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Modern conceptions on diffuse toxic goiter: etiology, pathogenesis, diagnosis, and treatment (review)

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Abstract. The article is devoted to the analysis and systematization of the latest scientific data on the problem of etiology, pathogenesis, diagnosis and treatment of diffuse toxic goiter. Much attention is paid to the role of diffuse toxic goiter in the structure of endocrine diseases, to the major factors defining its occurrence and progression, to the influence of environmental factors for its development. Modern conceptions on mechanisms triggering the pathological process in diffuse toxic goiter were described. The paper presents etiopathogenetic, morphological, clinical classifications of diffuse toxic goiter.

Keywords: diffuse toxic goiter, etiology, pathogenesis, diagnosis, treatment.

Diffuse toxic goiter, first described by the English physician Caleb H. Parry (1755-1822), is also known as Graves' disease (after Robert J. Graves) in the English-speaking world and as Basedow disease (after Karl A. von Basedow) in the rest of Europe. It is the most common diseases of endocrine system [23] that occurs in about 0.5% to 2.0% people according to the literature data [50]. The disease develops in people between the age of 40 to 60, and is 10-20 times more common in women than in men [35]. Graves' disease is systemic autoimmune disease characterized by persistent abnormal hyperfunction, hyperplasia and hypertrophy of the thyroid gland (TG) with the development of thyrotoxicosis, which is often combined with extra thyroidal disorders [7].

Etiology and pathogenesis

Graves' disease (GD) develops as a result of the thyroid stimulating immunoglobulins (TSI) production, which competes with thyrotropin (TSH) for its receptors and stimulates the formation of thyroid hormones. The disease belongs to multiple-factorial diseases where the genetic characteristics of the immune response are implemented on the background of environmental factors [35].

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Heredity and psychogenic effects are the factors provoking the autoimmune changes. Up to 80% of patients with Graves' disease have psychic trauma in anamnesis [10]. Emotional stress is seen as a factor of the immune system suppression and its adequate response to pathogenic environmental factors [86]. Acute and chronic infectious diseases [55], viral infections, ionizing radiation, solar insolation, pregnancy, menopause [33, 69] are preceded Graves' disease development in 17-20% cases. Iodine in pharmacological doses (amiodarone, radiopaque substances) can not only induce thyrotoxicosis, but complicate the GD treatment too [63, 83]. Often Graves' disease causes the iodine deficiency in some regions [81].

In genetically predisposed people, the disease development is affected by smoking that increases the risk of development and progression of Graves' ophthalmopathy (GO) [46].

A significant role of the genetic predisposition of the disease occurrence was confirmed by antibody screening test to thyroglobulin, toxic goiter or other thyroid pathology in several generations of patients' relatives with GD [35]. In identical twins the same incidence of toxic goiter and titers of antibodies to the thyroid antigens is observed. Study of histocompatibility (HLA-antigens) shows that the presence of HLA-DW3 and HLA-DR3 haplotypes increases the risk of disease in 3.86 and 5.9 times, respectively, compared to having only genes HLA-B8. Combination of Graves' disease with antigens HLA-DQA1*0501 is the most often observed [1]. In Graves' disease heredity, except the genes of HLA system, are involved other genes, that is evidence of the multiple-factorial type of heredity [86].

The main role in the development of Graves' disease belongs to various disorders of the immune system appearing by lymphoid infiltration and thyroid hyperfunction [20]. The role of STLA-4 gene association that is localized on 2q33 chromosome and encodes a protein of superficial cells of D28 molecules with HLA-B7 gene was defined. CTLA-4/B7 complex is competitive to CD28/B7, resulting in a negative signal that is obtained by T-cells, which is responsible for T-cell infiltration, cytokines formation and immune response. Expression of intracellular adhesion molecule type-1 (ICAM-1), that are of the IgG class is amplified in thyrocytes of patients with Graves' disease. They can also indicate the predisposition to Graves' disease and GO de-

velopment. These molecules are ligands to the lymphatic antigen-1 (LFA-1). ICAM-1 expression is regulated by a number of inflammatory cytokines, including interferon-γ, interleukin-1β, TNFα etc. ICAM-1 and LFA-1 interaction is a critical moment between the immune cells and tissue target-cells and it triggers the immune process occurring in the case of Graves' disease [1]. T. Arao et al. revealed for the first time that infiltration with lymphocytes, producing interferon-γ, stimulates thyrocytes proliferation throughout ICAM-1 and LFA-1 adhesion that is key factor in the enlargement of thyroid volume and Graves' disease development [37]. T-suppressors deficiency leads to mutation of forbidden T-helper clones, that stimulate the specific immunoglobulin production in B-lymphocytes that are capable to interact with thyrotropin receptors on thyrocytes [69].

A key element in the GD pathogenesis is the formation of stimulating antibodies to TSH receptor (TRAbs) in 88-98% of cases. These antibodies, binding to the TSH receptor, activate it by triggering the cAMP and phosphatidyl inositol cascades, which stimulate the thyroid iodine capture, synthesis and secretion of thyroid hormones and thyrocyte proliferation [1].

Interaction between oxidative stress and antioxidant system and participation of selenium compounds in this process is now considered in the pathogenesis of this autoimmune disease [57]. Excess of T_4 and T_3 causes increased oxygen uptake, stimulates the oxidation processes in tissues, separates the processes of oxidative phosphorylation and decreases the accumulation of energy in macroergic compounds. The dissimilation processes are prevailed, protein and glycogen destruction is increased in the organism. There is decreased in the tissues of the heart, liver, muscles, and fat mobilization from fat depots is increased [19].

