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ABSTRACT

of the dissertation for the degree of Doctor of Science

MODERN ASPECTS OF DIAGNOSTIC AND TREATMENT TACTICS OF AUTOIMMUNE THYROIDITIS DISEASE

Specialty: 3213.01 - Surgery

Field of science: Medicine

Applicant: **Fatta Gafar oglu Sadikhov**

Baku – 2024

The work was performed at the endocrine surgery department of the Scientific Center of Surgery named after M.A. Topchubashov and at the Scientific-Practical Center of Laser Medicine named after O.K. Skobelkin of the Medical-Biological Agency of the Federal State Budgetary Organization of Russia (Moscow).

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02-12-2024-ü

GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and degree of development. Autoimmune thyroiditis is the most common disease of the thyroid gland, accounting for 46% of all thyroid pathologies [1]. Its incidence is around 5%-10% among the elderly population. In children, it occurs from 0.1% to 1.2% [2]. In the literature sources of recent years, there was no evidence of a decrease in the incidence of autoimmune thyroiditis, but an increasing trend was recorded [3]. According to the results of the research conducted by Q.D. Jikayev (2016), thyroid gland pathology was found in 35.1% of the autopsies of people who had not been diagnosed with thyroid diseases during their lifetime and died for other reasons. Among them, autoimmune thyroiditis was 11.4% [4].

Autoimmune thyroiditis has no pathognomonic clinical signs; the course of the disease is long, not always pleasant, and accompanied by complications. In some cases, autoimmune thyroiditis is manifested under the mask of other thyroid pathologies. It is sometimes accompanied by the formation of a nodular or multinodular tumor, and sometimes, reaching large sizes, by a complex complicated clinical course with the development of clinical hypothyroidism or diffuse-thyrotoxicosis with the development of fibrotic hardening of the thyroid gland [5]. When evaluating the development direction of the

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[1] Antonelli, A. Autoimmune thyroid disorders / A. Antonelli, S. M. Ferrari, A. Corrado [et al.] // Autoimmunity Reviews. – 2015. 14 (2). – p. 174-180.

[2] Rozhko, V.A. Current state of the problem of autoimmune thyroiditis // – Gomel: Problems of health and ecology. – 2019. V. 60. № 2. – p. 4-13.

[3] Zdor, V.V. New participants in the violation of tolerance to thyroid antigens: towards the concept of immunopathogenesis of autoimmune diseases of the thyroid gland / V.V. Zdor, E.V. Markelova, B.I. Geltser // – St. Petersburg: Medical immunology. – 2016. V. 18. №3. – p. 209-220.

[4] Dzhikaev, G.D. Morphological criteria for the diagnosis of chronic autoimmune thyroiditis: / Diss. ...cand. honey. Sciences: / – Volgograd; - 2016. – 117 p.

[5] Shidlovsky, V.A. Is Hashimoto's thyroiditis a medical or surgical problem? (Literature review) / V.A. Shidlovsky, A.V. Shidlovsky, M.I. Sheremet [et al.] // International Journal of Endocrinology. – Kyiv: – 2020. V. 16. № 3. – c. 245-250.

disease, the risk of malignancy associated with the hardening of the thyroid gland structure, the formation of fibrous casts, and the proliferation of thyrocytes cannot be excluded. In this regard, patients with autoimmune thyroiditis are at high risk of developing thyroid cancer [6].

In most cases, accurate morphological verification of thyroid nodules by FNAB (fine needle aspiration biopsy) allows us to determine the nature of the nodule and carry out differential diagnosis in a less sophisticated way. However, it is not always possible to confirm the diagnosis of autoimmune thyroiditis with cytomorphological signs. Sometimes, morphologically, thyrocytes of benign follicular neoplasias are indistinguishable from follicular carcinoma cells [7]. Such facts significantly complicate the determination of pathological changes in cells in autoimmune thyroiditis. A group of researchers unites all nodular derivatives of the thyroid gland under the term "follicular derivative," including nodules that occur on the background of autoimmune thyroiditis [8].

Many aspects of the diagnosis and treatment tactics of autoimmune thyroiditis have not yet been resolved, and today it is considered a very complex problem in surgical endocrinology [9]. These aspects, in turn, show the importance of clarifying indications for surgical treatment and developing adequate surgical tactics based on the analysis of the clinical course of the disease and examination data.

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[6] Choi, Y.J. Core-needle biopsy versus repeat fine-needle aspiration for thyroid nodules initially read as atypia/follicular lesion of undetermined significance / Y.J. Choi, J.H. Baek, C.H. Suh // Head Neck. – 2017. 39 (2). – p. 361-369.

[7] Mikhailova, M.V. Diagnostic and therapeutic tactics for “follicular tumor” of the thyroid gland / M.V. Mikhailova, I.N. Zubarovsky, S.K. Osipenko // – St. Petersburg: Bulletin of Surgery named after I.I. Grekova. – 2015. V. 174. № 2. – p. 77-80.

[8] Timofeeva, L.A. Priority of radiation diagnostic methods in the verification of thyroid pathology // – Moscow: Russian electronic journal of radiation diagnostics. – 2019. V.9. № 1. – p. 227-233.

[9] Ferrari, S.M. Novel therapies for thyroid autoimmune diseases: An update / S.M. Ferrari, P. Fallahi, G. Elia [et al.] // Best practice & research. Clinical endocrinology & metabolism. – 2020. 34 (1): e101366.

Currently, there are no sufficiently effective methods for its conservative treatment, the indications for surgical operation have not been fully determined, and the issues of choosing the volume of surgical operations are debatable [10]. Thus, any surgical intervention in the thyroid gland aggravates the autoimmune process, and if it is not intervened, the separation of thyroglobulins due to the stimulation of immune autoaggression accelerates and makes the disease more progressive. Most authors recommend total removal of the thyroid gland during thyroid surgery in patients with complications of autoimmune thyroiditis and associate their position with an attempt to save the patient from disease recurrence [10].

It has already been proven by researchers that the method of intravenous irradiation of blood with low-intensity laser rays has a multifaceted positive effect on the body. The most important of them are the immunocorrective, anti-inflammatory, desensitizing, and free radical oxidation blocking effects, which indicate the importance of using intravenous laser blood irradiation in the complex treatment of patients with autoimmune thyroiditis and create a basis for its wider study [11]. Also, the effect of laser photodynamic therapy on tissues causes an anti-inflammatory and immunomodulatory effect due to the release of cytokines and immune mediators from cells [12]. This effect, in turn, creates new possibilities for applying laser photodynamic therapy in the treatment of diffuse autoimmune thyroiditis.

Thus, the increase in the frequency of autoimmune thyroiditis, the difficulties of its diagnosis, and the conflicting opinions of researchers in the treatment of this category of patients show the urgency of the problem. Therefore, it is important to research new

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[10] Ryabchenko, E.V. Features of surgical treatment of thyroid tumors in combination with chronic autoimmune thyroiditis // – Krasnodar: Scientific Bulletin of Health Care of Kuban. – 2018. T. 57. No. 3. – p. 29-38.

[11] Hossein-Khannazer, N. Low-Level Laser Therapy in the Treatment of Autoimmune Thyroiditis / N. Hossein-Khannazer, M. Kazem Arki, L. Keramatinia [et al.] // Journal of Lasers in Medical Sciences. – 2022. 24 (13): e34.

[12] Chilakamarthi, U. Giribabu, L. Photodynamic Therapy: Past, Present and Future // The Chemical Record. – 2017. 17 (8). – p. 775-802.

methods and clinical approaches in the diagnosis and treatment of autoimmune thyroiditis. All the listed significantly reduce the results of treatment. It highlights the importance of conducting new scientific research that can improve health, reduce economic costs and the degree of disability of patients, and prevent complications.

The object and subject of the research

The object of the research was the treatment and examination data of 437 patients who received various types of treatment methods for autoimmune thyroiditis in the Department of Endocrine Surgery of the Scientific Center of Surgery named after Acad. M.A. Topchubashov from 2008 to 2022, and of 44 patients who underwent fluorescence spectroscopy examination at the clinical base of the State Scientific Center for Laser Medicine named after O.K. Skobelkin of the Federal Medical and Biological Agency of Russia. In the course of scientific work, the results of examination and treatment of 481 patients diagnosed with autoimmune thyroiditis were analyzed by retrospective and prospective research methods. In 39 (8.1%) of them, the pathomorphological examination revealed signs of thyroid cell malignancy and atypia. Examination results of 442 (91.9%) patients were retrospectively examined. Long-term results of treatment were studied in 340 (70.7%) of patients.

The object of the study consisted of 3 groups: Group I – 129 (29.2%) of patients who received intravenous low-intensity laser blood irradiation along with the conservative treatment method. Group II – 106 (24.0%) patients who received intravenous low-intensity laser blood irradiation together with laser photodynamic therapy method. Group III – 207 (46.8%) patients who underwent surgery due to autoimmune thyroiditis. Intraoperative and early postoperative complications were compared in subgroup A and B patients with prospective studies. Subgroup A included 96 (46.4%) patients who were operated on by improved hydraulic dissection method using CO_2–laser rays, and 111 (53.6%) patients who were operated on using traditional surgical methods were included in subgroup B.

The purpose of the study is to improve the treatment results of autoimmune thyroiditis by developing optimal diagnostic and treatment methods.

Tasks of research:

1. To develop an optimal diagnosis and treatment algorithm of the disease by determining the differential diagnostic capabilities of existing examination methods based on retrospective analysis and applying modern laser technologies to treatment tactics;

2. To specify the indications for surgical treatment and prepare adequate surgical tactics based on the analysis of the clinical course of the disease, the nature of complications and examination data, taking into account the individual characteristics of autoimmune thyroiditis patients;

3. To improve intraoperative and early postoperative results of surgical treatment of patients with autoimmune thyroiditis using an improved surgical method during operative interventions (hydraulic dissection method using CO_2–laser rays for layer-by-layer separation of tissues in case of adhesion and fibrotic changes that disrupt the anatomical structure in the operative field);

4. To study the long-term results of improved surgical treatment in a comparative manner with the traditional method, determining the nature of the changes in the residual tissue of the thyroid gland based on clinical-laboratory, ultrasound, and pathomorphological examinations in order to assess the condition of patients after operations;

5. To justify the application of laser photodynamic therapy in the treatment of patients with a diffuse form of autoimmune thyroiditis, to study of the maximum accumulation time of the light-sensitive substance – photodiatase in the parenchyma of the thyroid gland, and to study the formation of an active photodynamic reaction with fluorescence spectroscopy data;

6. To develop the method of joint application of photodynamic therapy and intravenous blood irradiation with low-intensity laser rays in the treatment of diffuse autoimmune thyroiditis, to determine indications and application to clinical practice;

7. To comparatively study erythrocyte sedimentation rate – ESR, C-reactive protein – CRP, leukocyte intoxication index – LII, free T_3, free T_4, TTH, Anti-TG, and Anti-TPO indicators before and after treatment in order to evaluate the effectiveness of treatment methods between patients who received conservative treatment and patients who received laser photodynamic therapy sessions;

8. To study the specific amount of thyroid cell proliferation biomarker Ki-67(+), thyrocyte apoptosis biomarker p53(+), and thyroglobulins by immunohistochemical study of autoimmune changes occurring in the thyroid gland in patients diagnosed with autoimmune thyroiditis who received various types of treatment methods;

9. To comparatively study the nature of complications, their frequency, and the quality of life of patients with autoimmune thyroiditis after various treatment methods and laser technologies using the SF-12 questionnaire;

Research methods. Dissertation work was performed in several stages. In the first stage, current issues in this field were analyzed in detail by analyzing the scientific data of researchers. At this stage, the maximum accumulation time of the light-sensitive substance – photodiatase in the autoimmune inflamed parenchyma of the thyroid gland was studied by the fluorescence spectroscopy method, and the formation of an active photodynamic reaction after laser irradiation was studied.

