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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**MODERN ASPECTS OF IMPROVING
THE DIAGNOSIS AND SURGICAL TREATMENT
OF NODULAR GOITERS**

Specialty: 3213.01 – Surgery

Field of science: Medicine

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GENERAL CHARACTERISTICS OF SCIENTIFIC WORK

Relevance of the topic and the degree of its scientific elaboration. Nodular goiter is a widespread disease affecting approximately 5-7% of the world's population. About 70% of the population in endemic areas can detect nodules on thyroid gland ultrasound. Recently, thanks to improvements in modern diagnostic methods, these numbers continue to increase¹.

Ultrasound, fine-needle biopsy, hormonal blood tests, radioisotope scintigraphy, and computed tomography are the mainstays of nodule diagnosis. Fine-needle biopsy of small nodules detected by ultrasound reveals tumor cells in 12% of cases. Among patients with negative biopsy results from suspicious nodes, malignant degeneration is registered in about 20% of observations. Pathohistological examination of the gland removed during surgery confirms the presence of malignant tumor in 8.5-10% of cases^{2,3}.

There are 3 main approaches to the treatment of nodular goiter: clinical observation, hormonal suppressive therapy with levothyroxine, and surgery. Start hormonal suppressive therapy with levothyroxine for small nodules, continue conservative treatment if the size does not increase, and if the size increases, consider surgery. However, the efficacy of hormonal levothyroxine treatment in reducing the size of nodules and glands is controversial, and there are a number of negative side effects^{4,5}.

¹ Knobel, M. Etiopathology, clinical features, and treatment of diffuse and multinodular nontoxic goiters / M. Knobel // *Journal of Endocrinological Investigation*. - 2016. - Vol. 39. № 4. – P. 357-373

² Durante, C. The diagnosis and management of thyroid nodules: a review // *JAMA*. - 2018. Vol. 319. № 9. – P. 914

³ Bayani, M. Efficacy of levothyroxine on benign thyroid nodule / M. Bayani, M. Amani, Z. Moazezi – Text : direct. - 2012. – P. 4

⁴ Koc, M. Effect of low- and high-dose levothyroxine on thyroid nodule volume: a crossover placebo-controlled trial: Levothyroxine suppressive treatment of thyroid nodules // *Clinical Endocrinology*. - 2002. - Vol. 57. № 5. – P. 621-628

⁵ Gluvcic, Z. Levothyroxine treatment and the risk of cardiac arrhythmias – focus on the patient submitted to thyroid surgery // *Frontiers in Endocr.*-2021. -Vol. 12. – P. 758043

Prolonged drug treatment costs patients financially. Against the background of ineffective conservative treatment, in most cases people have to decide to undergo surgery, which leads to a violation of the quality of life of patients. On the other hand, long-term drug treatment has a damaging effect on organs and tissues. Overdiagnosis and early indications for surgery burden health care systems, increase costs and reduce resources for patients who need treatment the most^{6,7}.

There are no specific prognostic criteria that can accurately indicate the treatment of a patient with gland volume, size and number of nodes. Due to the size of the thyroid nodule, it is not considered adequate to keep the patients on hormonal treatment for a long time, because if it is not possible to predict whether the nodule will shrink or grow, it iatrogenically affects the functional state of other organs and systems⁸.

After some time, metabolic disturbances and absorption of already taken drugs in the liver reduce the effectiveness of hormonal treatment. This may lead to the ineffectiveness of the necessary hormone replacement therapy even after surgery^{9,10}.

Thus, some issues of diagnostics, prognosis and treatment of nodular goiter are still unsolved and today are considered as actual problems of surgical endocrinology. Our long-term practical experience, a sufficiently large amount of our clinical material gave us a reason to conduct a new retrospective and prospective clinical study in the mentioned area.

⁶ Qian, J. Real world evidence in effectiveness, safety, and cost savings of generic levothyroxine: a systematic review / J. Qian, K.A. Tanni – Text : direct // *Endocrine*. - 2021. - Vol. 74. № 2. – P. 228-234

⁷ Hegedüs, L. Primary hypothyroidism and quality of life // *Nature Reviews Endocrinology*. - 2022. - Vol. 18. № 4. – P. 230-242

⁸ Grani, G. Contemporary thyroid nodule evaluation and management // *The Journal of Clinical Endocrinology & Metabolism*. - 2020. - Vol. 105. № 9. – P. 2869-2883

⁹ Ianiro, G. Levothyroxine absorption in health and disease, and new therapeutic perspectives // G, Ianiro, F, Mangiola, TA, Di Rienzo [et al.] *Eur Rev Med Pharmacol Sci*. - 2014. - Vol.18, № 4. – P. 451-456

¹⁰ Ochani, S. Adverse effects of long-term levothyroxine therapy in subclinical hypothyroidism / S. Ochani, A. Siddiqui, A. Adnan – Text : direct // *Annals of Medicine and Surgery*. - 2022. - Vol. 76. – P. 103503

Object and subject of the study.