Participation of cytokines in the pathogenesis of autoimmune thyroid disease is actively studied. It is not proved how the level of opposition cytokines changes depending on the duration of autoimmune feedback and severity of thyrotoxicosis under the treatment with different methods and on the presence or absence of thyrotoxicosis complications [8, 45].

Much attention is paid to the mechanisms of the cardiovascular lesions development in patients with Graves' disease. Cytokines participation in this process is beyond any doubt, however, the methods

of its influence were not fully elucidated, and data from different studies are contradictory [31].

It remains not clear either thyrotoxicosis remission is induced with the specific immunomodulator influence of thyrostatics or occurs independently of their effects. Levels of antithyroid antibodies and TRAbs were not studied during thyrostatic therapy in patients at thyrotoxicosis remission peak.

Diagnosis

Clinical manifestation of Graves' disease is gradually developed. At the forefront are The symptoms of nervous, cardiovascular, digestive systems disorder, thyroid gland enlargement, ophthalmic signs, osteoporosis formation are symptoms of the first line [22].

Graves' disease is diagnosed taking into account the clinical symptoms (irritability, weight loss, muscle weakness, tachycardia, increased sweating, body tremor, heat intolerance, the presence of eye symptoms, goiter). The size of goiter, gland structure, consistency, mobility, sensitivity are determined according to the WHO classification [7].

Determination of TSH, T_4 and T_3 content in blood serum is generally accepted in GD diagnosis. The combination of low TSH level and elevated T_4 and T_3 levels (at least one of the two) indicates the manifestation of thyrotoxicosis. The T_3 and T_4 concentration within the reference values indicates subclinical thyrotoxicosis [25]. Basal TSH level is an accessible prognostic marker of disease relapse 4 weeks later after discontinuation of antithyroid agents (ATA) [51].

Ultrasound investigation of thyroid gland using Doppler sonography is of great importance both for diagnosis and for monitoring the treatment of Graves' disease. This method detects diffuse increase of thyroid, determines tissues hypoechogenity, specific increased blood circulation, local changes (nodal formations, cysts) in 80% cases [27]. Thyroid hypervascularization is determined at color cartogram, indicating accelerated blood circulation, laminar nature of which changes to turbulent («thyroid hell phenomenon»). These processes are stopped, that is correlated with a decrease of thyroid hormones during treatment [7].

To determine the degree of autoimmune process in the preoperative period, fine-needle aspiration puncture biopsy (FAPB) is used [35].

According to data of thyroid section of the German Society of Endocrinology, diagnosis of Graves'-Basedow's disease, immunogenic thyro-

toxicosis can be considered confirmed, if relevant results of the above study methods are received and there is Graves' ophthalmopathy present, and further diagnostic search is unpractical [35].

Determination of TRAbs titers is also considered in the Graves' disease diagnosis, it is positive in a case of active form of the disease in 80-90% patients. The indicator allows to differentiate Graves' disease with autoimmune thyroiditis, to determine thyrotoxicosis during pregnancy and to predict the relapse after thyreostatic therapy course [7]. The most sensitive and specific method to determine antibody titers is an immunoassay of the 2nd and 3rd generations [82].

In Graves' disease the elevated levels of antibodies to thyroid peroxidase can be detected in 90% cases and of thyroglobulin — in 50% cases [35]. Several authors emphasize the level of these antibodies has a direct correlation with clinical manifestations of ophthalmopathy, which determines the severity and prognosis of disease [34]. Determination of their level can also be used to assess the risk of thyrotoxicosis relapse development after thyreostatic therapy [21]. TRAbs determination as a method of Graves' disease remission assessment after thyreostatic therapy is not statistically based, and therefore the results of this test should be interpreted together with the results of other diagnostic methods [11]

Radioisotope diagnostic methods are used for assessing the functional activity of the thyroid gland. Thyroid scintigraphy with ^{131}I or ^{99m}Tc allows to determine the diffuse increase of isotope capture by thyroid gland and also is used in diagnosis of unexplained cases [35, 50].

Electrocardiography (ECG), except tachycardia and arrhythmia, detects the signs of left ventricular hypertrophy, which have functional character and disappear after elimination of thyrotoxicosis in a third part of patients with Graves' disease [48].

Graves' disease diagnosis in pregnant women has its own peculiarities. High level of T_3 and T_4 and low level of TSH in blood are observed [33]. However, some authors suggest that the latter indicator is not always informative, as far as in early terms of pregnancy TSH is increased under the influence of chorionic gonadotropin (CG), which is similar to its structure and can stimulate the thyroid function («gestational transient thyrotoxicosis») as TSH [12]. Control of TSH and fT_4 levels should be performed every 2-4 weeks at the start of treatment

and every 4-6 weeks after the achievement of desired outcomes [33, 40]. Increased TRAbs level is the most sensitive marker in pregnant women, who received thyreostatic therapy for Graves' disease, besides it is necessary to conduct the fetal ultrasound to detect signs of thyroid dysfunction [33].

As for optimal method of Graves' disease diagnosis sights of researchers do not coincide [42].

Treatment of Graves' disease

Thyroid hormones inhibition, hyperthyroidism correction and euthyroid state are the main treatment task of patients with Graves' disease [16]. Treatment methods of Graves' disease are divided into three main groups: conservative, surgical and radioiodine therapy [1].