In the second phase of the study, the examination and treatment results of 481 patients with the diagnosis of autoimmune thyroiditis who were treated from 2008 to 2022 were retrospectively analyzed. In order to evaluate the effectiveness of treatment methods between groups during the treatment process, the levels of thyroid and pituitary gland hormones, antibodies against thyroid tissue (free T_3, free T_4, TTH, Anti-TG, and Anti-TPO) in the blood serum of the patients before and after the treatment, the main laboratory indicators of the inflammatory reaction in the general blood analysis of the patients were investigated and the dynamics of the indicators of the degree of spread of autoimmune inflammation in the body were compared with

prospective studies. Specific amount of proliferation biomarker Ki-67(+), thyrocyte apoptosis biomarker p53(+), and thyroglobulins were studied by immunohistochemical study of thyroid autoimmune changes.

In the third stage of the research, the clinical diagnosis of the disease was determined based on the data of the ultrasound examination of the thyroid gland and the indicators of the hormonal status, cytological examination of the aspiration punctate taken with a fine needle, immunological, immunohistochemical, and pathohistological examinations. In order to create an optimal diagnostic algorithm for autoimmune thyroiditis, their differential diagnostic capabilities were determined based on the analysis of existing examination methods. This stage is dedicated to the development of an individual-differentiated optimal treatment algorithm by applying modern laser technologies to the treatment tactics of patients divided into different groups.

In the fourth phase of the study, the results of 442 (91.9%) of patients who received different types of treatment were analyzed. The long-term treatment results were studied in 340 (70.7%) of them ($t=8.8$, $p\leq0.001$). The quality of life in the post-treatment period was studied using the SF-12 questionnaire form. During surgical interventions on the thyroid gland, in addition to traditional surgical methods, improved hydraulic dissection method using CO_2–laser rays was applied and their early results were analyzed. Intraoperative and early postoperative complications, as well as the long-term treatment results, were compared in two subgroups of patients. In prospective studies, the results of photodynamic therapy and traditional conservative therapy in the treatment of autoimmune thyroiditis patients were compared before and after treatment.

In the fifth stage of the study, statistical analyzes were performed using non-parametric and parametric methods to assess the statistical integrity of indicators between patient groups.

Main clauses defended:

– In order to apply an individual approach to the diagnosis and treatment of autoimmune thyroiditis, at the first stage, a diagnostic

algorithm should be used that allows accurate verification of the diagnosis of autoimmune thyroiditis. In the second stage, it is necessary to correctly choose the optimal treatment tactics, which ultimately leads to a decrease in the frequency of complications, mortality, and an improvement in the quality of life of the treated patients.

– Against the background of autoimmune thyroiditis, the formation and growth of the nucleus, increased cell proliferation, very prominent cytomorphological changes, the presence of severe thyrotoxicosis, and the high risk of malignancy of the thyroid gland are indications for surgical intervention.

– Application of the improved hydraulic dissection method using CO_2–laser beams during thyroid surgery in patients with complications of autoimmune thyroiditis is an effective method, reducing the total number of patients with complications by more than four times, and allows the majority of operated patients to return to normal social life and work activities.

– In the treatment of patients with diffuse autoimmune thyroiditis, laser photodynamic therapy with the use of a light-sensitive substance – photodiatase expands the possibilities of conservative therapy. The simplicity of the method, ease of application, reliability, and weak thermal effects on the thyroid gland create wide opportunities for the application of this method in clinical practice.

– The complex use of modern laser technologies in the treatment of patients with autoimmune thyroiditis has led to a statistically significant improvement in the treatment results of patients suffering from this severe disease, and during surgical intervention, near-total resection of the thyroid gland and thyroidectomy-type operations should be performed using the hydraulic dissection method using CO_2–laser beams.

– In patients with diffuse, diffuse-pseudonodular autoimmune thyroiditis, and postpartum thyroiditis, application of the method of intravenous blood irradiation with low-intensity laser rays together

with laser photodynamic therapy are effective methods of treatment of these forms of the disease.

– Patients treated for autoimmune thyroiditis should be monitored during the first year by periodic examination (ultrasound examination of the thyroid gland, control of hormonal status, etc.). The algorithm developed in the case of hypothyroidism specifically allows choosing individual hormonal treatment tactics with a different approach to each patient.

Scientific novelty of the research:

1. By applying modern laser technologies to the treatment tactics of autoimmune thyroiditis, an optimal diagnosis and treatment algorithm for the disease has been developed. Based on clinical-laboratory, instrumental, and pathomorphological examinations, the proposed algorithm allows to detect the form of the disease, the nature of complications, to determine the characteristics of pathological changes in the thyroid gland, surrounding organs and tissues, to deny the malignancy process and to adequately determine the subsequent treatment tactics.

2. For the first time, during the surgical treatment of complications of autoimmune thyroiditis, the improved hydraulic dissection method using CO_2–laser rays was applied to clinical practice, which facilitated the mobilization of the thyroid gland. Taking into account the form of the disease, the nature of its clinical course, types of complications and metabolic characteristics, indications for surgical treatment have been specified.

3. For the first time, the uniform and maximum accumulation time of photodiatase in the parenchyma of the thyroid gland was determined to be 120-150 min using the fluorescence spectroscopy method. Furthermore, active photodynamic reaction has been proven after laser irradiation with an energy density of 25-30 J/cm^2.

4. In patients with diffuse autoimmune thyroiditis, the method of photodynamic therapy and intravenous blood irradiation with low-intensity laser rays was applied to clinical practice as a new treatment method. Incorporation of photodynamic therapy has been proven to provide superior clinical results compared to the traditional method.

5. The risk factors affecting the recurrence and development of the disease after the surgical operation were studied by hormonal-immunological, ultrasound, cytomorphological, and immunohistochemical examinations, and methods of their prevention were determined.

Theoretical and practical significance of research:

– Based on the results obtained in the study, the importance of using a new optimal diagnostic algorithm to clarify the diagnosis when examining patients with clinical symptoms of autoimmune thyroiditis was shown. Taking into account the nature of the clinical course of the disease, its form, the presence of complications, and the characteristics of laboratory indicators the correct treatment algorithm of autoimmune thyroiditis has been developed and indications for surgical treatment have been clarified.

– Based on the conducted research, more informative examination methods were selected based on the analysis of the data of the existing diagnostic methods of autoimmune diseases of the thyroid gland, and these methods made it possible to create a new optimal diagnostic algorithm to confirm the diagnosis of autoimmune thyroiditis.

– Using the improved hydraulic dissection method using CO_2– laser rays during thyroid surgery, performing the operation in an adequate volume, and applying the method of intravenous laser blood irradiation in the postoperative period in patients with autoimmune thyroiditis led to the reduction of postoperative complications. Thus, it allowed to reduce the number of patients with recurrent laryngeal nerve paresis $\chi^2=4.057$, $p=0.044$, $p<0.050$) and hypoparathyroidism by 4 times ($\chi^2=4.381$, $p=0.037$, $p<0.050$). It helped reduce postoperative bed days by 22% – from 9.6 to 7.4 days ($t=2.588$, $p=0.007$, $p<0.050$).

– For the first time, the dynamics of the maximum accumulation of the photosensitizer in the parenchyma of the thyroid gland after the intravenous application of the photosensitizer – photodiatase was determined by the fluorescent spectroscopy method in the diffuse form of autoimmune thyroiditis.

– When the proposed photodynamic therapy method is used in the treatment stages of autoimmune thyroiditis and during the subsequent evaluation of its effectiveness, the positive qualities of this method were recorded according to the following indicators: reduction of the body's local and general inflammatory response, normalization of the hormonal status and antibodies of patients with autoimmune thyroiditis, decrease in frequency of emergence of clinical signs of hypothyroidism. This method provides good and sufficient results in 77.5% of cases (χ^2=5.4, p=0.025), helps to reduce the duration of drug treatment, and improves the quality of life of patients.

– After conservative, photodynamic therapy and surgical treatment of autoimmune thyroiditis patients, the risk factors influencing the recurrence and development of the disease have been specified. Choosing the right treatment tactics, taking into account the individual characteristics of the patient, made it possible to significantly improve treatment results.

– The results obtained in the research can be used in the teaching process of departments of surgery, endocrinology, therapy, in the compilation of textbooks, monographs, and similar sections of clinical materials. The study is of practical importance for the diagnosis and treatment of patients with autoimmune thyroiditis in the Republican and city endocrine centers, polyclinics, hospitals, and medical institutions.

The relationship of research to the problem plan of medical sciences

The topic of the dissertation is included in the scientific research work plan of the Department of Endocrine Surgery of the Scientific Center of Surgery (SCS) named after M.A. Topchubashov of the Ministry of Health (State registration № 0106AZ00883).

Approval of research work

The scientific results of the research were reported and discussed:

– «Horizons of modern surgery» («Горизонты современной хирургии») International scientific-practical conference (Samarkand, 17-18 December, 2021);

– Scientific Council of the Federal State Budgetary Institution of the State Scientific Center for Laser Medicine named after O.K. Skobelkin (Moscow, 2020, 2022);

– Meeting of the Moscow surgeons scientific society of the Russian Association of Surgeons (Moscow, 20 February, 2020);

– VII International Congress of Surgeons of Kazakhstan, dedicated to the 75th anniversary of the establishment of NSCS named after A.N.Sizganov (Almaty, 30 September-1 October, 2021);

– "Relevant issues of surgery and transplantology" III Kazakhstan Congress of Surgeons with international participation (Almaty, 2-3 September, 2022);

– "Role of Academician M.A. Aliyev in the development of surgery in Kazakhstan" VIII Kazakhstan Congress of Surgeons with international participation (Almaty, 8-9 September, 2023);

– International scientific-practical conference dedicated to the 100th anniversary of Prof. B. Abasov's birth (Baku, 02 June, 2023);

– International scientific-practical conference dedicated to the 100th anniversary of the birth of the Great Leader Heydar Aliyev on the topic "Current problems of medicine – 2023" (Baku, 3-5 May, 2023);

– International scientific-practical conference dedicated to the 100th anniversary of the birth of Great Leader Heydar Aliyev (Baku, 06 May, 2023);

– "20th International Eurasian Congress of Hepatogastro-enterology and Surgery (Baku, 25-27 April, 2024);

– Trial defense was held at the inter-departmental joint meeting of the SCS PLE named after Acad. M.A. Topchubashov of the Ministry of Health (05.10.2023, Protocol № 05);

– It was discussed at the Scientific Seminar of the ED 2.06 Dissertation Council operating under Azerbaijan Medical University (15.01.2024, Protocol № 4).

Application of research results in practice. The main provisions and results of the dissertation were presented at the Department of Endocrine Surgery of the Scientific Center of Surgery named after M.A. Topchubashov and at the Federal Medical and

Biological Agency of Russia. was applied in the practical activity of the State Scientific Center for laser medicine named after O.K. Skobelkin.

The organization where the dissertation work was performed. The dissertation work was performed under the contract at the Department of Endocrine Surgery of the Scientific Center of Surgey named after Acad. M.A. Topchubashov of the Ministry of Health and the State Scientific Center of Laser Medicine named after O.K. Skobelkin of the Federal Medical and Biological Agency of Russia.