The material of clinical research was collected on patients who were on inpatient treatment with the diagnosis of nodal and multinodular nontoxic goiter in the Department of Endocrine Surgery of the Scientific and Surgical Center named after academician M.A. Topchubashov. The study consisted of retrospective and prospective analysis. The material of the retrospective part of the study consisted of 146 patients who were hospitalized and underwent surgery, diagnosed with nodal and multinodular goiter. On the basis of the analysis of the results of examination of these patients the prognostic criteria of nodules showing resistance to hormonal suppressive therapy were determined. The material of the prospective part of the study consisted of 174 patients with treatment-resistant nodules selected on the basis of the criteria determined by the retrospective analysis. Within this material, the results of treatment of patients who agreed to direct surgery and those who received hormonal treatment for 1 year and then underwent surgery were compared. Blood lipid profile, liver function tests, and quality of life were compared in both groups of patients.

Purpose of the study: To investigate the effectiveness of a new approach to improve the results of diagnosis and surgical treatment of patients with nodular goiter.

Objectives of the study:

1. To prepare prognostic criteria for nodules showing resistance to hormonal treatment based on factors such as age, gland volume, functional status, nodule size, number among patients undergoing surgery diagnosed with nodal goiter;
2. To test the detrimental effect of hormonal suppressive therapy on liver tissue as well as on the functional activity of the organ in comparison with the group of directly operated patients;
3. Comparative analysis of changes in lipid content and metabolism in blood as a result of long-term hormonal-suppressive treatment in patients undergoing direct surgical intervention;
4. Comparative study of quality of life in patients undergoing early surgery for thyroid nodules and long-term hormonal treatment using the SF-36 questionnaire.

Study Methods. Initially, 203 articles investigating surgical treatment of nodular thyroid disease, prognostic factors, factors affecting treatment outcomes, immediate and distant postoperative results, quality of life of patients after surgery were reviewed and a literature review was prepared in written and electronic literature.

At the next stage, the results of examination and treatment of patients operated on with the diagnosis of nodular thyroid diseases in the Scientific and Surgical Center named after academician M.A. Topchubashov were analyzed. The main purpose of this study was to compare patients in whom nodules decreased as a result of hormonal suppressive therapy and patients in whom hormonal treatment was ineffective. For this purpose, the results of anthropometric parameters, nutrition, lifestyle, blood tests and clinical and instrumental examinations were compared, and statistical analysis revealed predictors of nodules not subject to hormonal treatment.

At the third stage, the examinations of patients with predictors of nodules resistant to hormonal treatment were analyzed. The prospective study compared the results of treatment of patients who underwent direct surgical intervention and those who received hormonal suppressive therapy with levothyroxine for a long time before surgery. In these patients we compared the indicators of the functional state of the liver, indicators of specific enzymes and pigment metabolism, ultrasound results. At the same time, changes in blood lipid content were studied in a comparative order.

At the fourth stage, statistical processing of data was carried out. Parametric and nonparametric methods, IBM SPSS STATISTICS-20 program were used in statistical processing.

At the fifth stage, the quality of life was studied by communicating with the operated patients through questionnaires. The quality of life of patients who received hormonal treatment before surgery and patients who underwent direct surgical intervention was studied comparatively.

At the last stage, the results obtained during the study were summarized and presented in the form of conclusions and practical recommendations. It has been proved that patients with predictors of resistance to hormonal treatment do not need hormonal suppressive therapy.

The main provisions submitted for defense:

– There are no criteria in the literature that can predict whether levothyroxine treatment in nodular goiter will be effective or ineffective in shrinking nodules. In our study, using predictors determined from ultrasound examination of nodules, a prognostic assumption can be made as to whether a nodule will undergo hormonal treatment or show resistance.

– Patients with nodules with predictors of resistance to hormonal therapy should be offered direct surgical intervention. Hormonal treatment is ineffective in these patients. In addition to the ineffectiveness of conservative treatment, it causes economic damage to patients as well as psychological problems in daily life.

– Hormonal treatment for a long time has a damaging effect on hepatocytes and the functional capacity of the liver is depleted. Indicators of hepatocyte damage are increased activity of specific blood enzymes, pigment metabolism disorder. In cases where hormone replacement therapy is needed after surgery, the necessary effect cannot be achieved, because patients have impaired metabolism of the drug.

– Hormonal-suppressive therapy for a long time has a negative effect on lipid metabolism, accompanied by a decrease in the concentration of benign lipoproteins in the blood, an increase in cholesterol and other dangerous lipids.