The choice of treatment is dependent on many factors: patient's age, disease severity, size and location of goiter, geophysical conditions of residence, doctor qualification and experience, cost, presence of contraindications to the use of radioisotopes [70].

The questionnaire regarding the treatment choice in patients with Graves' disease established that radioiodine therapy will choose 22% in Europe, 22% — in China and 11% respondents — in Japan. Radioactive iodine therapy is the most frequently used in the US, regardless of the thyroid size, the terms of the disease and other factors [67]. However, antithyroid drugs are the first-line treatment choice in Korea, Japan and European countries [35]. More than 75% Russia doctors prefer the long-term, treatment with thyrostatics, 6% — surgical treatment and 3% — radioactive iodine therapy [4, 16].

Convincing evidence of the treatment choice and the relapses incidence occurring after each of these methods gives the assessment of the thyreostatic side effects. According to the data of meta-analysis, the thyreostatic therapy consequences, compared to surgical treatment, have significantly higher incidence of relapses and tendency to increase the incidence of side effects [77].

Some scientists consider surgical treatment method and treatment with radioactive iodine is more effective than others in 3.44 times [49].

Choice of optimal treatment method remains controversial [18] and requires further clinical studies.

Conservative treatment

Conservative treatment includes complex of anti-thyroid agents, such as thioamides, β-adrenoblockers, iodides, potassium perchlorate, lithium agents, glucocorticoids, sedative agents [1]. The effect of these agents is directed to reducing the thyroid hormones secretion by inhibition of their synthesis and release, as well as inhibition of the thyroid-stimulating antibody secretion [2]. However, according to the data of some authors, in a case of relapse after one course of thyreostatic therapy, the prescription of the second course is pointless [19].

Use of thyreostatic agents

More than half a century thioamides, which includes thiamazole (tyrosol, methimazole, mercazolil), carbimazole and propylthiouracil are used for Graves' disease treatment [35, 40, 64]. According to the recommendations of the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), a main agent in the treatment of Graves' disease is thiamazole [2]. This agent is registered under the name of tyrosol in Ukraine [16].

Inhibition of two stages of thyroid hormones biosynthesis: organification and condensation is a key mechanism of these agents effect. Entering the thyroid gland, thioamides suppress the activity of thyroid peroxidase, which deficiency decreases iodine oxidation, thyroglobulin iodination and iodotyrosine condensation. As a result, the thyroid hormones synthesis stops and thyrotoxicosis is cut off [16, 29, 35]. It is known that thiamazole does not affect the release of the synthesized thyronines of thyroid follicles. This explains the latent period of the drug effect, which can be preceded to normalization of T_3 and T_4 levels in the blood plasma that is to improve the clinical picture [40, 50].

Carbimazole that has good recommendations in Europe was also appeared in Ukraine in 2013 [16]. The therapeutic effects of these two drugs, thioamides, are equivalent, but carbimazole causes fewer side effects and allergic reactions. Propylthiouracil can suppress T_4 deiodination to active T_3, that makes it possible to use it for severe hyperthyroidism [16, 35, 38].

Thioamides influence the immunological disorders — increasing the activity and the amount of certain lymphocytes subpopulations, decreasing immunogenicity of thyroglobulin as result of reducing its iodination, and decreasing the production of E2 prostaglandins, interleukin-1, interleukin-6, and the production synthesis of heat shock proteins by thyrocytes [35]. Immunosuppressive and immunomodulatory effects are not the same for all thyreostatic drugs, there are data, which show a significant reduction in the TRAbs concentration

and increase of T-suppressors number under carbimazole compared to propylthiouracil in treatment Graves' disease patients [36].

Thiamazole is accumulated in the thyroid gland; its half-life period consists of 4-6 hours that allows to prescribe the drug 1-2 times per day. Propylthiouracil has less half-life period — 75 min. Therefore it is needed more frequent intake (3-4 times per day) at a dose 10 times higher than thiamazole [52]. In turn, propylthiouracil is a drug of choice for treating pregnant and breast-feeding women, because of its limited transfer through the placenta and breast epithelium [50].

Thyreostatic drugs are used in a dose titration regimen. Treatment starts with the highest therapeutic doses (30-40 mg/day of thiamazole or 75-150-300 mg/day of propylthiouracil), with gradually dose reducing to maintaining euthyroid state during long time with minimal dose (thiamazole 5-10 mg/day, propylthiouracil 50-100 mg/day) [35]. Thioamides block the T_4 biosynthesis in the thyroid gland only de novo, so their clinical effect appears 3-4 weeks later after drug intake starting [16].

According to the results of four randomized clinical trials comparing the different periods of disease course — 6, 12, 18, 24 months it was found that optimal for achieve the lasting remission is treatment with thyrostatics for — 18 months [36], that was also confirmed by other authors [1, 20].