Published scientific works: 20 journal articles and 25 theses on the topic of the dissertation were published in periodical scientific publications. The author applied to the Russian Patent Center (Application: № 2023123890) to obtain a patent for the invention on "Treatment of patients with diffuse autoimmune thyroiditis by photodynamic therapy and intravenous blood irradiation with low-intensity laser rays" and passed the formal examination with a positive opinion.

Scope and structure of work. The thesis is written in Azerbaijani language in A_4 format, "Times New Roman" 14 font, and 1.5 line spacing. It is given in 289 pages (425182 characters in total) consisting of table of contents (3939 characters), introduction (28037 characters), literature review (83415 characters), chapter II on research materials and methods (57566 characters), chapter III covering the results of personal research (52656 characters), chapter IV on justification of the choice of treatment method and results obtained (58094 characters), chapter V on assessment and discussion of near and far results after treatment methods (37732 characters), conclusion (95668 characters), results (4656 characters), and practical recommendations (3419 characters). The dissertation work is illustrated with 13 graphs, 2 equations, 34 tables, and 20 pictures. Literature list includes 375 sources; 18 of them are the works of Azerbaijani scientists, and 357 are from Russian and other foreign scientists.

MATERİALS AND METHODS OF RESEARCH

The material of the research consisted of 437 patients who received various types of treatment methods for autoimmune thyroiditis in the Department of Endocrine Surgery of the Scientific Center of Surgery named after Acad. M.A. Topchubashov from 2008 to 2022, and 44 patients who underwent fluorescence spectroscopy examination at the clinical base of the State Scientific Center for Laser Medicine named after O.K. Skobelkin of the Federal Medical and Biological Agency of Russia. In order to conduct the research, the permission of the Ethics Commission, the inter-institutional agreement, and the written consent of the patients were obtained.

The object of the study was the treatment and examination data of 481 patients who received various types of treatment methods with autoimmune thyroiditis. The criterion for exclusion from the study was malignancy of thyroid cells, signs of atypia, and confirmation of malignant derivative of the thyroid gland in pathomorphological examination in 39 (8.1%) of patients. The examination results of 442 (91.9%) treated patients were retrospectively analyzed. Long-term treatment results were studied in 340 (70.7%) patients. The observation period was from 1 to 5 years and more. The age range of the patients was between 27 and 73 years, of which 438 (91.1%) were women and 43 (8.9%) were men.

A laser electron-spectral multi-chamber fiber-optic probe analyzer [LESA-01-Biospek] was used to conduct spectral-fluorescence diagnostics for the purpose of studying the dynamics of the collection of the photosensitizer "Photodiatase".

AFS "Harmony" laser device equipped with diffuse monoquartz optical fiber, adjustable output power up to 7 W, wavelength 661±0.03 nm was used to conduct a photodynamic therapy session to a patient with diffuse autoimmune thyroiditis. Both parts of the thyroid gland were irradiated for 12-15 minutes, at an energy density of 25 J/cm^2, with an optical power of 5 W in continuous mode. The distance between the light transmitting optical fiber and the irradiated area was 10-15 cm.

Intravenous laser blood irradiation with low-intensity laser rays (ILBI-LILR) sessions were carried out with the help of a light-transmitting fiber (BRAUN company) installed in a peripheral venous catheter through the laser device "Solaris". With the "Solaris" device (λ = 400-630 nm), the radiation power at the end of the light transmitting fiber is 5MW, the irradiation time is 20 min. 7-10 sessions were conducted in 1 course. The device used complies with all safety requirements of GOST P 50 267.0 and is made in type BF of type P class. During the sessions of intravenous laser blood irradiation with low-intensity laser rays, disposable sterile quartz illuminant monofilament KIV L-01 was injected into the peripheral vein of the wrist at a depth of more than 1 mm from the length of the puncture needle according to the instructions.

Ultrasound examination of the thyroid gland and cervical lymph nodes was performed on LOGIQ 7 (General Electric, USA) and Toshiba Aplio 500 (Japan) devices. A multi-frequency linear sensor (operating frequency 12-14 MHz) was used in the examinations.

In order to clarify the nature and extent of damage to the central and peripheral vascular network of the thyroid tissue, ultrasound examination methods: ultrasonographic duplex angioscanning, color doppler mapping, and visualization methods in color doppler energy mode were applied to the patients.

Fine-needle aspiration biopsy (FNAB) of thyroid nodules during autoimmune thyroiditis was performed either by a simple method in case of diffuse lesions of the gland or under ultrasound control in nodular forms. FNAB was performed under aseptic conditions in the bandage room under ultrasound control. Standard needles № 22, with an outer diameter of 0.8 mm and a length of 4 cm, were used while performing the FNAB. Puncture was performed with sterile 10-20 ml syringes without prior anesthesia. When performing a puncture, the end of the needle is visualized on the monitor of the ultrasound device, which allows you to aim it in any direction. The material obtained from the aspiration puncture was spread evenly on a glass slide, dried at a temperature of 18-22 ºC, and then stained with Hematoxylin-Eosin.

The algorithm of laboratory examination of patients with autoimmune thyroiditis includes traditional tests: general and biochemical examinations of blood, general examination of urine and feces, hemocoagulogram, determination of electrolytes in blood, tests of liver and kidneys, examination of infections, etc. All laboratory examinations were carried out in the biochemical laboratory of the Scientific Center of Surgery named after Acad. M.A. Topchubashov, in the laboratory of the biochemistry department of the Medical University, and in private laboratories. In these examinations, the indicators of free T_3 and T_4 hormones of the thyroid gland, TTH hormone of the pituitary gland, and antibodies against thyroid tissues (Anti-TG, Anti-TPO) in the blood serum of the patients were studied in dynamics by the immunoenzyme method.

During the determination of humoral and local immunity indicators, blood plasma laboratory tests were performed in 150 (33.9%) patients with long-lasting autoimmune thyroiditis in different age groups. Here, information about the level of immunoglobulins A, G, M (IgA, IgG, IgM), α_2-MG, interleukin-6 (IL-6), lactoferrin (LF), tumor necrosis factor α (TNF α) was determined in blood samples by immunoenzyme method. The level of LF, TNF-α, IL-6 and γ-IFN was examined using the "Vector Best" test systems by method of enzyme-linked immunosorbent assay ELISA. The reagents were obtained from the base of the Scientific Research Immunology Laboratory of the Russian Federal Medical and Biological Agency.

In cytomorphological examinations, the quantitative composition of cells was studied using the morphometric method. Analysis of the quantitative composition of neutrophils, macrophages, plasmatic cells, lymphocytes, fibroblasts, and other cells was performed in cytological preparations. Pathomorphological examinations were carried out in the pathomorphological laboratory of the Scientific Center of Surgery named after Acad. M.A. Topchubashov, the Baku pathology center, and the pathomorphological laboratory of the National Oncology Center. All material submitted for pathomorphological examination was divided into two groups:

Group I: from the material of 280 non-surgical patients taken by diagnostic fine-needle aspiration biopsy from thyroid gland tissue;

Group II: from the material of 207 patients presented with thyroid gland preparations during surgery.

Histological examinations were carried out using the standard method on paraffin sections with Hematoxylin and Eosin staining, picrofuchsin according to Van Gizon, Heydenhayen modification of Mallory, and toluidine blue. The PAS (Periodic Acid - Schiff) reaction was used to determine the colloid, and the result was semi-quantitatively graded by the intensity of the colloid staining as a weak positive, medium and strong positive reaction. Urgent pathohistological examination of thyroid nodes and regional lymph nodes in Hematoxyl was performed by a standard method based on taking sections from stained, frozen sections without fixation.

Immunohistochemical examinations were performed by the peroxidase-antiperoxidase method using standard diagnostic protocols. Monoclonal antibody Dako Cytomation (chromogranin) was used for immunohistochemical verification of the process. Against biomarkers (Thermo Fisher Scientific), Ki-67(+) (Clone SP6, primary antibodies diluted 1:200) and p53(+) (protein apoptosis) (Clone SP5, primary antibodies diluted 1:100), monoclonal rabbit antibodies were used; against human thyroglobulin monoclonal mouse antibodies (Clone SPM517, primary antibodies diluted 1:200) were used.

The expression of biomarkers was calculated using a quantitative method. The method of unmasking antigens was performed according to the protocol recommended by the manufacturing companies during the incubation of primary antibodies. For the detection system, a polymer system – Ultra Vision Quanto detection systems (Thermo Fisher Scientific) was used. Positive and negative control antibodies were used to validate the results. A 1% solution of 3,3 diaminobenzidine tetrachloride was used as a chromagen. The specific number ratio of immunopositive cells was evaluated as percentages.

Patients' complaints, clinical and anamnestic indicators, results of instrumental and laboratory examinations were analyzed in accordance with the methodology of evaluation of near and far treatment results. We studied the quality of life in the post-treatment period using the SF-12 questionnaire form.

During the statistical processing of the obtained results, descriptive statistics methods were used taking into account modern recommendations. Non-parametric methods (Wilcoxon-Mann-Whitney U-test, Kruskal-Wallis H-test, Friedman's test, Pearson's χ^2 test) and parametric Student's T-test (independent sample, according to the average indicators) statistical analyzes were carried out. In the scientific study, 95% confidence interval (95% CI) of some indicators and analysis of variance (ANOVA F-test) were used for quantitative indicators. In all analyzed cases, the statistical indicator was considered statistically significant at the level of $p<0.050$. Windows SPSS-20 was used for statistical data processing, "MS Office Excel 2016" was used for presentation of obtained results, used pictures and graphs.

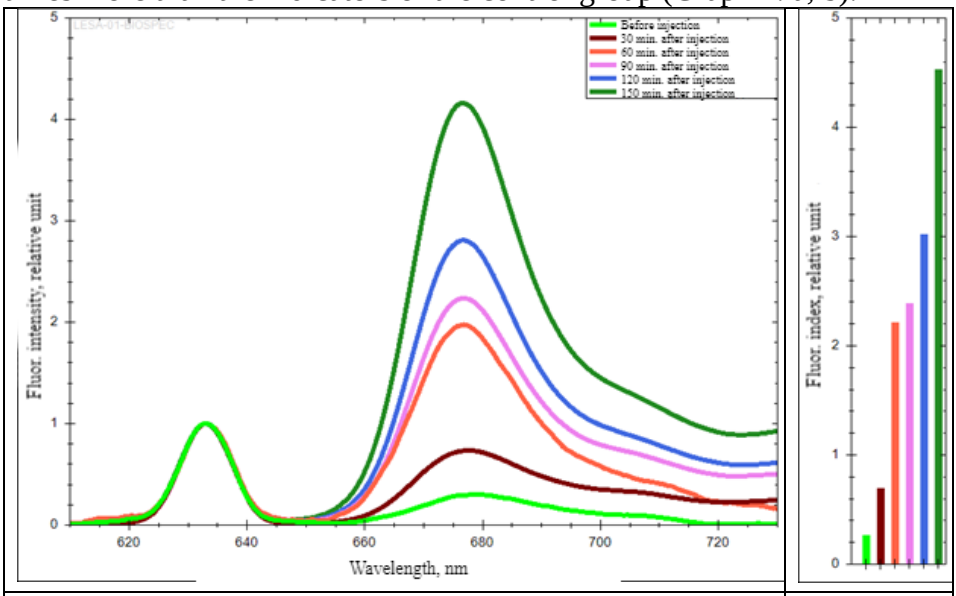
ANALYSIS OF OBTAINED RESULTS

One of the tasks of our research work was the justification of the clinical application of the laser photodynamic therapy (PDT) method in patients with autoimmune thyroiditis. For this purpose, we investigated the characteristics of photosensitizer accumulation in thyroid parenchyma in patients with diffuse autoimmune thyroiditis. These data are important for the development of the photodynamic therapy method in the treatment of autoimmune thyroiditis patients and its effective clinical application.