– Patients who underwent direct surgery had better outcomes than patients who received hormonal suppressive therapy before surgery. This is reflected in both quality of life indicators and functional parameters of the digestive system.

Scientific novelty of the research work:

1. Prognostic criteria have been developed, allowing to determine in advance the nodes resistant to hormone-suppressive treatment in patients with nontoxic nodal and multinodular goiter on a large clinical material.

2. Side effects of prolonged hormonal treatment on the liver in patients with nodular goiter showing resistance to treatment have been established. As a result of fatty degeneration of the liver and impaired functional activity of hepatocytes, hormone replacement therapy after

thyroidectomy does not give the necessary effect or requires an increase in the dose of hormone.

3. In patients receiving long-term hormonal-suppressive treatment, there are changes in the lipid composition of the blood, increasing the risk of atherosclerotic process in the vessels and the occurrence of diseases of the cardiovascular system.

4. The quality of life of patients with early surgery of nodular goiter and long-term hormonal treatment has been comparatively studied. In 3, 6 and 12 months after the operation it was found out which parameters of the quality of life change in dynamics.

Practical relevance of the work:

The ability to predict in advance the ineffectiveness of hormonal suppressive therapy in nodular goiter may allow the selection of adequate treatment tactics in this type of patients, as well as improve the results of surgical treatment of nodular goiter.

Adequate assessment of changes in liver function and blood lipid composition due to the effect of hormone suppressive therapy may lead to improved treatment outcomes.

The study of the quality of life of patients who received hormone suppressive therapy for a long time after the diagnosis of nodal goiter and patients who underwent direct surgical intervention will be able to provide new recommendations in the rehabilitation of patients.

Relation of the research to the problem plan of medical sciences:

The topic of the dissertation is included in the scientific plan of the Department of Endocrine Surgery of the Scientific and Surgical Center named after academician M.A. Topchubashov PLE.

Approval of the work:

The dissertation was discussed at a joint meeting of the departments of Endocrine, Vascular, Hepatic, biliary and pancreatic surgery, Surgery of the esophagus, Stomach and duodenum, coloproctology and the Clinical diagnostic laboratory department of the Scientific Surgical Center named after academician M.A.Topchubashov PLE Ministry of Health (13.01.2023) and at the Scientific Seminar at the Scientific and Surgical Center named after academician M.A.Topchubashov (protocol № 1 of 09.10.2023).

Application of the work in practice. The obtained results were used in the treatment of patients of the endocrine surgery department of Scientific Surgical Center named after academician M.A.Topchubashov PLE.

Organization where the dissertation work was performed. The dissertation work was performed on the basis of the endocrine surgery department of the Scientific and Surgical Center named after academician M.A.Topchubashov PLE of the Ministry of Health.

Published scientific works: 11 scientific articles and 6 theses on the subject of the dissertation were published in periodical scientific editions.

Scope and structure of the work. The dissertation is written in Azerbaijani language in A4 format, "Times New Roman" 14 font and 1.5 line spacing, including table of contents (2891 characters), introduction (15551 characters), literature review (47705 characters), II chapter on research materials and methods (25636 marks), chapter III covering personal research (19900 marks), discussion of obtained results chapter IV (36109 marks) covering results and their discussion V (12822 marks), conclusion (41012 marks), results (1635 marks), practical recommendations (8902 signs), consisting of sections, is given on 151 pages (total volume with signs is 206,220). The dissertation is illustrated with 9 tables and 23 pictures. The bibliography includes 203 sources, 30 of which are works by local scientists and other works of Russian and other foreign scientists.

RESEARCH MATERIALS AND METHODS

To address the goals and objectives of the scientific work, retrospective and prospective studies were conducted. Basically, the material of the study consisted of patients who were on inpatient treatment with the diagnosis of nodular goiter in the endocrine surgery department of the Scientific and Surgical Center named after academician M.A. Topchubashov.

The material of the retrospective study consisted of 146 patients who underwent surgery with the diagnosis of nodular and multinodular nontoxic goiter, 138 of them were women and 8 men. The patients

were conditionally divided into 3 places depending on the area of residence: Absheron peninsula, endemic zones and other regions. Of the 146 patients, 77 were residents of the Absheron Peninsula, 8 were from the endemic zone, and 61 patients were from other regions. The age range of retrospectively analyzed patients ranged from 16 to 69 years, the mean age was 44.8 ± 1.03 years, and the duration of history was 5.5 ± 0.45 years. The patients were divided into 3 groups depending on the duration of the disease. In 86 patients (58.9%) the duration of the disease was less than 5 years, in 45 patients - from 5 to 10 years, in 15 patients - more than 10 years.

On admission, the main complaints of patients were discomfort in the neck, a feeling of tightness in the throat, difficulty breathing or choking, swallowing disorders, hoarseness of voice in some patients, dry cough in cases of pressure of the nodule on the trachea, cosmetic change in the configuration of the pharynx.

