disturbances lasting up to 6 months, and persistent disturbances which last over 6 months [10, 25].

Usually, during the early postoperative period, the available instrumental methods do not allow objective differentiation of pareses and paralyse

Table 4. **Comparative analysis of late postoperative complications in patients with GD**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Vocal fold paresis	1 (1.5%)	2 (3.1%)
Persistent hyperparathyroidism	1 (1.5%)	3 (4.6%)
Thyrotoxicosis recurrence	0	2 (3.1%)

All  $p > 0.05$ .

Table 5. **TSHR-Ab levels (IU/mL) observed in GD patients during different postoperative periods after ST and TT**

Period	Group 1 (n = 65)	Group 2 (n = 65)
6 months	13.93 ± 3.7	19.89 ± 4.2
12 months	8.55 ± 3.08	11.61 ± 3.97
5 years	1.15 ± 0.13	5.48 ± 0.42*

\* The difference between the groups is statistically significant ( $p < 0.05$ ).

the recurrent laryngeal nerves, whereas the impaired mobility of vocal folds can be diagnosed [4, 15]. During this early postoperative period, the unilateral damage of a recurrent laryngeal nerve can cause reflex spasms of a contralateral vocal fold, thus simulating the complete laryngeal paresis [12, 16].

The analysis of each clinical case of damaged recurrent laryngeal nerves revealed hoarseness, aphonia, moderate or severe breathing disorders, and coughing fits in 16 (12.14%) patients on the 1st postoperative day.

During the mirror laryngoscopy, paresis of a right vocal fold was detected in 3 (2.3%) patients, paresis of a left vocal fold — in 4 (3.0%) patients, and bilateral paresis — in 4 (3.0%) patients, paresis of a left vocal fold, and paresis of a right vocal fold — in 2 (1.54%) patients, paresis of a right vocal fold and paresis of a left vocal cord — in 1 (0.76%) patient, and bilateral paresis, of vocal folds — in 2 (1.54%) patients. The comparison of the occurrence of this complication did not show any statistically significant difference for both groups.

Thus, summarizing the results obtained during the study of early postoperative complications, we can conclude that no probable differences related to the occurrence of such complications as bleeding, hyperparathyroidism, and paresis of the recurrent laryngeal nerves were observed for both of the

studied surgical methods of treatment of GD (ST and TT) ( $\chi^2$ -test according to the criterion).

Late postoperative complications include vocal fold paresis, persistent hyperparathyroidism and recurrences of thyrotoxicosis. The development of these late postoperative complications was analyzed based on the clinical and hormonal examination of patients within periods from 6 to 12 months (for vocal fold paresis, and persistent hyperparathyroidism) and five years (for thyrotoxicosis recurrences) after the surgery.

The analysis of late postoperative complications in patients with GD is given in Table 4.

No statistically significant difference was detected for the occurrence of vocal fold paresis, persistent hyperparathyroidism and thyrotoxicosis recurrence in the study groups. After surgeries (ST and TT), the postoperative hypothyroidism was diagnosed in 124 (95.4%) patients; after ST surgeries, the euthyroid state was observed in 6 (4.6%) patients, and two of them had delayed thyrotoxicosis recurrences: after 16 months and within 24 months after surgery. The radioiodine treatment was administered in case of thyrotoxicosis recurrences ( $I^{131}$ ).

All patients with postoperative hypothyroidism (95.4%) were prescribed thyroid hormones (Euthyrox, L-thyroxin) as the substitution therapy. Daily doses of hormonal drugs in the group of patients after ST was  $125.5 \pm 12 \mu\text{g}$ , and in the group of patients after TT —  $131.75 \pm 14 \mu\text{g}$ . Thus, no probable difference in the thyroid hormone doses was observed for patients of both groups ( $p > 0.05$ ).

According to the aims of the study, a comparative analysis of TSHR-Ab levels during different postoperative periods was carried out. The patterns of the reduction of TSHR-Ab levels in ST and TT patients one year after surgery and in the late (5 years) period after it were studied. Table 5 provides levels of TSHR-Ab during different post-ST and post-TT periods.

The long-term observation (5 years) showed that the TSHR-Ab level reduced by 76.2% (compared with the initial value) in the group after ST, and by 91.7% — in the group after TT. The difference is statically significant ( $p < 0.05$ ). The post-TT level of TSHR-Ab was  $1.15 \pm 0.13 \text{ IU/L}$ , thus corresponding to the normal level. However, the same improvement was not observed in ST patients. After ST, the TSHR-Ab level for the same period was statistically significantly higher than reference levels.

The analysis of the patterns of the TSHR-Ab levels determined that long-term levels of the anti-thyroid antibodies were statistically significantly lower in patients after TT than in patients after ST ( $p < 0.05$ ).