Delivery of laser beams and recording of fluorescence was carried out with the help of a Y-shaped fiber-optic probe. 44 patients studied for photosensitizer accumulation in thyroid gland parenchyma were divided into 6 groups, one of which was the control group and 5 formed the main group. 38 (86.4%) of them were women and 6 (13.6%) were men, the age range was between 27 and 70 years. Four patients in the control group were not injected with photosensitizer. The remaining patients were divided into 5 equal groups – 8 people in each group. 30-150 minutes before the examination, photosensitizer "Photoditazine" was injected intravenously to the patients of the main group in a dose of 0.8 mg/kg dissolved in 100 ml of physiological sodium chloride solution. The main group of patients differed from each other according to the time of conducting spectroscopy: so, 30 min., 60 min., 90 min., 120 min., and 150 minutes from the moment of injection of the photosensitizer; later spectroscopy was performed.

Fluorescence indicators in the control group patients who were not injected with "Photoditazine" were in the range of 0.270±0.01 fluorescence unit (F.u.) and reflected the background of fluorescent activity of the thyroid gland. During spectroscopy 30 minutes after the injection of "Photoditazine" in the patients of the 1st main group, the fluorescence indicators were 0.694±0.02 F.u., and it was observed that the photosensitizer was evenly collected in the entire parenchyma of the thyroid gland. As a result, the increase in fluorescence activity increased by 2.6 times. In patients of the second main group, the level of spectroscopy indicators increased to 2.217±0.04 F.u., which is 8.2

times higher than in the control group. In the third main group, on average, a gradual increase in the level of fluorescence spectroscopy indicators was observed, which is 2.388±0.02 F.u. on average. This fluorescence unit is 8.8 times more than the control group and 16.7% more than the first main group. In the fourth main group, an increase in the level of fluorescence spectroscopy indicators was observed up to 3.023±0.02 F.u. This is, respectively, 11 times higher than the control group and 7.9% higher than the indicators of the 2nd main group. The level of fluorescence spectroscopy indicators of the fifth main group is observed to increase to 4.531±0.02 F.u., which is 17 times more than the indicators of the control group (Graph 1. a, b).



a b

Graph 1. a – fluorescence spectra of inflamed tissue at different time intervals, b – fluorescence units (1 to 5 are the curves of the main group, 6 - the control group.)

Data from the analysis of fluorescence spectra showed that photodiatase was evenly accumulated in the entire tissue of the thyroid gland. As a result, the peak of the maximum accumulation falls into the time interval between 120 min. (3.02 F.u.) and 150 min. (4.53 F.u.),

with a moderate decrease of the spectrum in the following hours. After recording the fluorescence spectroscopy readings for each studied zone, the fluorescence unit was calculated. At this time, the ratio of the fluorescence activity of the areas irradiated with a laser with a wavelength of λ=660 nm to the activity of the areas characteristic for photoditazine was calculated by fluorescence spectroscopy. This ratio made it possible to evaluate the dynamics of accumulation of the photosensitizer photodytase in the damaged tissues of the thyroid gland.

Spectroscopy results confirm that the optimal effective moment for laser intervention on the thyroid gland in patients with autoimmune thyroiditis occurs 120-150 minutes after the intravenous injection of "Photoditazine" photosensitizer. After determining the maximum accumulation time of the photosensitizer, laser radiation with a wavelength of 661±0.03 nm, a power density of 0.25 W/cm^2 (protecting the surrounding tissues from thermal damage), and an energy density of 25-30 J/cm^2 is applied to the thyroid gland in continuous mode. Repeated fluorescence spectroscopy was performed 5 minutes after the parenchyma of the thyroid gland was exposed to laser irradiation.

According to the obtained results, it can be said with certainty that laser irradiation sessions of 4.531±0.02 F.u. at the peak phase of the photosensitizer's fluorescence intensity caused this indicator to decrease by more than 3.6 times, to the level of 1.255±0.01 F.u. The obtained data confirm that the photosensitizer concentration in the thyroid tissue decreases under the influence of laser radiation with a phototherapy source with a maximum wavelength of 661±0.03 nm.

According to fluorescence spectroscopy data, irradiation of the thyroid gland led to a decrease in fluorescence intensity up to 72.3% ($p \leq 0.001$) compared to the initial data, which clearly shows the positive effect of the photosensitizer, the occurrence of a high degree of photodynamic response, and the effectiveness of photodynamic therapy in diffuse forms of autoimmune thyroiditis.

In order to compare the effectiveness of the complex treatment methods performed during autoimmune thyroiditis on the general

condition of patients, an analysis of the clinical examination indicators of the patients before and after the treatment was carried out in two groups of patients. During the treatment process, the dynamics of indicators of the degree of spread of autoimmune inflammation in the body were studied in the patients of both groups. The leukocyte intoxication index (LII) was calculated from the leukogram using the formula proposed by Y.Y. Galf-Galif (1941). This indicator is an indicator of pathological-degradative changes caused by the autoimmune inflammatory process in the thyroid gland. These data are reflected in table 1 (table 1).

Table 1

Average indicators of the inflammatory response in the examined groups

Groups	Indicators of inflammatory response on day 5 of treatment			Indicators of inflammatory response on day 10 of treatment		
	LII	ESR mm/s	CRP mg/l	LII	ESR mm/s	CRP mg/l
I group n=129	1.85± 0.23	14.62±1. 35	11.25± 1.20	1.47± 0.07	9.75± 0.96	10.33± 1.02
II group n=106	1.77± 0.16	13.00± 0.21	11.61± 1.06	1.47± 0.05	10.02± 0.96	10.56± 0.87

Dynamic monitoring of the average indicators of the body's inflammatory reaction showed a faster normalization of the level of indicators in the blood of group II patients. Before treatment, a statistically significant difference was observed between slightly elevated levels of the leukocyte intoxication index (2.43±0.34 and 2.24±0.21, respectively) (norm=1.45±0.08) in groups II and I (U_{emp}=526.5, p=0.008). Reduction of these indicators in 5 days of treatment (respectively, 1.77±0.16 in group II, 1.85±0.23 in group I) in 26 (24.5%) patients in group II and 16 (12.4%) in group I was observed in the patient. A statistically significant difference is found between the number of patients in groups I and II (χ^2=5.9, p=0.010). In group II, the indicators of LII before treatment did not differ statistically significantly from the indicators on the 5th day of treatment (t=1.76, p≥0.050). In group I, there was no statistically

significant difference in the indicators of LII before treatment and on the 5th day of treatment (t=1.25, p≥0.050). On the 5th day of treatment in the II group, a statistically significant difference was found between the indicators of LII and the same indicators of the I group (U_{emp}=1010.5, p=0.043).

Before treatment, both groups of patients with diffuse form of autoimmune thyroiditis had high ESR levels (respectively, 17.84±2.24 mm/s in group II, 16.05±2.33 mm/s in group I), and on the 5th day of treatment 33 (31.1%) patients in group II and 21 (16.3%) patients in group I (statistical difference between the number of patients χ^2=7.18, p=0.010) showed a decrease in ESR indicators (in group II 13.00± 0.21 mm/s, 14.62±1.35 mm/s in group I). In group II, there was a statistically significant difference between ESR indicators before treatment and ESR indicators on the 5th day of treatment (t=2.15, p≤0.050). In group I, there was no statistically significant difference in ESR indicators before treatment and on the 5th day after treatment (t=0.70, p≥0.050). Before treatment, there was a statistically significant difference between ESR indicators in group II and ESR indicators before treatment in group I (U_{emp}=426.00, p≤0.001), and on the 5th day of treatment, the difference in ESR indicators between groups was statistically significant U_{emp}=1442.5, p≤0.001.

A similar downward trend was observed in the dynamics of C-reactive protein indicators. CRP indicators before treatment in group II were 15.45±0.51 mg/l, and in group I 15.80±0.77 mg/l (normal up to 11.0 mg/l). Before treatment, there was a statistically significant difference between CRP values in group II and corresponding values in group I (U_{emp}=1039.0, p≤0.021). A statistically significant difference between CRP indicators before treatment and corresponding indicators on the 5th day of treatment in group II q (t=3.84, p≤0.050). In group I, there was a statistically significant difference between CRP values before treatment and on the 5th day after treatment (t=3.20, p≤0.050). A trend of decrease in the dynamics of C-reactive protein indicators was observed in 34 (32.1%) patients of group II and 17 (13.2%) patients of group I (χ^2=12.24, p=0.0005). There was no statistically significant difference between CRP

concentration on the 5th day of treatment in group II and the corresponding indicators in group I (U_{emp}=661.5, p=0.183). A similar trend was found on the 10th day of treatment in both groups of patients under observation. On the 10th day of treatment, the number of patients whose indicators were normal increased, and in group II there were 90 (84.9%) patients on LII, 93 (87.7%) on ESR, and 86 (81.1%) on CRP.

In group I, the dynamics of the indicators were similar, but on the 10th day of treatment, the percentage indicators were relatively low: LII – 82 (63.6%), ESR – 77 (59.7%); CRP – 74 (57.4%) patients. On the 10th day of treatment, the number of patients with normal indicators of the inflammatory reaction in group II was greater than the number of patients in group I (respectively, the coefficient of statistical significance for LII – χ^2=13.8, p=0.005; according to ESR – χ^2=38.3, p=0.005; for CRP – χ^2=15.1, p=0.005).

In group II, there was a statistically significant difference between the pre-treatment LII indicators and the LII indicators on the 10th day of treatment (t=2.79, p≤0.050). In group I, there was a statistically significant difference between the indicators of LII before treatment and on the 10th day after treatment (t=3.50, p≤0.050). There was no statistically significant difference between the indicators of LII on the 10th day of treatment in group II and the corresponding indicators on the 10th day in group I (U_{emp}=787.5, p=0.904).

In group II, there was a statistically significant difference between ESR indicators before treatment and ESR indicators on the 10th day of treatment (t=3.20, p≤0.050). In group I, there was a statistically significant difference between ESR indicators before treatment and on the 10th day after treatment (t=2.52, p≤0.050). There was no statistically significant difference between ESR indicators on the 10th day of treatment in group II and corresponding indicators on the 10th day in group I (U_{emp}=664.0, p=0.191).

In group II, there was a statistically significant difference between CRP indicators before treatment and CRP indicators on the 10th day of treatment (t=4.89, p≤0.010). A statistically significant difference in CRP indicators before treatment and on the 10th day after

treatment was found in group I (t=4.27, p≤0.010). There was no statistically significant difference between CRP indicators on the 10th day of treatment in group II and corresponding indicators in group I (U_{emp}=671.5, p=0.216). Thus, on the 10th day of the treatment process, an increasing trend was observed in the number of patients with normalization of the main indicators of the inflammatory reaction. On the 10th day of treatment, a statistically significant difference was observed between the numbers of normal indicators of group I and II patients (p≤0.0001).

In order to evaluate the effectiveness of the intravenous low-intensity laser irradiation of blood (ILBI-LILR) method together with the laser photodynamic therapy (PDT) method, we have conducted a study to evaluate the indicators of hormones that indicate the function of the thyroid gland in dynamics. We divided the patients into two groups without a statistical difference (p≥0.05) and analyzed them. The first group included 50 (38.8%) patients out of 129 patients who received a course of traditional conservative therapy. The second group included 40 (37.7%) of 106 patients who were treated with the method of intravenous low-intensity laser irradiation of blood together with the method of laser photodynamic therapy (χ^2=5.1, p=0.050).