Thyreostatic treatment can cause immunosuppressive effect on autoimmune process in thyroid gland. This prompted the clinicians to explore different treatment schemes to decrease the incidence of relapses [35, 77]. After treatment of hyperthyroidism with methimazole in a dose of 10 mg and 40 mg there were no difference in the relapse rate (58.3% and 57.8%, respectively) [43]. Minimum thyreostatic dose that is necessary for Graves' disease treatment provides the same remission as the high dose; risk of complications is reduced [17]. Some authors, taking into attention the metabolic rate of thiourea derivatives, recommend taking a single daily-dose of drug. It should be noted that at the start of therapy, high doses of drug (30-40 mg) should be divided into 3-4 intake for minimizing the risk of side effects. Later, when the dose is reduced and its use does not cause the side effects, scheme can be replaced by once per day [16, 36]. A single-day dose of thyrostatics was investigated in two groups of patients with Graves' disease. Patients of the first group received methimazole in a

single dose 15 mg/day, of the second one — 150 mg of propylthiouracil for 12 weeks. At the end of the study authors concluded that methimazole in a dose of 15 mg/day was more effective in inducing euthyroidism than propylthiouracil. Metimazol therapy by the scheme of single-day dose not only quickly reduced the levels of T_3 and T_4 in blood serum, but also increased euthyroidism achievement in 4 times comparing with propylthiouracil treatment according the analogic scheme [52].

Long-term results of combined therapy in Graves' disease are widely discussed in literature [16, 28, 35]. To prevent iatrogenic hypothyroidism in cases of using high doses of thyrostatics, some clinicians use the combination therapy «block and replace», namely 10-15 mg of thiamazole and 50-100 mcg of levothyroxine (L-T_4): one drug blocks the gland, another replaces the deficiency of thyroid hormones. This scheme is simple to use, allows to block thyroid hormones production preventing a relapse of thyrotoxicosis [12, 83]. Maintenance of normal levels of TSH and T_4 is criterion of adequacy of therapy. Course of treatment lasts from 12 to 24 months. This scheme allows to avoid the enlargement of thyroid size in case of medicamentous hypothyroidism development during thyrostatics use [16].

However, this therapy has been supported not by all researchers. It has been analyzed the patients' thyrostatics treatment results in 12-15 months after treatment with thyrostatics. Groups were divided by risk factor — the size of the goiter, TRAbs level — with L-T_4 administration in different suppressive doses. The authors have found the hyperthyroidism relapses in all groups (% in a year, 32% in 2 years). In patients who did not receive additional L-T_4, the relapse rate was 18% and 24%, respectively. Studies have been shown that L-T_4 does not prevent hyperthyroidism relapse after euthyroid function recovery by thyrostatics, and has no effect on TRAbs level and does not reduce the size of the goiter [18, 23, 51, 63]. The searching the optimal method to treat patients with Graves' disease continues.

Side effects of the thyrostatics use

The thyrostatics use can cause the side effects in nearly 13% of patients: dyspepsia, pain and swelling in the joints, vasculitis, cholestasis, skin rash, itching [7, 18]. Dangerous complication is agranulocytosis, aplastic anemia in 0.2-2.0% cases as a result of high doses thyrostatics [79]. It is well known the

toxic effects of thyrostatics on the liver: metazole can cause cholestasis [18] apropiltiouracyl — systemic vasculitis associated with the formation of anti-neutrophil cytoplasmic antibodies [66].

β-adrenoblockers in the treatment of Graves' disease

In the complex treatment of Graves' disease, along with ATD, if euthyroidism is not achieved, β-blockers are used, which affect the symptoms caused by catecholamines: anxiety, sweating, fear, tremor, tachycardia [7, 50, 78]. Propranolol is prescribed in a dose of 40 mg every 6 hours [7, 18]. According to some authors, it is better to prescribe the cardioselective β-adrenoblockers, which block myocardial 1-adrenergic receptors and do not affect the bronchi 2-adrenergic receptors: atenolol (50-100 mg/day), metoprolol (100-200 mg/day), bisoprolol (5-10 mg/day), and is recommended to decrease the dose with interval of 10-14 days in the process of treatment [16, 35, 50]. These drugs are also included Spesicor, Concor. The signs of dose adequacy are decrease of heart beat, heart pain, absence of side effects [78].

Treatment of Graves' disease by lithium agents

As an independent therapy for thyrotoxicosis of mild and moderate severity, and, in some cases, for complex treatment of Graves' disease lithium is used in addition to the traditional thyrostatics [44]. Lithium acts as a membranes stabilizer, reduces sensitivity of tyrocytes to stimulating effect of thyrotropin and thyroid-stimulating antibodies, and reduces the release of thyroid hormones from the thyroid gland into the blood. This provides a quick effect and the euthyroidism state [7, 44]. Depending on the symptoms severity, lithium carbonate is prescribed in a dose of 900-1500 mg/day [18]. Thyroid sensitivity to lithium is stored for 3-4 months, then comes «slipping phenomenon». Because of this, lithium can not be used for a long-term treatment [7, 44]. Lithium can have toxic effects on the body: it can cause nausea, increase tremor, damage of kidneys and heart. As normotonic drug, it can cause drowsiness, increase fatigue. The drug is permeable through the placenta, so it can not be used to treat pregnant women [7].

Treatment of patients with Graves' disease by inorganic iodine agents

Today the use of inorganic iodine agents are limited in Graves' disease. They are used in patient's with thioamide intolerance. Iodides (Lugol's io-dine, saturated solution of potassium iodide) reduce their own transportation to the thyroid gland, inhibit the iodine organification and quickly block the T_3 and T_4 release from the gland that promotes rapid euthyroidism attainment [7]. However, antithyroid effect of iodides is stopped in some days or weeks, and thyrotoxicosis is restored or even become more pronounced [7].

The average thyroid volume was significantly increased in patients treated with potassium iodide that was revealed by ultrasound examination in patients with Graves' disease. The increase of thyroid gland exceeded 30% in 17% cases [91].