All patients included in the material were diagnosed with nontoxic nodular and multinodular goiter and were categorized according to the degree of gland growth based on the classification proposed by O.V.Nikolayev. Out of 146 patients, 76 (52.1%) patients were found to have grade III nodules, 46 (31.5%) to have grade IV nodules, and 24 (16.4%) to have grade V nodules. Goiter of all 3 degrees are divided into uninodular and multinodular groups.

At ultrasound, total gland volume averaged 45.5 ± 4.11 cm³, right lobe volume was 22.3 ± 3.19 cm³ and left lobe volume was 17.6 ± 1.67 cm³. Node size was generally based on three measurements: node length (mm); Node width (mm) and node thickness (mm) were calculated and determined for each column separately. Thus, the dimensions of knots in the right part on average were as follows: knot length, 15.3 ± 0.75 mm; knot width, 13.7 ± 0.96 mm; knot thickness, 25.4 ± 6.28 mm. In the right part, the smallest size was 7 mm and the thickness of the largest knot exceeded 62 mm. The average size of knots in the left part was as follows: knot length, 14.8 ± 0.68 mm; knot width, 12.7 ± 0.78 mm; knot thickness, 29.5 ± 5.09 mm. The thickness of the smallest knot in the left side was 9 mm, and the thickness of the largest knot was more than 52 mm. As for the size of the nodules on the neck, in 20 patients it was possible to determine only the length

and width of the node. Thus, the length of the nodes was 15.6 ± 1.89 mm; the width of the nodes was 12.9 ± 2.23 mm. In 1 patient, the thickness of the node in the isthmus was measured to be 30 mm.

All patients with thyroid nodules underwent general blood and urine analysis and biochemical blood analysis. The concentration of TSH in the blood of patients was on average 3.63 ± 0.52 mU

/l, T4 - (total) on average 7.81 ± 0.47 $\mu\text{g/dl}$, free T4 on average 1.04 ± 0.07 ng/dl was.

In phase II of the study, a prospective analysis of surgical patients diagnosed with nodular and multinodular nontoxic goiter was performed. A total of 174 patients presenting with a diagnosis of nodular goiter who presented with treatment-resistant nodules on examination were selected. These patients were informed about the results obtained in phase I of the study and offered direct surgery. 88 patients (main group) agreed to the proposal and were operated on soon after the first visit. Since the remaining 86 patients (control group) did not agree to surgery, they were started on hormone-suppressive drug treatment with levothyroxine.

Patients in the control group were under observation. After 3, 6, and 12 months, he was invited to the clinic and examined. Since after 6-12 months the treatment did not give the expected effect, the patients were again offered surgery, and after obtaining consent, the surgery was performed. The activity of liver-specific enzymes was studied in the blood analysis of control group patients immediately before surgery. The main purpose of the study was to compare the functional analysis of the liver of the main group of patients with the liver function tests of patients who had been receiving hormonal-suppressive therapy for a long time.

All numerical indicators obtained during the study were statistically analyzed taking into account modern recommendations. The mean (M), standard error (m), minimum (min) and maximum (max) values of this indicator were calculated for the indicators in the groups. The Wilcoxon (Mann-Whitney) criterion (U) was used to refine the results obtained taking into account the number of indicators in the groups and to determine the difference between the indicators in the groups. All calculations were performed in the EXCEL table, and

the results were summarized in tables and diagrams. IBM SPSS STATISTICS-20 program was used to calculate prognostic criteria and prognostic indicators. The receiver operating characteristic (ROC) curve is plotted to determine the cutoff value for various parameters.

ANALYSIS OF THE OBTAINED RESULTS

During the analysis of retrospective material it was found that in 90 out of 146 patients (61.6%) against the background of suppressive hormonal therapy it was possible to prevent the growth of nodules in the thyroid, and there was a statistically unreliable decrease in the size of individual nodules. In 56 patients (38.4%), despite hormonal treatment, the sizes of nodules not only decreased but also increased ($p < 0.05$). The nodules in these patients are commonly referred to as "treatment-resistant nodules".

Retrospective analyse showed, that there is no association between the age and sex of the patients and the response of the nodules to hormone suppressive therapy.

The total volume of the thyroid gland with treatment-resistant nodules was $53 \pm 5.85 \text{ cm}^3$, the right lobe volume was $28 \pm 5.03 \text{ cm}^3$, and the left lobe volume was $24 \pm 2.63 \text{ cm}^3$. Patients with treatment-resistant nodules had smaller thyroid gland size. Thus, the right lobe volume was 49.6% smaller to $15 \pm 2.95 \text{ cm}^3$ ($p < 0.01$), the left lobe volume was 38% smaller to $15 \pm 3.44 \text{ cm}^3$ ($p < 0.05$), and the total thyroid volume was 39% smaller at $33 \pm 5.50 \text{ cm}^3$ ($p < 0.05$). As previously mentioned, thyroid gland size was smaller in patients with treatment-resistant nodules compared to treatment-responsive nodules, and the difference between groups was statistically significant ($p < 0.05$).