When analyzing the obtained data, it should be noted that the Anti-TPO, TTH, free T_4, and free T_3 indicators in group II patients (the indicators before treatment were 176.80±16.29 IU/mL, respectively; 6.54±0.47 mlU/ml; 10.20±2.05 pmol/L and 2.99±1.01 pmol/L) were clearly improved and approached the reference values.

Analyzing the received data, it is known that the symptoms of hypothyroidism disappeared after treatment in group II patients. Also, Anti-TPO, TTH, free T_4, and free T_3 indicators of group I were 326.28±46.89 IU/mL, respectively, before treatment; 9.99±1.34 mlU/ml; 6.69±1.36 pmol/L and 3.10±0.66 pmol/L. There was a statistically significant difference between the Anti-TPO values of group I and those of group II before treatment (U_{emp}=1600.0, p≤0.001). In group II, the statistical difference between the indicators before treatment and on the 15th day after treatment is t=8.39, p≤0.001, respectively; t=4.78, p≤0.001; t=3.51, p≤0.010 and t=1.42,

p≥0.050. In group I, the statistical difference between the indicators before treatment and on the 15th day after treatment is t=5.40, p≤0.001, respectively; t=4.37, p≤0.001; t=5.11, p≤0.001 and t=1.66, p≥0.050 (table 2).

Table 2

Levels of hormonal indicators of patients before treatment and on the 15th day of treatment in the compared groups

Average indicators	Before treatment (avg/min/max)		On day 15 of treatment	
	I group (n = 50)	II group (n = 40)	I group (n = 50)	II group (n = 40)
TTH mlU/ml n. 0.27-4.2	9.99±1.34 [6.04-11.85]	6.54±0.47 [5.65 –7.54]	3.13±0.82 [1.49-4.77]	3.00±0.21 [2.58-3.42]
Free T_4 pmol/L n.12.0-22.0	6.69±1.36 [8.98 – 4.91]	10.20±2.05 [12.95 –7.63]	16.40±1.9 13.62-19.18]	19.15±1.52** [16.11-22.19]
Free T_3 pmol/L n. 3.1-6.8	3.10±0.66 [4.38 – 2.07]	2.99±1.01 [4.53 – 1.47]	4.89±0.86 [3.17 – 6.61]	5.11±1.10 [2.91 – 7.31]
Anti-TPO <34 IU/mL	326.28±46.89 248.03-399.02	176.80±16.29 [147.3-205.0]	65.95±9.31 [47.33-84.57	31.57±5.75** [20.07-43.07]

Note: p≤0.001** statistically significant differences between the groups

On the 15th day after treatment, there was no statistically significant difference (U_{emp}=917.0, p=0.260) between the TTH indicators of group II (3.00±0.21 mlU/ml; 95% confidence interval 2.58 – 3.42) and corresponding TTH indicators of group I (3.13±0.82 mlU/ml) ml; 95% confidence interval 1.49 – 4.77). On the 15th day after treatment, a statistically significant difference (U_{emp}=134.0, p≤0.001) was observed between the free T_4 indicators of group II (19.15±1.52 pmol/L; 95% confidence interval 16.11 – 22.19) and corresponding free T_4 indicators in group I (16.40±1.39 pmol/L; 95% confidence interval 13.62 – 19.18).

15 days after treatment, no statistically significant difference was observed between the free T_3 values of group II (5.11±1.10 pmol/L; 95% confidence interval 2.9–7.31) and the corresponding free T_3 values of group I (4.89±0.86 pmol/L; 95% confidence interval 3.17 – 6.61) (U_{emp}=698, p=0.326). On the 15th day after treatment, the Anti-TPO indicators of the II group (31.57±5.75; 95% confidence

interval 20.07 – 43.07) and the corresponding Anti-TPO indicators of the I group (65.95±9.31 IU/ml; 95% confidence interval 47.33 – 84.57) a statistically significant difference ($p \leq 0.001$) was observed.

The results obtained from the study clearly demonstrate the normalization of free T_4, free T_3 hormones, and TTH on the 15th day of the treatment of group II patients treated with the method of intravenous laser blood irradiation with low-intensity laser rays (ILBI-LILR) together with the method of laser photodynamic therapy. At the same time, in group II, the average indicators of Anti-TPO approach the normal limit (31.57±5.75 IU/ml). In group I, the average values of Anti-TPO (65.95±9.31 IU/ml) were very high, 1.9 times higher than the normal limit ($t=3.15$, $p \leq 0.050$).

Among the indicators of the first group of patients, there were some changes, primarily a 3.2-fold decrease in the level of TTH hormone (9.99±1.34 mlU/ml before treatment, 3.13±0.82 mlU/ml on the 15th day after treatment; $t = 6.9$, $p \leq 0.001$), a 1.58-fold increase in free T_3 concentration (3.10±0.66 pmol/L before treatment and 4.89±0.86 pmol/L on day 15 after treatment; $t=4.3$, $p \leq 0.005$), and a 4.94-fold decrease in Anti-TPO values (326.28±46.89 IU/mL before treatment and 65.95±9.31 IU/mL on day 15 after treatment; $t=5.4$, $p \leq 0.001$). In other words, in this group of patients, conservative treatment gave a positive result in only 82 (63.6%) patients, while in 47 (36.4%) of 129 patients, structural changes of the thyroid gland lasted longer (21 days or more), along with subclinical hypothyroidism. As a result, it was not possible to achieve complete recovery of all 129 patients.

The obtained results clearly show the effectiveness of applying the method of intravenous laser blood irradiation with low-intensity laser rays (ILBI-LILR) in the treatment of diffuse autoimmune thyroiditis and postpartum thyroiditis, together with the laser photodynamic therapy method.

According to daily spontaneous and mitogen-stimulated synthesis of TNF-α and lactoferrin (LF) cytokines in blood serum of patients before treatment prescribed for autoimmune thyroiditis, the functional activity of total blood mononuclear cells was studied as an

in vitro reaction. We investigated the parameters of inflammatory cytokines, inflammatory mediators, immunoglobulins, and endothelial growth factors in the blood of patients with various forms of autoimmune thyroiditis. In all forms of autoimmune thyroiditis, the level of TNF-α in blood plasma is slightly higher both in thyrotoxicosis and in the decompensation stages of autoimmune thyroiditis, although it did not deviate from the reference values (5 μg/l).

When patients with autoimmune thyroiditis were examined, clinical signs of hormonal disorders were manifested against the background of changes in the level of TTH and free T_4. The concentration of α_2-MG – 1.77±0.16 in the blood increased by 1.9 and 1.3 times on average in both thyrotoxic and hypertrophic forms, respectively. Against the background of treatment with thyrotoxic form, its levels decreased statistically and remained statistically higher than the comparison group, although it was slightly lower than before treatment with hypertrophic form.

When patients with autoimmune thyroiditis were examined, clinical signs of hormonal disorders were manifested against the background of changes in the level of TTH and free T_4. The concentration of α_2-MG – 1.77±0.16 in the blood increased by 1.9 and 1.3 times, respectively, in thyrotoxicosis and AIT. Against the background of treatment in thyrotoxicosis, its levels decreased statistically significantly and remained statistically significantly higher than in the control group, although it was slightly lower than before treatment with hypertrophic form.

Statistical evaluation was performed using the H-Kruskal-Wallis test. There is a significant statistical difference ($H=140.038$, $p<0.001$) between the study groups (control, hypertrophic, atrophic, relapse, thyrotoxicosis) according to the H-Kruskal-Wallis criterion. The maximum value is observed in the "hypertrophic" group (average value=19.84), and the minimum value is observed in the "thyrotoxicosis" group (average value =0.127). There is a statistically significant difference between study groups according to free T_4 ($H=141.429$, $p<0.001$). The maximum value is observed in the

"thyrotoxicosis" group (mean value =55.309), and the minimum value is observed in the "atrophic" group (mean value =6.612).

There is a statistically significant difference between study groups according to TNF-α (H=107.466, p<0.001). The maximum value is observed in the "hypertrophic" group (mean value =8.554), and the minimum value is observed in the "control" group (mean value =5.45). There is a statistically significant difference between study groups according to α_2-MG (H=121.233, p<0.001). The maximum value is observed in the "thyrotoxicosis" group (mean value =3.413), and the minimum value is observed in the "control" group (mean value = 1.767). According to the IL-6 indicator, a statistically significant difference between the research groups is recorded (H=146.033, p<0.001). The maximum value is observed in the "hypertrophic" group (mean value =14.161), and the minimum value is observed in the "control" group (mean value =3.003) (table 3).

Table 3

The concentration of immunoregulatory proteins and anti-inflammatory cytokines in the blood of patients

Form of thyroiditis	TTH mlU/ml	Free T_4 pmol/L	TNF-α (pg/ml)	α_2-MG g/l	IL-6 (pg/ml)	LF mg/l
control g. n=40	2.43± 0.34	17.71± 2.46	5.45± 0.51	1.77± 016	3.00± 0.21	1.44± 0.20
1 g. hypertro phic n=32	19.84± 2.54	7.09± 1.22	8.55± 0.66	3.10± 0.38	14.16± 1.10	5.88± 1.03
2 g. atrophic (n = 28)	16.81± 1.44	6.61± 1.30	8.20± 0.89	2.31± 0.43	11.90± 0.72	5.04± 0.70
3 g. relapse (n = 30)	15.8± 0.70	9.06± 0.67	7.61± 0.42	2.41± 0.38	12.39± 0.39	3.98± 0.66
4 g. thyro toxicosis n=30	0,13± 0,08	55,31± 16,75	8,36± 0,39	2,85± 0,1	9,8± 0,48	3,85± 0,48

Note: *- the values of the quantitative characteristic in the marked group are statistically significant (p<0.05).

According to LF indicators, there is a statistically significant difference between the study groups (H=130.678, p<0.001). The maximum value is observed in the "hypertrophic" group (mean value =5.879), and the minimum value is observed in the "control" group (mean value =1.442).

In patients with autoimmune thyroiditis, the average indicator of TTH level was 13.16±1.19 mlU/ml, and the concentration of free thyroxine was correspondingly lower. The T_4 level was 19.52±5.0 pmol/L, TNF-α was 8.18±0.62 pg/ml, α_2-MG was 2.81±0.4 g/l, IL-6 was 12.06±0.67 pg/ml, and LF was 4.69±0.72 mg/l. During the decompensation phase, the concentration of α_2-MG in blood serum before treatment increased in both thyrotoxicosis and AIT. During treatment, the levels in thyrotoxicosis decreased statistically significantly, and in the hypertrophic form, although they were slightly lower than before treatment, they remained statistically higher than in the comparison group.

The amount of lactoferrin (LF) was statistically significantly higher in AIT by 3.5 times and by 2.7 times in thyrotoxicosis. Treatment did not significantly affect its concentration. Although the level of anti-inflammatory cytokine TNF-α was slightly higher than normal in thyrotoxicosis (8.36±0.39 pg/ml) and AIT (8.2±0.89 pg/ml) in the decompensation stage, it did not deviate from the reference indicators. Lactoferrin (LF) also has antibacterial and antiviral properties, regulates the synthesis of cytokines, and is a highly sensitive marker of the inflammatory process. Excess secretion of cytokines (especially IL-6 for α_2-MG and chemokine IL-8 for LF) activates the synthesis of these proteins. At the same time, the obvious inflammatory process leads to the oxidation of α_2-MG molecules and their accumulation in the bloodstream, which is confirmed by the results of our study.

The accumulation of immunoglobulins in autoimmune thyroiditis was as follows. As the age of patients increases, we have observed that the level of immunoglobulins tends to increase. Thus, the IgA index in blood plasma in patients of the first age group (16-35 years) was 4.37 [3.33-5.29] g/l, in patients in the middle age group (36-59 years) it was 4.93 [3.35- 6.2] g/l, in the elderly (60-74 years) IgA level was 6.24 [4.73-7.8] g/l.