Glucocorticoids treatment of patients with Graves' disease and Graves' ophthalmopathy

Complex treatment of patients with Graves' disease, along with thyrostatics includes also glucocorticoids. Their use is appropriated in the cases of significant activation of autoimmune mechanism in disease and clinical signs of adrenal insufficiency, one of which is the increased hyperpigmentation [20]. Glucocorticoids (dexamethasone in a dose of 8 mg/day, prednisone 15-30 mg/day with decreased dose every 5 days up to 5 mg) cause a direct antithyroid effect, inhibit thyroid hormones secretion and T_4 to T_3 conversion [7, 17]. There is evidence that the effect of pulse therapy with methylprednisolone is temporary and does not increase the remission time in patients with Graves' disease [58].

As Graves' ophthalmopathy is mostly combined with Graves' disease, stable euthyroid is sufficient to decrease or disappearance of its manifestations [17]. Taking into account that GO is an organspecific autoimmune disease, glucocorticoids that are prescribed for a long time with high initial dose are included into treatment scheme [7, 40]. It is proved that oral corticosteroid intake is effective in 60% of cases, and retrobulbar administration — in 40%. The use of necessary high doses may be accompanied by some side effects. The relapse of GO is a common problem after a decrease of a dose or discontinuation of glucocorticoids. An orbital radiation therapy is used either alone or in combination with glucocorticoids, but there are various opinions of its effectiveness [80].

The results of prospective randomized trial comparing the efficacy and safety of oral and intravenous glucocorticoid therapy of complicated GO found both variants of treatments effective, pulse therapy was closer to the optimum, efficient, and safer [65].

Additional method of Graves' disease treatment

To increase the effectiveness of thyrotoxicosis treatment, immunomodulators are proposed to use [3]. Today are continuing studies of Rituximab immunomodulatory. Its high effectiveness is revealed in 91% patients with GO, but this agent is expensive and produces side effect [20, 41, 73]. Some scientists offer the herbal products, as an alternative in case of allergy against thyrostatics, decreasing the levels of T_3 and T_4 [59]. Phenobarbital is the drug, which indirectly affects the content of thyroid hormones, and accelerates the metabolism of T_4 and cause the sedative effect [7]. Low molecular antagonists of TSH receptor have therapeutic potential as the active agents blocking stimulation of antibodies in Graves' disease [71]. Plasmapheresis, the therapeutic effect of which is associated with the removal of thyroid hormone excess, antibodies, toxic substances is used in a case of the allergic reactions to thyrostatics [7]. As the correlation between an oxidative stress and antioxidant system was proven; selenium compounds are useful in Graves' disease treatment [57].

The treatment problem of pregnant women with Graves' disease

A separate issue is Graves' disease treatment during pregnancy. Data of Graves' disease rate in pregnancy are controversial and varies from 0.05% to 4% (about 1 case per 1000 pregnancies) [7, 33]. The immediate abortion in Graves' disease is not discussed. An adequate treatment of patients with thyrotoxicosis begins from the early stages of gestation that is a crucial condition for improving pregnancy course. If a compensation state is reached during pregnancy, the threat for the mother and fetus is minimal [7, 33, 92].

Thyrostatics are prescribed for treatment of pregnant women with Graves' disease. Thiamazole (metimazol) is associated with the development of skin aplasia, esophageal atresia and other congenital anomalies of the fetus, propylthiouracil are more preferred [92]. The initial dose is propylthiouracil consists of 100-300 mg/day, metimazol — 20 mg/day and is conditioned by the degree of hyperthyroidism. Further it carry monthly maintenance dose adjustment for T_4 at the upper limit of normal or slightly above normal For preventing fetal hypothyroidism monthly dose correction is realized to maintenance T_4 at the upper limit of a norm or slightly above a norm [2] Medicamentous treatment is not stopped after the child birth [7, 26]. a small amount of thyrostatics are secreted into the mother's milk but propylthiouracil in a dose of 750 mg/day or methimazole in a dose of 20 mg/day that are taken by mother during lactation do not affect the function of the child's thyroid gland that was shown in prospective clinical studies [92].

β-adrenoblockers can be used in pregnant women only for a short period of her preparation for surgery or in the case of thyrotoxic crisis [33, 36].

Subtotal thyroidectomy or thyroidectomy may be performed in the women with allergy or severe adverse reactions against thyrostatics, in the necessity of thyreostatics high doses and in cases of compliance absence in pregnant, and it is preferable at the second trimester [7, 33, 92, 93].

Iodine-131 therapy is contraindicated during pregnancy [13].

Congenital hyperthyroidism is caused by the increased secretion of thyroid hormones in fetus (as a result of crossing thyroid stimulating antibodies through placenta). The disease can be manifested after child birth as well as in utero. The risk of fetus hyperthyroidism depends on the mother's thyroid stimulating antibodies, but not on her hyperthyroidism [7, 33].

Thus, conservative therapy of Graves' disease is a method of treatment that is not psychologically traumatic ones and provides relatively rapid therapeutic effect: health normalization and decrease of thyroid hormones in the majority of patients within 4-6 weeks after start of treatment [88]. Stable remission of disease is achieved in 20-25% patients, according to the data of some authors [12, 23, 88], according to others — in 40-60% patients [23]. The absence of clinical symptoms of hyperthyroidism, normalization of thyroid sizes, TSH, T_3 and T_4 levels, ultrasound thyroid echogenicity, absence of TRABS and improvement of the psychological state in patient are considered as criteria of stable euthyroidism by the greatest part of researchers [7, 9].