When studying the number of nodules by lobes, it was found that the incidence of a single nodule was higher in patients with treatment-resistant nodules than in patients subject to treatment. The number of nodules in the right and left lobes of the gland were studied separately in a comparative manner. The study found that 31 patients (55.4%) and 25 patients (44.6%) had a single nodule in the right side of the gland in patients with treatment-resistant nodules. In patients on

treatment, the occurrence of a single nodule in the right lobe was recorded in 32% and in the left lobe in 35.6% of patients. In the comparative analysis in both groups, the presence of a single node in treatment-resistant patients was statistically significantly higher than in the other group ($p < 0.05$).

Another interesting finding was that sonographic examination of the thyroid gland of patients with treatment-resistant nodules revealed calcinates in the nodules in 16 of 56 patients (28.6%).

The analysis of our retrospective study revealed that in 90 (61.6%) of 146 patients, the size of the nodules in the gland did not change over time or slightly decreased with the difference not statistically significant. In 56 patients (38.4%), despite hormonal treatment, the size of the nodes not only decreased but even increased ($p < 0.05$). We conventionally named such patients as patients with treatment-resistant nodule (TRN). When comparing the results of examination of TRN patients and other patients, we found that if the size of the nodule exceeds 17 mm and calcinosis is found in the nodule, and the concentration of hormones in the blood is within the normal range, these nodules should be considered as treatment-resistant nodules. Retrospective analysis gave us reason to argue that in patients with treatment-resistant nodules, hormonal drug treatment will have no effect and there is no need to treat it for a long time.

As a result of preoperative examination it was proved that the activity of such enzymes as ALT and AST in patients of the control group was statistically significantly higher ($p < 0.05$) compared to patients of the main group. When analysing the results of total bilirubin and its fractions in blood, it was found that the amount of total bilirubin in the control group was higher than in the main group.

After surgery, both main and control group patients were treated with hormone replacement therapy. In 3, 6, 12 months after surgery these patients were re-examined and their quality of life was studied using a questionnaire. The activity of liver-specific enzymes: ALT, AST, ALP and GGT was determined, the amount of total bilirubin and its fractions was studied, liver ultrasound was performed. A comparative analysis of the results in the main and control groups was carried out.

The patients of both groups were operated. In biochemical blood tests performed 3, 6 and 12 months after surgery, different results were observed in the activity of liver-specific enzymes in patients of the main and control groups. Thus, in the main group ALT and AST were within normal limits in observations 3 months after treatment. In the control group ALT increased to 32.8 ± 0.86 V/l, AST - to 45.9 ± 1.73 V/l. If it is possible to assess the ALT index as the upper limit of normal, but it is reflected that AST is higher than normal. At 6 months after surgery, enzyme activity in the control group continued to increase. Blood tests taken after 6 months showed that both ALT and AST were above normal. In observations 12 months after treatment, the increase in enzyme activity was more intense in the control group.

In order to assess the functional activity of hepatocytes in participation of pigment metabolism, the concentration of total bilirubin and its fractions in blood in the main and control groups was comparatively studied. In the course of the study it was found that blood analyses taken 3 months after the operation showed that the concentration of total bilirubin in the blood of patients of the control group was higher than normal ($23,0 \pm 0,6$ $\mu\text{mol/l}$). In 6 months after the operation total bilirubin decreased by 4.6%, and in 12 months it increased by 31.2% and reached 31.5 ± 0.83 $\mu\text{mol/l}$. The study of bilirubin fractions revealed such an interesting fact that the increase of free bilirubin concentration is more intensive. The change of total bilirubin was characterised predominantly within the normal range. Only 12 months after the operation in patients of the control group the total bilirubin fraction was slightly higher than normal (5.29 ± 0.18 $\mu\text{mol/l}$), and in the main group the total bilirubin fraction fluctuated within the normal range.

It is known that the liver plays an important role in metabolism in the body. With prolonged use of levothyroxine, some damage to hepatocytes occurs. As a result of imbalance of thyroid hormones synthesis, disturbance of cholesterol-triglyceride metabolism, changes in physicochemical properties of bile, bile thickening, increase of its viscosity create favourable conditions for development of cholelithiasis causing dyskinesia, stasis and stasis in biliary tracts ¹¹.

¹¹ Vergani, L. Lipid lowering effects of iodothyronines: In vivo and in vitro studies

A clinical case of the development of acute liver failure in a man treated with levothyroxine for a long period of time has been published in the literature ¹².