Statistical evaluation of IgA, IgM, and IgG levels was performed using the U-Mann-Whitney criterion. In patients of the first age group (16-35 years), the IgA index in blood plasma is statistically different

compared to patients in the middle age group (36-59 years) (U_{emp}=291.0, p<0.019). The IgA index in the blood plasma of patients in the middle age group (36-59 years old) is statistically significantly higher than that of older patients (60-74 years old) (U_{emp}=146.0, p<0.001). In patients of the first age group (16-35 years), the IgA index in blood plasma is statistically significantly higher than in older patients (60-74 years) (U_{emp}=155.0, p<0.001).

In the study of IgM, although there was a slight increase in the mean values, no statistically significant difference was observed between the studied groups. IgM indices in the first age group were 3.93 [3.2-4.5] g/l, in the second age group 3.57 [3.0-4.1] g/l (U_{emp}=676.5, p≤0.001), and in the group of elderly patients, the level of IgM in blood plasma was 2.66 [2.1-3.18] g/l. In middle-aged patients, the IgM index in blood plasma is statistically significantly higher than in elderly patients (U_{emp}=886.0, p<0.001) (table 4).

Table 4

Indicators of immunoglobulins in blood in patients of different age groups

Age groups	Indicators of immunoglobulins		
	IgA (0.7- 4 q/l)	IgM (0,4-2,3 q/l)	IgG (7-16 q/l)
Group 1 (n = 30) (16-35 years old)	4.37±0.60* [3.33-5.29]	3.93±0.40* [3.2-4.5]	29.06±0.83* [27.7-30.38]
Group 2 (n = 30) (36-59 years old)	4.93±0.93* [3.35-6.2]	3.57±0.32* [3.0-4.1]	30.85±1.58* [28.13-33.43]
Group 3 (n = 30) (60-74 years old)	6.24±0.95** [4.73-7.8]	2.66±0.33** [2.1-3.18]	37.02±0.74** [35.6-38.88]
Thyrotoxic n=30	1.90±0.21** [1.64-2.35]	0.90±0.18** [0.72-1.32]	13.01±0.23** [12.61-13.41]

Note: the values of the quantitative characteristic in the indicated group are statistically significant *(p<0.050), **(p≤0.001)

When analyzing the indicators of IgG, statistically significantly higher indicators of these immunoglobulins were recorded in elderly people than in young groups (p<0.050, for each pair of comparisons with both groups). The level of IgG in patients in the first group was 29.06 [27.7-30.38], in the second group it was 30.85 [28.13-33.43] (U_{emp}=160.0, p≤0.001), and in the third group IgG the indicators were

37.02 [35.6-38.88] and there was a statistically significant difference ($p \leq 0.001$).

There is a statistically significant difference between IgA, IgM, and IgG indicators in the thyrotoxicosis form of autoimmune thyroiditis and the same indicators in the blood plasma of patients in the groups of young, middle-aged, and elderly people ($p<0.001$). Statistical evaluation in the thyrotoxic form of autoimmune thyroiditis was performed using the W-Shapiro-Wilk criterion. According to IgA indicators in the thyrotoxic form, the "zero" hypothesis is confirmed in 96.6% of cases (W=0.966), deviations from the norm are 19.1%. According to IgM indicators, the "zero" hypothesis is confirmed in 95.7% of cases (W=0.957), and deviations from the norm are observed in 33.3% of cases. According to IgG indicators, the "null" hypothesis is confirmed in 96.5% of cases (W=0.965), and the deviation from the norm is 13.0%.

Thus, in elderly patients with long-standing autoimmune thyroiditis, there is a tendency of decreasing TNF indices, which is an indicator of the severity of the pathological process. An increase in immunoglobulin (IgA and IgG) indicators is observed in elderly patients with a long-term inflammatory process in the thyroid gland. In this category of patients, changes in the immune system (α_2-MG - negative reactant of inflammation) negatively affect all physiological processes due to defective forms. Thus, this leads to pathological changes controlled by the negative reactant of inflammation, including the stimulation of cytokine synthesis. Accordingly, the absence of a decrease in the concentration of LF in the blood serum against the background of treatment, especially the high amount of cytokines, indicates a negative prognosis and indicates a high risk of recurrence of the process in the near future. In general, in thyrotoxicosis and AIT, α_2-MG appears as a positive slow reactant of the inflammatory process, which is released slowly from the bloodstream, so the non-normalization of this indicator in the blood after treatment is not considered so informative.

For a more detailed analysis of some morphological features of pathological changes in the thyroid gland in patients with autoimmune

thyroiditis, we investigated the proliferative activity of thyrocytes using Ki-67(+) monoclonal antibodies (a marker of cell proliferation), protein p53(+) (a marker of thyrocyte apoptosis), and thyroglobulins.

30 patients with autoimmune thyroiditis were examined. 25 (83.3%) of them were women and 5 (16.6%) were men, the age range was between 27 and 70 years. All patients were divided into 5 types, 6 patients each, according to the forms of autoimmune thyroiditis, and compared with 6 patients in the control group.

Statistical evaluation of the results of immunohistochemical studies of the thyroid gland in different forms of autoimmune thyroiditis was carried out using ANOVA – F and Kruskal-Wallis-H criteria. According to the criteria of ANOVA (F), statistical differences between the forms of autoimmune thyroiditis (control, thyrotoxic, atrophic, diffuse-nodular, diffuse-pseudonodular) according to Ki-67(+) are revealed ($F=1428.687$, $p<0.050$) (Table 5).

Table 5

Results of immunohistochemical studies (in absolute and %)

Forms of AIT	Ki-67(+) Specific amount in cells %	p53(+) Specific amount in cells %	Thyroglobulins (+) Sp. amount in cells %
Diffuse n=6	13.85±0.40	16.0±0.28	24.31±0.32
Dif. pseudo nodular n=6	17.37±0.31	21.01±0.23	58.33±0.35
Diffuse nodular n=6	21.44±0.38*	27.42±0.48	67.28±0.68**
Atrophic n=6	12.00±0.36	14.71±0.51	19.32±0.59
Thyrotoxicosis n=6	16.46±0.57	31.25±0.59**	48.25±0.59
Control n=6	5.39±0.48	4.58±0.53	16.84±0.50

Note: quantitative trait values are statistically significant *($p<0.05$), **($p\leq0.001$)

The maximum value is observed in the "diffuse-nodule" group (mean value = 21.44), and the minimum value is observed in the "control" group (mean value =5.392). According to the Kruskal-Wallis - H criterion, a statistical difference is revealed between the forms of

autoimmune thyroiditis (control, thyrotoxic, atrophic, diffuse-nodular, diffuse-pseudonodular) according to p53(+) and thyroglobulins (+) (H=19.323, p<0.001**). The maximum value is observed in the "thyrotoxic" and "diffuse-nodular" groups (mean value 31.25; 67.28, respectively), and the minimum value is observed in the "control" group (mean value 4.58; 16.84, respectively).

The Wilcoxon - T, Mann-Whitney – U, and Student - T criteria were also used in the statistical evaluation of the results of immunohistochemical studies of the thyroid gland in various forms of autoimmune thyroiditis. According to the specific amount of Ki-67(+), p53(+), and thyroglobulins, a statistical difference is observed between different forms of autoimmune thyroiditis in cells ($T_{emp.}$, $U_{emp.}$=21.0, p=0.028*, respectively).

High expression of protein Ki-67(+) was observed in the zone of lymphoid infiltration, in the reproduction centers of lymphoid follicles and reached 21.44±0.38%. On the contrary, the expression in interfollicular areas decreased and amounted to 17.37±0.31%. Compared to the indicators of the control group, a statistically significant difference was observed (p<0.050). In the nodular form of autoimmune thyroiditis, the expression of p53(+) in the changed tissue of the gland was moderately increased by 21.01±0.23%, and the expression of p53(+) was higher in the proliferation foci of the follicular epithelium.

The indicators of cytoplasmic expression of thyroglobulins were statistically significant. In the diffuse and atrophic forms of autoimmune thyroiditis, the expression of thyroglobulins was 24.31±0.32% and 19.32±0.59%, respectively, lower than in the diffuse-pseudonodular form (58.33±0.35%), in the nodular form of the gland it was higher (67.28±0.68%) in the changed tissue areas. Thus, the correct assessment of the proliferative activity of the thyroid gland tissue in immunohistochemical examinations with the determination of Ki-67(+), p53(+) biomarkers, and thyroglobulins allows prediction of the risk of recurrence and malignancy of nodular forms of autoimmune thyroiditis.

In order to improve the results of surgical treatment, improved hydraulic dissection method using CO_2–laser rays was applied in 96 (46.4%) of 207 operated patients during operative interventions of the thyroid gland. The analysis of the early results of surgical treatment was performed in two subgroups of patients An improved surgical method was applied to subgroup A patients, and a CO_2–laser (penetration depth 0.1 mm) with a high absorption rate in water and organic compounds was used as a tool to perform operative procedures during surgical interventions. The surface effect of the laser allows for easier dissection of tissues without causing deep burns. 96 (46.4%) patients who underwent surgery were included in this subgroup.

Subgroup B consisted of 111 (53.6%) patients operated using traditional surgical methods. Conventional surgical methods and standard conventional postoperative management were used during thyroid surgery in these patients. A comparative analysis of intraoperative and early postoperative complications (within one month after surgery) was performed in two subgroups of patients (Table 6).

Table 6

Intraoperative and early postoperative complications in two subgroups of patients operated on for autoimmune thyroiditis

Subgroups	Nature of complications				
	Recurrent laryngeal nerve paresis	Hypopara thyroidism	Wound suppuration	Bleed from a wound	Average bed day
Subg. A (n=96)	2 (2.1%)	1 (1.1%)	-	-	7.4±0.3
Subg. B n=111	9 (8.1%)	7 (3.6%)	2 (1.8%)	2 (1.8%)	9.6±0.8
Significance coefficient (p)	p<0.050 p=0.044	p<0.050 p=0.037			p<0.050 p=0.007
Total (n=207)	11 (5.3%)	8 (3.9%)	2 (1.0%)	2 (1.0%)	8.5±0.5

Note: Quantitative values of p>0.050 are not statistically significant
Quantitative values of p<0.050 are statistically significant

Table 6 shows that the frequency of complications in subgroup A patients (3) is more than 5 times lower than the same indicators of subgroup B patients (16) (χ^2=7.870, p=0.006, p<0.050). The indicators of the average bed day are also 22% lower in subgroup A patients (t=2.588, p=0.007, p<0.050 there is a statistically significant difference). In the compared subgroups, a statistical difference was observed between patients with complications in the form of laryngeal paresis (χ^2=4.057, p=0.044, p<0.050), a statistical difference was also observed in complications in the form of hypoparathyroidism (χ^2=4.381, p=0.037, p<0.050).

All patients were divided into three age groups: the first group (young people 27-35 years old) – 24 (11.6%) patients with an average age of 32.0 [27.0-35.0]; the second group (middle age people 36-59 years) – 118 (57.0%) patients with an average age of 51.0 [36.0-59.0] years; the third group (elderly people aged 60-74) – 65 (31.4%) people, the average age of the representatives of this group was 69.0 [60.0-74.0] years. Statistically significant differences between the number of young and middle-aged patients, as well as the number of elderly patients in subgroups A and B are not revealed (χ^2=2.454, χ^2=2.449, p≈0.570, p>0.050, respectively). Taking into account different forms of autoimmune thyroiditis, we have compared the characteristics of two subgroups of operated patients (Table 7).