The main disadvantage of the thyreostatic treatment is a high risk of hyperthyroidism relapse, that is occurring in 30-82,5% cases after conservative therapy [60], in most cases during the first year after discontinuation of treatment [9, 10].

Among unresolved questions are optimal starting dose of thyreostatics, duration of their use, rationality of their combination with thyroid agents. Advantages of one or another agent are unclear till the end.

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Treatment of patients with Graves' disease by radioactive iodine

Radioiodine therapy is an effective method for treating Graves' disease, which ensures elimination of hyperthyroidism in 70-95% of patients [34, 63, 67, 72]. In many European countries and in Japan radioiodine is used in hyperthyroidism relapses after conservative and surgical treatments of Graves' disease. Iodine-131 therapy is the method of choice for treating new-onset of Graves' disease in many countries [89].

In Graves' disease treatment drug of choice is iodine-131 with a short half-life (8.04 days). The therapeutic effect of this isotope is caused by β-radiation, which destroys the thyroid tissue with increased function, resulting in euthyroidism or hypothyroidis [30].

Iodine-131 treatment in a dose of 10-15 mCu is the sufficient therapy in patients with Graves' disease according the ATA / AACE recommendations confirmed by the results of treatment [67]. Many endocrinologists prefer high doses of iodine-131 for thyroid tissue destruction and the achievement of persistent hypothyroidism [30]. The attempts to prescribe the low radioiodine dose lead to treatment failure or persistent subclinical hyperthyroidism [87]. Dose consisted of 30-40 Gy is considered an optimal, as euthyroidism is seldom achieved as a result of iodine-131 treatment [23]. However, there is evidence where hypothyroidism incidence is 50% in 10 years and is independent of radioiodine dose since lymphoid infiltration and thyroid tissue destruction are developed [50]. Some authors claim that the dose should be chosen individually depending on the mass of thyroid [89]. Thus, choice of the optimal iodine-131 dose for treatment for Graves' disease is controversial [63, 84]. Almost all the researchers agree that iodotherapy is contraindicative for pregnant and breast-feeding women [7, 35]. The advantage of this treatment is the ability to assign it without pretreating patients with thyreostatics [87].

Usually iodine-131 is prescribed in 2-10 days after cessation of thyreostatic therapy [35, 50]. There is evidence that treatment with iodine-131 prescribed after thyreostatics withdrawal, does not reduce its effectiveness [87]. The investigation of prior thyreostatic therapy effect on patients treated with iodine-131 showed that in patients with thyroid mass more than 60 g, who were taking propylthiouracil, the hypothyroidism incidence was significantly lower than in patients receiving methimazole in 3 and 6 months after radioiodine therapy [4].

It is shown the prescription of adjuvant therapy with lithium carbonate decreases the percentage of patients with thyrotoxicosis in 1.5 months after radioiodine therapy. In patients who were not taken lithium hypothyroidism was developed up to the 3rd month. By the 6th month of treatment, the disease was not dependent on the use of this drug [6].

Several authors believe that factors of progression and exacerbation of Graves' ophthalmopathy after radioiodine therapy is the presence of ophthalmopathy before treatment, smoking, high TRAbs level, thyroid hormones, not timely detected hypothyroidism after radioiodine therapy etc. [34, 89].

The problem regarding possible use of radioiodine therapy in young patients (including children) remains debatable [28, 72], because iodine-131 radiation can cause carcinogenic effects on the thyroid gland [7]. However, some authors proved the absence of such effect [67].

Unfortunately, the use of radioiodine therapy in treatment of Graves' disease patients' in Ukraine, as in many other countries of the world, is difficult of access.

Patient preparation for surgical treatment of Graves' disease

Currently, the preparation of patients for surgical treatment of Graves' disease is an urgent problem [7]. There is a point of view that in the preoperative period the attention must be paid to the patient's age, disease duration and thyreostatic use as these factors affect the state of extrafollicular epithelium and the stroma and regenerative ability of the thyroid gland [18, 23].

An important role preparing for surgery belongs to β-blockers, which have antithyroid indirect effects. β-blockers slow the T_4 peripheral tissues conversion to T_3, increasing the number of reverse T_3, potentiate the thyreostatics effect, allowing to quickly reach the euthyroid state without thyreostatics dose increase [7].

Many authors support the advisability of iodide prescription with thyreostatic effect [7, 16]. As it was show the 7-10-daily preoperative treatment with Lugol's solution blocks the thyroid hormones secretion and decreases thyroid vascularization, thereby improving the quality of operative intervention and decreasing a number of postoperative complications quantity (bleeding, temporary vocal cords paralysis and hypoparathyroidism) [47]. To decreasing the thyroid vascularization in case of iodine intolerance before surgery, lithium drugs are used [7, 44].

The immunomodulators use normalizes immune parameters, decreases the preparation of preoperative period, improves the results of surgical treatment and reduces the rate of postoperative hypothyroidism and disease relapse [3]

Some authors propose plasmapheresis use to remove thyroid-stimulating immunoglobulin thereafter surgery is performed on a back ground of glucocorticoids treatment [7].

However, the problems of the effect of various treatment regimens and patient preparation to surgery on the complications development in early and late postoperative periods are not fully clarified, and their researches stay actual ones.

Surgical treatment of Graves' disease

Surgery is the oldest method of treatments in Graves' disease patients among the three main ones. It is used in a stable and long-lasting medicamentous euthyroidism [5]. There are hemithyroidectomy, thyroidectomy, subtotal resection distinguished by the size of interventions [3, 10, 28, 75].