The results of our studies led to the formation of the following opinion: long-term administration of levothyroxine does not cause a decrease in the size of nodules in all patients, in some cases, on the contrary, it causes nodule growth within a short period of time or the formation of additional nodules. It was also confirmed that long-term use of levothyroxine causes changes in morphological structure and functional activity of the liver. A statistically significant increase in ALT and AST activity, which are signs of hepatocyte damage, was observed in patients of the control group.

Lipid metabolism is disturbed during hormone therapy, which causes fatty dystrophy of hepatocytes of the liver. As a result of changes in the functional activity of the thyroid gland, prolonged administration of hormones, conditions for the development of hepatic steatohepatosis due to metabolic disorders are created. The use of substitution therapy in these patients after surgery intensified this background. The concentration of total bilirubin in the blood increased mainly due to the increase of the free fraction as a result of the loss of the ability of hepatocytes with advanced fatty dystrophy to capture free bilirubin in the blood in patients of the control group.

In addition to the study of the changes in the functional state of the liver, the study of the changes in the lipid content of the blood as a result of systematic examinations in patients with nodular goiter and who have received hormonal suppressive treatment for a long time is also of interest.

First of all, it should be noted that in patients of the control group who had been receiving hormone-suppressive therapy for a long time, a number of changes in blood lipid composition were detected in blood tests taken before surgery. We checked the concentration of total

on rat liver / L. Vergani // World Journal of Hepat. - 2014. - Vol. 6. № 4. –P. 169

¹² Yu, H. Liver dysfunction induced by Levothyroxine Sodium Tablets (Euthyrox®) in a hypothyroid patient with Hashimoto's thyroiditis: case report and literature review // Endocrine Journal. - 2019. - Vol. 66. № 9. – P. 769-775

cholesterol, triglycerides, low and high density lipoproteins in the blood and compared the corresponding indices in the main group.

The amount of total cholesterol in the blood of the control group patients before surgery was calculated as 205.8 ± 6.55 mg/dl, whereas in the main group patients it was equal to 181.3 ± 5.65 mg/dl. In both groups, the amount of total blood cholesterol in the main group was statistically significantly lower than in the control group ($p < 0.05$).

As for the amount of triglycerides in the blood, both the control (150.4 ± 4.79 mg/dl) and the main group (148.9 ± 4.6 mg/dl) patients had the values of this indicator within the normal range, the difference between the results in the groups it was not statistically honest ($p > 0.05$).

The concentration of high-density lipoproteins in the blood of patients of the control group in the preoperative period averaged 50.08 ± 1.62 mg/dl, and in the main group of patients this index was equal to 52.8 ± 1.64 mg/dl. This index is also within the normal range and statistically significantly does not differ from the index in the control group. Low density lipoproteins in the blood of the control group were equal to $129,9 \pm 4,14$ mg/dl, which is very close to the dangerous concentration. In the main group of patients the concentration of this type of lipoproteins in the blood was at the level of 111.0 ± 3.46 mg/dl and was statistically significantly lower than the index in the control group ($p < 0.001$).

All patients were invited to the clinic 3, 6, and 12 months after surgery and the above lipids in venous blood in the morning after a 12-hour fast. In blood tests performed 3 months after surgery, total cholesterol increased by 9.1%, high-density lipoproteins by 12.4%, triglycerides decreased by 7%, and low-density lipoproteins by 2%. In the control group, an increase in the concentration of all lipid-containing substances was recorded. Compared with preoperative indices, cholesterol increased by 8.9% to 224.1 ± 3.03 mg/dl, triglycerides increased by 11.8% to 168.1 ± 2.27 mg/dl, while high-density lipoproteins increased by 10.3% to 56.0 ± 0.76 mg/dl and low-density lipoproteins increased by 3.6% to 134.5 ± 1.82 mg/dl. The difference in the values of the above indices in the control group was statistically significantly different from those of the main group, as well as from the preoperative indices of this group ($p < 0.05$).

The rate of increase in blood cholesterol and triglycerides in the control group patients was chosen because it was more intense than in the main group. In the control group, 6 months after surgery, total cholesterol increased by 17.6% and triglycerides by 45.3%, and in the results obtained 12 months after surgery, the mentioned parameters increased even more and finally cholesterol was 257.7 ± 3.49 mg/dl and triglycerides reached 245.4 ± 3.32 mg/dl. The results of both total cholesterol and triglycerides obtained 12 months after surgery were statistically significantly higher than those in the main group ($p < 0.05$).