Table 7

Characteristics of two subgroups of patients operated on with different forms of autoimmune thyroiditis

Subgroups	Forms of AIT			Total
	Diffuse-nodular	Diffuse-pseudo nodular	Relapse	
Subgroup A (n=96)	46 (47.9%)	35** (36.5%)	15* (15.6%)	96 (100%)
Subgroup B (n=111)	60 (54.0%)	20** (18.0%)	31* (28.0%)	111 (100%)
Significance coefficient (p)	p>0.050 p=0.418	p<0.010 p=0.002	p<0.05 p=0.034	
Total (n=207)	106 (51.2%)	55 (26.6%)	46 (22.2%)	207 (100%)

Note: * p<0.050, ** p<0.010 statistically significant differences

106 (51.2%) of the operated patients had diffuse-nodular; 55 (26.5%) – with a diffuse-pseudonodular form of AIT; 46 (22.2%) patients were re-operated with AIT recurrence. The statistical difference between the number of patients with diffuse-nodular and diffuse-pseudonodular forms of AIT in subgroups A and B was $\chi^2_{emp.}$=0.798, p=0.418, p>0.050 and $\chi^2_{emp.}$=8.947, p=0.002, p<0.010, respectively. A statistically significant difference was observed between the number of patients with a recurrent form of AIT in subgroups A and B ($\chi^2_{emp.}$=4.459, p=0.034, p<0.050).

We investigated the complications encountered in the early postoperative period of 207 operated patients. Specific complications were observed in 3 (3.1%) patients in subgroup A and 16 (14.4%) patients in subgroup B (χ^2=7.870, p=0.006, p<0.050). In order to compare the early results of surgical interventions using the improved surgical method and CO_2–laser, we examined the indicators of intraoperative blood loss and duration of surgery between subgroup A and B patients (Table 8).

Table 8

Comparison of indicators of intraoperative blood loss and duration of surgery in two subgroups of patients

Subgroups	Intraoperative blood loss (ml)	Duration of operation (min.)	Number of patients with complications	Number of inpatient deaths
Subgroup A (n=96)	172.4±37.2	92±23.1	3 (3.1%)	1 (1.0%)
Subgroup B (n=111)	213.0±43.4	104±19.7	16 (14.4%)	4 (3.6%)
Significance coefficient (p)	p>0.050 p=0.492	p>0.050 p=0.665	p<0.050 p=0.006	p>0.050 p=0.230
Total (n=207)	196±40.3	98.0±21.4	19 (9.2%)	5 (2.4%)

Note: Quantitative values of p>0.050 are not statistically significant
Quantitative values of p<0.050 are statistically significant

Intraoperative blood loss (t=0.710, p=0.492, p>0.050) and duration of surgery (t=0.395, p=0.665, p>0.050) were not statistically significant differences between subgroups. A statistically significant

difference was observed in the number of patients with specific complications in subgroups A and B (χ^2=7.870, p=0.006, p<0.050). There was no statistically significant difference between the number of deaths in the hospital (χ^2=1.396, p=0.230, p>0.050).

Our comparative analysis confirms that the use of CO_2–laser along with improved surgical techniques for performing operations on the thyroid gland has an absolute advantage over the use of traditional surgical methods. This method is applied in the presence of adhesion and fibrous changes that disrupt anatomical connections in the surgical field, which allowed to reduce the number of patients with laryngeal paresis (χ^2=4.057, p=0.044, p<0.050) and hypoparathyroidism by 5 times (χ^2=4.381, p=0.037, p<0.050). It helped reduce postoperative bed days by 22%, from 9.6 to 7.4 days (t=2.588, p=0.007, p<0.050, statistically significant difference is detected).

A statistically significant difference is observed between groups I, II, and III due to the non-determination of Anti-TG titer (respectively I and II – χ^2=73.1, p≤0.001; I and III – χ^2=8.6, p≤0.010; II and III – χ^2=14.0, p≤0.010). Due to non-determination of Anti-TPO titer, no statistically significant difference is observed between group I and group II (χ^2=0, p≥0.050); Group III is statistically significantly different from groups I and II (χ^2=82.3, p≤0.001).

Group I is statistically different from groups II (χ^2=22.6, p≤0.010) and III (χ^2=27.0, p≤0.010) according to the determination of the low level of Anti-TG titer, and a statistically significant difference was not observed between groups II and III (χ^2=0, p≥0.050). Due to the determination of a low level of Anti-TPO. Group III is statistically significantly different from groups I (χ^2=54.0, p≤0.001) and II (χ^2=44.7, p≤0.001), there is no statistically significant difference between groups I and II (χ^2=0, p≥0.050).

According to the determination of the high level of Anti-TG titer, the indicators of group III are statistically significantly different from groups I and II (χ^2=11.1, p≤0.010; χ^2=15.3, p≤0.010, respectively), no statistically significant difference between groups I and II (χ^2=0.36, p≥0.050). There is no statistically significant difference between groups I and II in determining the high level of Anti-TPO titer

($p \geq 0.050$).

Quality of life studies have shown adequate and good results in most patients with adequate conservative therapy, including hormone replacement therapy. According to "good" results, there is no statistically significant difference between I and II clinical groups ($\chi^2=1.2$, $p \geq 0.050$); A statistically significant difference is observed between I and III, II and III clinical groups ($\chi^2=13.2$, $p \leq 0.010$ and $\chi^2=5.2$, $p=0.025$, respectively). There are statistically significant differences between groups I and II, II and III, I and III according to "adequate" results ($\chi^2=1.2$, $p \geq 0.050$; $\chi^2=0.4$, $p=0.90$; $\chi^2=3.7$, $p=0.100$). According to "insufficient" results, there is a statistically significant difference between I, II, and III clinical groups ($\chi^2=42.5$, $p \leq 0.001$).

When evaluating the quality of life, we used the SF-12 questionnaire and applied a 10-point numerical evaluation scale: here the number 1 means "Insufficient" result, the number 10 means "Good" result, the number 5 is "Sufficient" result, if there is difficulty in answering the question ("difficult to answer") is marked with the number 0. The majority of patients (287 out of 340 patients (84.4%)) in all three groups rated their quality of life as sufficient or good.

Taking into account the treatment methods, during the statistical analysis of the quality of life assessment data in the three groups of patients, Pearson's χ^2 criterion showed that there was no significant difference between the indicators of the I, II, and III patients in the general evaluation according to the scores: for 1 – score, Pearson's $\chi^2=10.4$, $p=0.025$; $\chi^2=0.16$, $p=0.990$ for 5 – point; $\chi^2=6.0$, $p=0.050$ for 10 – point; $\chi^2=0.27$, $p=0.990$ for 0 – score; According to the joint assessment of 5 – points and 10 – points, $\chi^2=10.9$, $p=0.025$.

The indicators of patients with high Anti-TG indices before treatment were determined when analyzing by groups: Pearson's χ^2 criterion was ($\chi^2=41.4$, $p \leq 0.001$) for all three groups of examined patients. There is no statistically significant difference between group I and II patients according to Anti-TG before treatment ($\chi^2=0.94$, $p \geq 0.050$); There is a statistically significant difference between group I and III patients ($\chi^2=24.8$, $p \leq 0.005$); There is a statistically significant difference between group II and III patients ($\chi^2=32.7$, $p \leq 0.005$).

Pearson's χ^2 criterion was χ^2=4.38, p≤0.050: a statistically significant difference is noted between the patients of group I and II (χ^2=4.50, p≤0.050); There is no statistically significant difference between group I and III patients (χ^2=1.03, p≥0.050); There is no statistically significant difference between group II and III patients (χ^2=1.74, p≥0.050). After 6-8 months, Pearson's χ^2 criterion for all three groups of patients was p<0.00001. There is a statistically significant difference between group I and group II patients (χ^2=62.5, p≤0.001); There is a statistically significant difference between group I and III patients (χ^2=78.3, p≤0.0001); There is no statistically significant difference between group II and III patients (χ^2=0.15, p≥0.050).

Statistical processing of similar data for patients with high Anti-TPO values showed the following results: Pearson's χ^2 criterion before treatment was (χ^2=14.9, p≤0.010) for all three groups of patients. Pearson's χ^2 criterion for group I and II patients is χ^2=2.1, p=0.100, for group II and III patients, χ^2=4.3, p=0.025, and for group I and III patients, χ^2=14.2 , the value was p<0.010.

Pearson's χ^2 criterion for patients of all three groups 3-6 months after treatment was (χ^2=22.9, p≤0.010); χ^2=22.4, p≤0.010 for group I and II patients; χ^2=10.0, p<0.01 for group II and III patients; For group I and III patients, this indicator was χ^2=4.8, p=0.025.

Pearson's χ^2 criterion for all patient groups 6-8 months after treatment was χ^2=9.1, p≤0.050. Pearson's χ^2=6.5, p=0.010 for patients in groups I and II; For patients in groups II and III χ^2=0.1, p≥0.050, and for patients in groups I and III, this indicator was χ^2=6.8, p=0.010.

Statistical analysis of the obtained data shows that patients with high Anti-TG and Anti-TPO indicators were statistically significantly higher before treatment, but significantly decreased from 3-6 months to 6-8 months after treatment. This trend was noted in all three groups of patients.

From 58.9% to 45.7% in group I for Anti-TG; A reduction of 72.9% to 32.6% was noted for Anti-TPO. 65.1% to 21.7% in the second group for Anti-TG; For Anti-TPO, there was a decrease from

64.2% to 17.0%. In the third group, a decrease was observed for Anti-TG from 58.4% to 24.3% and for Anti-TPO from 52.0% to 19.8%.

In general, the best results were obtained in patients of group III, who underwent ILBI-LILR sessions after surgery, and in patients of group II, where ILBI-LILR sessions were performed together with PDT. The total percentage of patients with good and sufficient results of treatment in these groups was 95.5% in group III and 77.5% in group II.

During the statistical processing of the received data, it was confirmed that the percentage of patients with good and sufficient distant results of treatment among patients in III and II groups is significantly higher. Pearson's χ^2 criterion for all three patient groups was $p \leq 0.05 - p < 0.001$. During statistical processing of the received data, when comparing indicators between group I and II patients, it is possible to confirm that they represent significant differences (good and sufficient results) $\chi^2=5.4$, $p=0.025$. The same result is valid for values between group II and III patients (insufficient result) ($\chi^2=28.1$, $p \leq 0.010$).

RESULTS

1. Based on the retrospective analysis of existing diagnostic methods, the differential diagnostic capabilities of clinical, laboratory-immunological tests, instrumental and immunohistochemical examination methods were determined, and modern laser technologies were applied to the treatment tactics of autoimmune thyroiditis, which enabled the development of a new optimal diagnosis and treatment algorithm of the disease [14].

2. The presence of large tumors in the thyroid gland against the background of the complications of autoimmune thyroiditis, the formation and growth of nodular or multinodular tumors, the presence of severe thyrotoxicosis, and the risk of developing a malignant neoplasm of the thyroid gland should be indications for surgical intervention. In the surgical treatment of the disease, near-total resection of the thyroid gland and thyroidectomy with the improved hydraulic dissection method using CO_2–laser rays are the operations of choice [16,18].

3. Application of improved hydraulic dissection method using CO_2–laser rays to perform surgical operations on the thyroid gland in patients with autoimmune thyroiditis and performing the operation in an adequate volume has an advantage over the use of traditional surgical methods ($p \leq 0.050$). This method is applied in the presence of adhesion and fibrous changes that disrupt the anatomical structure in the surgical field, which has allowed to reduce the number of patients with laryngeal paresis ($\chi^2=4.057$, $p=0.044$, $p<0.050$) and hypoparathyroidism by 4 times ($\chi^2=4.381$, $p=0.037$, $p<0.050$), reduced the postoperative bed days from 9.6 to 7.4 days ($t=2.588$, $p=0.007$, $p<0.050$) [15].