Thyroidectomy is considered an optimal method by some authors [49, 54, 76], while others prefer subtotal thyroid resection [7, 18, 23]. Thyroid surgery allows to achieve an euthyroidism by reducing a number of hyperfunctioning follicular cells [35], hypothyroidism or relapse can develop in the future [5].

The indications for surgical treatment were formulated: unsuccessful conservative therapy, occurrence of complications complications during therapy; relapse; goiter of large sizes, compression of neck organs by the increased gland; nodular forms of goiter; the young age of patients; pregnant women or people who are planning a pregnancy; a condition when the patient requires the rapid elimination of hyperthyroidism, but cannot take thyreostatics [5, 10, 84]. The discussion about appropriate indications for surgical treatment of Graves' disease is continued [5, 17]. Surgery should be mandatory in a case of nodule formations in patients with Graves' disease because in 3.4-13.5% of cases they are a sign of thyroid carcinoma [54].

After surgical treatment of patients with Graves' disease may be noted early and late complications [10]. The most significant of them is bleeding (0.3-5%), which can lead to fatal outcome as a result of asphyxia and injury of the laryngeal nerve (0.2-2.0%) [39]. Postoperative hypoparathyroidism — transient or steady with 2.5-7.0% rate can also be occurred [10]. Late postoperative complications include relapse of hyperthyroidism (0,6-20%) [5, 10] and hypothyroidism which rate is ranged from 5% to 80% [5].

The risk of postoperative relapse and hypothyroidism

As it was noted, most authors prefer subtotal resection of the thyroid gland, because it can be possible to use the differentiated approach to the remaining part of tissue [62]. The remaining part of thyroid stump should be such that can preclude relapse of thyrotoxicosis or hypothyroidism development, and to ensure a sufficient euthyroid state [23]. Some scintists accent that the functional state of thyroid stump after surgery is dependent not on its volume but of the autoimmune process intensity in patient: after subtotal resection hypothyroidism is achieved approximately in 80% of patients, in 10% of patients — euthyroidism, in 10% operated persons hyperthyroidism is kept or relapse is developed [5, 15].

K. Sugino et al., comparing the group of patients with Graves' disease, who were subjected to subtotal and total thyroidectomy with a control of the thyroid function in 2 and 3 years after surgery, concluded that the result of reducing the residual thyroid stump mass from the first to the third periods was the reduction of thyrotoxicosis relapse by 13%, but the number of patients who had hypothyroidism, increased by 50% [76].

According to the data of P. Moreno et al., high rate of euthyroidism is observed in patients in those cases where the stump mass varies within range of 6 to 8 g. The authors prove that after subtotal thyroidectomy euthyroidism is better achieved when there is smaller stump mass in elderly age women and the greater — in the young men [68].

E.A. Valdina reports that thyroid remnant should be determined from calculation of 50-60 mg/kg of patient body mass (3.4 g) in group of patients of patients with risk of thyrotoxicosis relapse, and postoperative hypothyroidism — 100 mg/kg (7.8 g) in the group of postoperative hypothyroidism risk. In other cases, the mass of remaining part should be calculation of 80 mg/kg body mass (5.6 g) [4].

V.G. Aristarkhov believes that for determining the mass of remaining thyroid tissue it is necessary to take into account the state of the morphological structure of the thyroid gland, the patient's age, disease duration, use of thyreostatics that directly effect on the follicular epithelium, as well as the gland regenerative ability. For example, in a pa-

tient aged 50 years with disease duration of more than two years and a large tight gland should be leaved about 1 / 7-1 / 8 gland mass; in patients aged 25-30 and 50-1/10 part of the thyroid gland; person aged 25-30 years with disease anamnesis up to one year, and with the small gland — 1/12 lobe of thyroid mass. To achieve euthyroidism the immunomodulatory effect on the thyroid stump with a wavelength of 0.89 microns [23] laser radiation is nessessery.

By dynamic ultrasound control of thyroid tissue after resection E.E. Khoroshko et al. identified certain changes of its stages. Echostructure normalization and functional adaptation of thyroid parenchyma were occurred within 3-6 months after surgery and were finished up to a year in patients without replacement therapy, while this process was stopped in thyroxin treated patients [32]. Discussion on the necessary and the sufficient volume of the thyroid remnant after surgery is lasted for decades [18].

Prognostic factors of complications in surgery of Graves' disease are genetic and immune characteristics of the body [5, 25], in particular some genetic markers. An increased rate of thyrotoxicosis relapse is observed after surgery in patients with the phenotype HLA-B8 and DR3; that is too great in patients with both antigens [5, 10, 25]. The presence of thyroid-stimulating antibodies in blood serum of patients with Graves' disease, which preservation is correlated in patients after surgery with the rate of thyrotoxicosis relapse, has prognostic significance [51].

N.C. Suaryshvili et al. believe that pronounced autoimmune process in thyroid gland is a risk factor of postoperative thyrotoxicosis relapse, and recommend to calculate the necessary volume of thyroid remnant depending on the stage of autoimmune process in the preoperative period, determined with using fine-needle aspiration (FNA) [24]. Other authors did not find this connection.

To determine the NIS mRNA content (sodium iodide symporter) in extracted thyroid tissues as an indicator of postoperative hypothyroidism after partial thyroidectomy is offered by some authors [66].

There is reason to believe that cytotoxic autoantibodies, which together with cellular mediators of immune response support the destructive processes in the thyroid gland, are played an important role in the formation of post-operative hypothyroidism [25].