On the other hand, in the control group, changes in blood lipoprotein composition were more pronounced. Thus, in patients of the control group, the concentration of high-density lipoproteins in the blood, considered relatively benign, decreased by 12% at 6 months after the operation compared with the first 3 months and by 6.8% at 12 months after the operation. Thus, the concentration of high-density lipoproteins in the blood of patients in the control group, which is considered to be relatively benign, decreases by 12% 6 months after surgery compared to the first 3 months, and by 6.8% after 12 months of surgery, finally 45.9 ± 0.62 mg down to /dl. Compared with the result obtained 3 months after surgery, a 17% increase in the concentration of low-density lipoproteins was observed in blood tests taken 6 months later, and after 12 months it increased to 161.4 ± 2.18 mg/dl.

It was found that total cholesterol and low-density lipoproteins in the blood of the control group patients receiving long-term hormonal suppressive therapy were significantly higher in the blood of the main group patients compared to the main group patients. The concentration of triglycerides was characterised by an unfair difference between the groups.

The concentration of high-density lipoproteins in the blood of the control group patients included in our study averaged 50.8 ± 1.62 mg/dl, which is lower than in the main group patients. The concentration of cholesterol and low-density lipoproteins in the control group of patients is high, and high-density lipoproteins are insufficient, which indicates the disorders of lipid metabolism in patients who received suppressive treatment for a long time. The aim to emphasise the facts obtained in our analysis is that low

concentration of high density lipoproteins is a risk factor for the development of atherosclerosis. On the contrary, an increase in the concentration of low-density lipoproteins has a stimulating effect on the process of atherosclerosis.

In the postoperative period of 3, 6 and 12 months in both groups there was an increase in the concentration of cholesterol, triglycerides and low-density lipoproteins. But in the main group the rate of increase of these changes in lipid metabolism was more moderate. If in the main group the level of high-density lipoproteins fluctuated near the lower limit of the norm, in the control group it decreased to 45.9 ± 1.62 mg/dl, which is considered dangerous.

Thyroid nodule volume reduction has been observed as a result of levothyroxine therapy only in a certain proportion of patients with nodules. In patients receiving long-term levothyroxine therapy, nodule growth or formation of new nodules is observed after sudden withdrawal of the drug. Changes in blood lipid composition occur in patients receiving long-term hormonal suppressive therapy, which creates conditions for the development of atherosclerotic process in vessels. A milder character of changes in blood lipid composition after surgery in patients selected according to the criteria of treatment-resistant nodules was noted. The concentration of "benign lipoproteins" (high-density lipoproteins) in the blood of patients of this group is higher than in patients who were treated with levothyroxine for a long time. In the control group, changes in blood lipid composition tend to worsen in dynamics, increasing the risk of cardiovascular diseases in these patients. In order to correct lipid metabolism disorders in patients it is necessary to prescribe additional drugs, which requires taking two drugs (levothyroxine and lipostatic).

One of the important moments in the postoperative period is the determination of the quality of life index of patients. We studied the quality of life of patients undergoing thyroidectomy in the postoperative period. For this purpose, the SF-36 questionnaire (Short Form of Medical Outcomes Study) was used. In this form, the assessment is made on 8 scales, by scoring a certain number of points, it is possible to give a conclusion about the quality of life of patients. The 8 main parameters assessing the quality of life of patients are:

Physical activity (PA); Daily physical activity (DPA); Body pain (BP); General health (GH); Life activity (LA); Social action (SA); Emotional state (ES); Mental health (MH) was studied. The values of each scale range from 0 to 100. 100 is an indicator of complete health. The integrity of the difference between ranks is determined on the basis of Student's coefficient, the difference between the indicators is considered reliable at $p < 0.05$.

To assess gastrointestinal discomfort at 3, 6, and 12 months after surgery, patients were approached by telephone and asked to rate their overall digestive discomfort using the GSR scale. A special questionnaire was sent to the patients and the results of the responses were compared between the patients in the main and control groups.

In the course of our study, it was found that the quality of life index in the patients of the main and control groups according to the results of the examination 3 months after surgery was almost the same. However, analysis of the scores for the parameter "Mental health" showed that the patients of the control group had a lower mental status than the patients of the main group. When examined 6 months after surgery, the main group of patients had a better quality of life according to the parameters Physical Activity, Body Pain, and Emotional Status, and the difference between the results was statistically significant (Fig. 1).

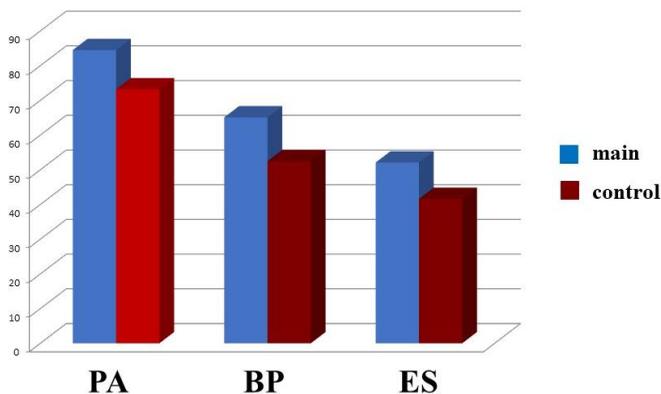


Figure 1: Parameters are significantly different between groups 6 months after surgery. Note: PA - Physical activity; BP - Body pain; ES - Emotional state.