4. Among patients with good and sufficient long-term treatment results, the percentage (95.5% – $p \leq 0.005$) of group III patients who underwent surgery was statistically significantly high (good result – $\chi^2=13.3$, $p<0.001$, sufficient result – $\chi^2=3.7$, $p=0.100$). Based on clinical-laboratory, ultrasound, and pathomorphological examinations, by identifying patients in whom autoimmune processes

may redevelop due to the thyroid gland (included in the risk group), it is possible to predict the probability of postoperative recurrence of the disease or hypertrophy of the residual tissue [6,11].

5. As a result of the studies conducted by the method of fluorescence spectroscopy, it was proved that the time required for the maximum accumulation of the photosensitizer in the parenchyma of the thyroid gland inflammation after the intravenous injection of the photosensitizer – photodiatase in a dose of 0.8 mg/kg is 120-150 minutes. According to fluorescence spectroscopy data, irradiation of the thyroid gland caused a decrease in fluorescence intensity by 72.3% ($p \leq 0.001$) compared to the initial data, which clearly demonstrates the effective impact of the photosensitizer, the occurrence of a high degree of photodynamic response, and the effectiveness of photodynamic therapy in diffuse forms of autoimmune thyroiditis [4].

6. The joint application of photodynamic therapy and intravenous laser blood irradiation with low-intensity laser rays is highly effective as a new approach in the treatment of autoimmune thyroiditis. Diffuse and uncomplicated diffuse-pseudonodular forms of the disease, as well as postpartum thyroiditis, are indications for treatment with this method, and in 77.5% ($p \leq 0.001$) of cases, good and sufficient distant results have been achieved (when comparing the indicators between group I and II patients, a statistically significant difference is revealed $\chi^2 = 5.4$, $p = 0.025$), which justifies the application of photodynamic therapy as an effective method in clinical practice [3,7].

7. Analysis of laboratory-hormonal indicators of patients before and after treatment was carried out to compare the effectiveness of treatment methods between patients who received laser photodynamic therapy session and patients who received conservative treatment during autoimmune thyroiditis. Statistically significant differences ($p \leq 0.001$) observed in the dynamics of indicators of thyroid hormones (TTH: $t = 6.9$, $p \leq 0.001$; Free T_4: $t = 3.4$, $p \leq 0.010$), antibody concentration (Anti-TPO: $t = 8.4$, $p \leq 0.001$), and inflammatory response of the body ($\chi^2 = 5.9$, $p = 0.010$) confirm that the results of treatment are

more effective in patients who received a laser photodynamic therapy session [13].

8. In the immunohistochemical examination of thyroid autoimmune changes, a statistically significant difference ($p \leq 0.050$) is observed between different forms of autoimmune thyroiditis according to the thyroid cell proliferation biomarker Ki-67(+), thyrocyte apoptosis biomarker p53(+), and thyroglobulins (according to $T_{emp.}$, $U_{emp.}$=21.0, p=0.028). Correct evaluation of the proliferative activity of the thyroid tissue in immunohistochemical examinations with the determination of Ki-67(+), p53(+) biomarkers and thyroglobulins allows predicting the risk of recurrence and malignancy of nodular forms of autoimmune thyroiditis [17].

9. The correct determination of the treatment method of autoimmune thyroiditis and the selection of optimal surgical tactics improved the quality of life and treatment results of all studied patients, with good and long-term results in 81.8% ($p \leq 0.001$) cases (Pearson's χ^2 criterion p for all three patient groups ≤ 0.050 - $p<0.001$ was worth) [6,9].

PRACTICAL RECOMMENDATIONS

1. When applying an individual approach to the diagnosis and treatment of autoimmune thyroiditis, for reliable verification of the diagnosis of autoimmune thyroiditis, when examining the patient, it is recommended to use the optimal diagnostic algorithm that we have compiled on the basis of complex clinical, instrumental, laboratory, and morphological examination methods. At the next stage, it is necessary to choose the correct treatment tactics, which ultimately allows reducing complications and improving the patient's quality of life.

2. The clinical course of autoimmune thyroiditis detected in the form of diffuse-nodular and diffuse-pseudonodular forms with complications, very prominent cytomorphological changes in the thyroid gland (active lymphoplasmacytic infiltration of the gland parenchyma, formation of nodular changes, increased activity of cell proliferation of thyrocytes, and a high risk of developing thyroid cancer) should be indications for treatment.

3. In diffuse, diffuse-pseudonodular forms of autoimmune thyroiditis and when conventional conservative therapy is ineffective, it is recommended to use ILBI-LILR sessions ($\lambda \approx 405$ nm) together with laser photodynamic therapy as the main treatment method for patients with postpartum thyroiditis. In most cases, the clinical course of these forms of the disease is manifested by symptoms of subclinical hypothyroidism (38.5%). Only 14.5% of patients have obvious clinical signs of hypothyroidism.

4. When the clinical course of autoimmune thyroiditis is complicated by diffuse-nodular, diffuse-pseudonodular, and thyrotoxic forms of the disease, near-total resection of the thyroid gland or thyroidectomy with the use of CO_2–laser is recommended. In order to prevent laryngeal paresis and hypoparathyroidism after surgery, it is recommended to use an improved operative technique that provides visualization of the localization zones of the returning laryngeal nerve and parathyroid glands.

5. In the treatment of diffuse autoimmune thyroiditis, the joint application of photodynamic therapy and intravenous blood irradiation with low-intensity laser rays completes the arsenal of effective methods of disease treatment. The simplicity of the method, ease of application, reliability, and absence of thermal effects on the thyroid gland are grounds for recommending the application of this method to clinical practice.

6. ILBI-LILR sessions (λ≈405 nm) together with conservative (replacement) hormonal therapy, based on the principle of taking levothyroxine in the arsenal of existing treatment methods for autoimmune thyroiditis patients, give effective results. Giving good and sufficient results in 64.1% of cases, this method is recommended for clinical application as an adjunctive therapy in patients with the atrophic form of autoimmune thyroiditis and postpartum thyroiditis. A euthyroid state is achieved by prescribing levothyroxine in a dose of 50 mg/kg/day.

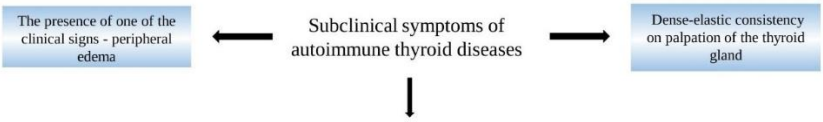
7. ILBI-LILR courses (λ≈405 nm) along with conservative replacement therapy are recommended for atrophic forms of autoimmune thyroiditis and postpartum thyroiditis. Most patients with atrophic form (61.9%) have subclinical hypothyroidism, and only 4.7% have obvious (clinical) hypothyroidism. Pathomorphological changes are characterized by limited sclerosis of the gland stroma, retention of small lymphoid infiltration foci, disappearance of plasmatic cells from these foci, and poor degree of cytological changes (grade I-II).

8. ILBI-LILR sessions together with traditional conservative (replacement) therapy are recommended for auxiliary treatment together with independent and complementary treatment methods in patients who have undergone surgery on the thyroid gland due to autoimmune thyroiditis and have hypothyroidism in the long post-surgery period. Application of the method allowed the majority of operated patients to return to normal social life and work.

Scheme

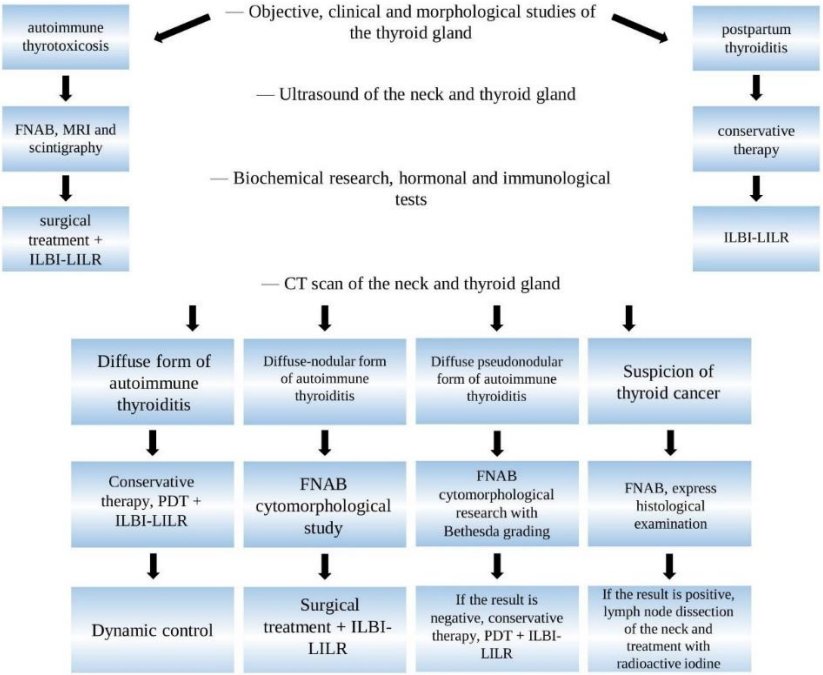
Algorithm for the diagnosis of autoimmune diseases of the thyroid gland

I. Anamnestic data of autoimmune diseases of the thyroid gland



Identification of autoimmune thyroiditis based on anamnestic and objective data, further examination in specialized endocrinological departments

II. Clinical symptoms of autoimmune diseases of the thyroid gland



List of scientific works published on the subject of the dissertation:

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List of abbreviated words

ANOVA	–	analysis of variance
Anti TG	–	antibodies against thyroglobulin
Anti TPO	–	antibodies against thyroperoxidase
CO_2	–	carbon dioxide
CRP	–	C-reactive protein
DTG	–	diffuse toxic goiter
ESR	–	erythrocyte sedimentation rate
FNAB	–	fine needle aspiration biopsy
Free T_3	–	free triiodothyronine
Free T_4	–	free tetraiodothyronine or thyroxine
HILR	–	high intensity laser radiation
IFNγ	–	interferon γ
IgA	–	immunoglobulin A
IgG	–	immunoglobulin G
IL-6	–	interleukin 6
ILBI	–	intravenous laser blood irradiation
IgM	–	immunoglobulin M
Ki-67	–	cell proliferation marker
LF	–	lactoferrin
LII	–	leukocyte intoxication index
LILR	–	low intensity laser radiation
PDT	–	photodynamic therapy
p53	–	transcription factor, regulatory cellular protein
SCS	–	Scientific Center of Surgery
SF	–	Short Form Health Survey
TNF-α	–	Tumour Necrosis Factor alpha
TTH	–	pituitary thyrotropin hormone
USE	–	ultrasound examination
α_2-MG	–	alpha 2-macroglobulin

The defense will be held on the 8th of January at 14⁰⁰ at the meeting of the Dissertation council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

Address: AZ 1022, Baku city, A. Qasimzade str. 14 (conference hall).

Dissertation is accessible at the Azerbaijan Medical University Library

Electronic version of the abstract is available on the official website of the Azerbaijan Medical University (amu.edu.az).

Abstract was sent to the required addresses on the 2nd of December 2024.

Signed for print: 14.11. 2024
Paper format: 60x84 $^{1}/_{16}$
Volume: 79788 characters
Number of hard copies: 100
"Tabib" publishing house