The incidence of complications developing with different surgical strategies used for GD (TT and ST) was comparable while long-term postoperative TSHR-Ab levels were statistically significantly lower in patients after TT compared with patients after ST. It justifies the use of TT for these patients.

## Conclusions

The long-term (5 years) postoperative level of TSHR-Ab was statistically significantly lower in the group of patients after TT and made up  $1.15 \pm 0.13$  IU/L (thus corresponding to the normal level).

Total thyroidectomy is an optimal surgical technique and is more appropriate compared with subtotal thyroid gland resection. It should be noted that TT has the same risk of causing complications but no recurrence of thyrotoxicosis.

## AUTHOR CONTRIBUTIONS

Study concept and design, data collection and analysis, article writing, review, and final article approval — S. L. Shliakhtych; study concept and design, data collection and analysis, review, and final article approval — V. R. Antoniv.

## DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare.

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# Результати хірургічного лікування хвороби Грейвса залежно від показників антитиреоїдних антитіл

С. Л. Шляхтич<sup>1,2</sup>, В. Р. Антонів<sup>1</sup>

<sup>1</sup> Національний медичний університет імені О. О. Богомольця, Київ

<sup>2</sup> Київська міська клінічна лікарня № 3

Хвороба Грейвса (ХГ) — це спадкове аутоімунне захворювання, що характеризується стійкою патологічною гіперсекрецією тиреоїдних гормонів із розвитком синдрому тиреотоксикозу. Частота ХГ у різних регіонах становить від 0,5 до 2,0%. У 46% пацієнтів розвивається ендокринна офтальмопатія. Хвороба Грейвса часто є причиною інвалідизації працездатного населення віком до 60 років. Упродовж останніх років поширення ХГ в Україні зросло на 9,9% — зі 106,2 до 117,9 випадку на 100 тис. населення. Це може бути пов'язано як з поліпшенням діагностики і активним виявленням захворювання, так і зі збільшенням кількості аутоімунних уражень щитоподібної залози. Тривають дослідження з профілактики специфічних ускладнень і рецидивів при оперативному лікуванні ХГ.

**Мета** — порівняти рівні антитіл до рецептора тиреотропного гормону (АТ-РТТГ) у різні строки після хірургічного лікування, а також частоту ранніх та пізніх післяопераційних ускладнень при різному обсязі хірургічного лікування хвороби Грейвса.

**Матеріали та методи.** Проведено порівняння результатів хірургічного лікування 130 пацієнтів з ХГ (29 чоловіків і 101 жінка віком від 19 до 76 років (середній вік —  $(44,1 \pm 3,2)$  року), які перебували на лікуванні у Київському центрі ендокринної хірургії в період з 2010 до 2018 р. Тривалість захворювання на момент операції становила від 1 до 30 років (у середньому —  $(4,6 \pm 1,2)$  року). Пацієнтів рандомізували на дві групи залежно від обсягу хірургічного втручання: у першій ( $n=65$ ) проведено тотальну тиреоїдектомію (ТЕ), у другій ( $n=65$ ) — субтотальну резекцію щитоподібної залози (СРЩЗ). Проаналізовано тривалість оперативного втручання, кількість ранніх (кровотечі та пошкодження поворотних гортанних нервів) та віддалених результатів операційного втручання (розвиток стійкого гіпотиреозу і рецидивів тиреотоксикозу) залежно від обсягу операції. Також вивчено динаміку зменшення вмісту АТ-РТТГ у різні строки після операції.

**Результати.** При порівнянні результатів ТЕ та СРЩЗ не виявлено статистично значущої різниці за такими критеріями оперативного втручання, як середня тривалість операції, середній об'єм інтраопераційної крововтрати і середня тривалість післяопераційного стаціонарного лікування. Групи статистично значущо відрізнялися за об'ємом кукси щитоподібної залози, середньою кількістю виділень по дренажу. Отримані результати дають підставу вважати ТЕ оперативним втручанням з меншим ризиком виникнення ускладнень. За кількістю ранніх післяопераційних ускладнень статистично значущої різниці між групами не виявлено ( $p > 0,05$ ). Через 5 років після ТЕ рівень АТ-РТТГ знижувався до референтних значень ( $(1,15 \pm 0,13)$  МО/л), після СРЩЗ — залишався високим ( $(5,48 \pm 0,42)$  МО/л;  $p < 0,05$ ).

**Висновки.** Вважаємо ТЕ порівняно із СРЩЗ оптимальним за об'ємом оперативним втручанням з меншим ризиком виникнення ускладнень з огляду на статистично значущо нижчий рівень АТ-РТТГ у віддалений післяопераційний період.

**Ключові слова:** антитіла до рецептора тиреотропного гормону, хвороба Грейвса, субтотальна резекція щитоподібної залози, тиреоїдектомія.

## FOR CITATION

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