12 months after surgery, the assessment of all the above-mentioned quality of life parameters was better in patients of the control group, the difference between the results was statistically significant ($p < 0.05$).

On the other hand, prolonged administration of levothyroxine can manifest itself in disorders in the digestive system. On the background of dyspeptic disorders may manifest changes in biliary function of the liver as a result of the effects of hormonal treatment.

During the prospective analysis, the results of the questionnaire given to the patients were analysed to verify the disorders caused by the digestive tract organs according to the GSRS scale. Evaluation of complaints of pain and heaviness in the right upper abdomen, foaming, nausea, discomfort by scores showed that the intensity of complaints was lower and less frequent in the main group of patients.

Thus, the occurrence of the criteria we have defined in patients with nodular goiter allows us to predict in advance that hormonal suppressive therapy may be ineffective in these patients. According to this tactic, patients with nodules showing resistance to treatment do not need hormonal suppressive therapy, will not have the expected effect, and should be taken immediately to surgery. Since prolonged hormonal treatment given in the preoperative period will lead to iatrogenic changes in blood lipid composition in the direction of increased atherogenicity. These changes will further lead to the development of fatty liver dystrophy, as well as to the occurrence of pathological processes in the cardiovascular system in patients. Thus, having selected patients with nodular goiter in advance, it is possible to insure patients from changes in blood lipid composition in the postoperative period and at the same time to provide better quality of life.

RESULTS

1. Age, sex, place of residence of the patient, concentration of TTG, Anti-TPO and Anti-TG in blood have no prognostic value in terms of thyroid nodule resistance to hormonal treatment. Thyroid volume $\leq 15.8 \text{ cm}^3$, node size $\geq 17 \text{ mm}$, 1 node and presence of calcification in the node have prognostic value and are predictors of treatment-resistant nodes.
2. Hepatocyte dysfunction started 3 months after surgery in the control group receiving levothyroxine. After 6 months, ALT and AST were above normal and GGT activity increased by 25% and differed from the main group ($p < 0.05$). After 1 year, an increase in ALT and AST activity of 26.8% and 50.1% ($p < 0.05$), respectively, is an indication of hepatocellular damage due to hormonal treatment.
3. In the control group 6 months after surgery in the control group, cholesterol increased by 17.6% and triglycerides by 45.3%, and after 12 months increased by $257.7 \pm 3.49 \text{ mg/dl}$ and $245.4 \pm 3.32 \text{ mg/dl}$. Its increase indicates an increase in atherogenicity of blood. Whereas in the main group, the level of high density lipoproteins fluctuated within the lower limit of normal, in the control group it decreased to $45.9 \pm 1.62 \text{ mg/dl}$ ($p < 0.05$), which is considered dangerous. In the control group, deterioration of blood lipid content increases the risk of cardiovascular diseases.
4. Quality of life in the main group was only Mental Health (57.6 ± 1.4 points) at 3 months after thyroidectomy and at 6 months Physical Activity (84.5 ± 1.8 points), Body Pain (65.1 ± 2.5 points) and Emotional State. (52.1 ± 1.3 points) criteria were better ($p < 0.05$). At 12 months after surgery, all quality of life parameters of the patients in the main group were evaluated with a higher score than the control group. The quality of life in the control group was relatively low, and the difference between the results was statistically significant ($p < 0.05$).

PRACTICAL RECOMMENDATIONS

1. Prolonged administration of hormonal therapy for nodular goiter is not without complications for patients. Using the prognostic criteria we have established, it is possible to continue hormonal therapy or determine an early indication for surgical intervention in patients with this condition.
2. When choosing the dose of hormone replacement therapy after thyroidectomy, attention should be paid to the functional state of the liver and take into account the results of ultrasound.
3. In patients receiving long-term hormonal treatment, it is clinically and practically important to diagnose blood lipid composition indices, assess the dynamics and take adequate measures in the direction of prevention of cardiovascular diseases atherosclerosis.
4. Improving surgical tactics is important in terms of optimising surgical outcomes as well as further improving the quality of life of patients.

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Conditional abbreviations

ALT – Alanine aminotransferase;
AST – Aspartate aminotransferase;
GGT – Gamma-glutamyltransferase;
ALP – Alkaline phosphatase;
TG – Triglycerides;
TSH – Thyroid stimulating hormone;
T₃ – Triiodothyronine;
T₄ – Tetraiodothyronine or Thyroxine;
USD – Ultrasound

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