It is proved that the risk factor of postoperative thyrotoxicosis relapse is a high level of free T_4 and low indices of TSH before surgery [25]. As was noted by some authors, thyrotoxicosis relapse occurs more often in young women with large goiter [76]. No sex significant differences in development of postoperative hypothyroidism risk were not found [14].

Most exposed patients [14], to develop postoperative hypothyroidism are those older than 50 with long-term course (up to 2 years) of thyreostatic treatment in Graves' disease with, with high levels of antibodies to tireoperoxidase, and most importantly, the presence of thyroid lymphoid infiltration tissue. There is evidence that elevated preoperative level of serum TSH after thyreostatic treatment (more than 3.0-3.5 mlIU/l) increases the risk of postoperative hypothyroidism development almost in 60% [76], that agreed to the data of other authors.

To determine the surgery volume, the prognostic significance have such clinical signs: age and sex of the patient, the thyrotoxicosis severity, the gland size, thyreostatic therapy duration, regimen of patients' thyreostatic treatment in preoperative period [3, 5]. Prophylaxis of recurrent goiter is thyroidectomy or maximum subtotal thyroid resection, adequate replacement therapy with thyroid hormones under control of TSH and free T_4 levels in postoperative period [76].

Thus, today scientists' opinions on prediction of complications like relapse and postoperative hypothyroidism are rather contradictory. The effect of preoperative treatment with different thyreostatic combinations on the development of postoperative complications in patients, hypothyroidism in particular was not studied.

The current state of postoperative hypothyroidism treatment

Now, the majority of scientists believe that postoperative hypothyroidism is the aim of surgical treatment of patients with Graves' disease and it is not a complication [5]. The rate of primary hypothyroidism consisted of 2-7% in the world [56]. The conception of this condition treatment was changed by the appearance of synthetic thyroid hormone drugs with exactly dosage. It is believed the postoperative hypothyroidism is easily compensated and does not lead to decrease of life quality in patients [5]. The therapy hypothyroidism with L-T_4 drug is rightly considered «Gold standard» [53].

The principles of hypothyroidism replacement therapy are well known [5] and are summarized in the recommendations of the International laboratory diagnosis of thyroid disease. It was based on: initial dose of L-T$_4$ and period to achieve full replacement therapy is individually determined and is dependent on age, body mass and presence of concomitant heart pathology; euthyroidism in adult is achieved with prescription of the L-T$_4$ drug in a dose of 1.6 mg/kg body mass/day; the aim of replacement therapy is to maintain TSH level within 0.5-1.5 mIU/l; the typical variant of the gradual achievement of the total replacement dose is its increase by 25 mg every 6-8 weeks; patients receiving L-T$_4$ matched dose are recommended to annual control of TSH level [53].

In recent years, an attention to the use of combination therapy with L-T$_4$ and triiodothyronine was increased in a case of hypothyroidism. The published results of researches demonstrate the superiority of this therapy. Blood lipid profile, mood, memory were improved in patients [90].

Early postoperative hypothyroidism is accompanied by secondary immunodeficiency, activation of lipid peroxidation and decreased antioxidant defense [15]. So, the use of thyroid drugs and immunomodulating effect, including laser therapy are contributed to reparative regeneration of remaining thyroid extrafollicular cells [23].

So, summarizing data of literature review, one can conclude that all three methods of Graves' disease treatment have advantages and disadvantages. Thyreostatic prescription is the method of choice for initial therapy of thyrotoxicosis.

Recently, the incidence of postoperative complications is significantly decreased by improving preoperative preparation and surgery technique. However, there are significant differences in predicting the results of surgery.

The risk factors of hypothyroidism development after subtotal thyroid resection of are not fully investigated

Great importance has necessity to development and scientific substantiation of methods for preoperative preparation of patients with Graves' disease.

There are no criteria for predicting the results of surgical treatment of Graves 'disease because the determination of the risk factors in development of postoperative complications in different periods after subtotal resection of the thyroid gland in patients with Graves' disease have not lost their actuality and require further investigation.

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Современные представления о диффузном токсическом зобе: этиология, патогенез, диагностика, лечение (обзор литературы)

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Резюме. Проведен анализ и систематизация современных на-учных данных о диффузном токсическом зобе (ДТЗ). Отмечено место ДТЗ в структуре заболеваний эндокринной системы, основ-ные факторы, определяющие его возникновение и прогрессиро-вание, роль экологических факторов риска развития. Описаны современные представления о механизмах, обусловливающих реализацию патологического процесса при ДТЗ. Представлена этиопатогенетическая, морфологическая, клиническая классифи-кация ДТЗ.

Ключевые слова: диффузный токсический зоб, этиология, пато-генез, диагностика, лечение.

Сучасні уявлення про дифузний токсичний зоб: етіологія, патогенез, діагностика, лікування (огляд літератури)

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Резюме. Проведено аналіз та систематизацію сучасних наукових даних про дифузний токсичний зоб (ДТЗ). Визначено місце ДТЗ в структурі захворювань ендокринної системи, основні чинники його виникнення та прогресування, роль екологічних чинників ризику розвитку. Надані сучасні уявлення про механізми, що зумовлюють реалізацію патологічного процесу при ДТЗ. Наведено етіопатогенетичну, морфологічну, клінічну класифікацію ДТЗ.

Ключові слова: дифузний токсичний зоб, етіологія, патогенез, діагностика, лікування.