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Immunological and Pathogenetic Aspects of Thyroid Gland Diseases: A Literature Review

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Abstract The article presents an analysis of scientific sources that publish clinical-experimental data on immuno-pathogenetic aspects of thyroid diseases, mechanisms of changes in the immune system, cellular and humoral immunity, and cytokine status. The immunological efficiency of various treatment methods has been shown.

Keywords Thyroid gland, Diffuse toxic goiter, Hypothyroidism, Immune and cytokine status, Immunopathogenesis

1. Introduction

According to the World Health Organization (WHO), thyroid gland (TB) diseases rank second among endocrine pathologies after diabetes. 665 million in the world. more than 1.5 billion people suffer from QB pathologies. There is a risk of developing diseases caused by iodine deficiency. In 2008, the World Thyroid Day was approved by the initiative of the European Thyroid Association [18].

According to recent studies, the prevalence of hyperthyroidism is 1.5% among the younger generation and 4.5% among people over 60 years old. In women, QB hyperfunction is diagnosed more often than in men, it is characterized by the development of systemic disorders in the body, which worsens the patient's quality of life. The prevalence of hyperthyroidism is 2-3% among women and 0.2-0.8% among men, and diffuse toxic goiter (DTB) accounts for 50-80% of hyperthyroid cases. In rare cases, hyperthyroidism can be caused by toxic adenoma, multinodular toxic goiter, pituitary TTG-producing adenoma [2,13].

Thyroid pathology caused by iodine deficiency Fadeev V.V. According to [19], it ranks 1st in terms of territorial distribution and number of living population. According to WHO data, 655 million people in the world die of iodine deficiency. endemic goiter in humans, 43 million. a person has brain dysfunction and retardation of mental development.

According to the data of a study conducted in the USA in 1988-1994, manifest hyperthyroidism was observed in 0.5% of the population aged 12-80 years, and subclinical hyperthyroidism was observed in 0.8% of cases. Hyperthyroidism was found in 2% of women, its prevalence in women was 10 times higher than in men. The prevalence of postpartum thyroiditis varied from 1.1% in Thailand to 21.1% in Canada. The prevalence of this disease varies in different countries: 5.5-6.5% in Japan, 3.3-8.7% in Europe, 5-16.7% in Great Britain, 10.3% in Australia and 14.6% in Brazil. 3.3-8.8% prevalence in the USA [22].

According to experts, the increase in the number of diseases is mainly caused by nodular forms of goiter, which is mainly related to the deterioration of the environmental situation, which is affected by industrial enterprises, radioactive pollution of some areas. According to most researchers, under the influence of harmful production factors, radiation, iodine deficiency, the number of nodular and autoimmune diseases has increased significantly in recent decades. In addition to iodine deficiency, the genesis of goitre formation is complicated in regions with high levels of other stromogenic factors that additionally block QB function [3].

DTB was first described by the English doctor Caleb Hillier Parry in 1825, by the Irish doctor Robert James Graves in 1835, and in 1840 by the German doctor Carl Adolf von Basedow, who described a set of symptoms consisting of exophthalmos, tachycardia and goiter (Merzburg triad). The frequency of new cases of DTB varies from 30 to 200 per 100,000 people per year. DTB is one of the main reasons why the population turns to endocrinological care, QB hyperfunction accounts for up to 80% of all cases, occurs more often in the age group of 20-40 years, and women are affected 10-20 times more often [18].

The structural similarity of QB hormones with catecholamines is important in the pathogenesis of DTB: both catecholamines and QB hormones are derivatives of the amino acid tyrosine. As a result of the sympathomimetic effect of thyroid hormones, the functional activity of all organs and systems of the body increases [18].

Kadyrov A. E. and co-dependent According to [14], DT B risk from 30 to 60 years has been women 3% for and men for 0.5%. Authors, DTB thyroid antigens, especially T TG to receptors immune tolerant k from violation come It turns out, thyrotoxicosis serum antibodies and in the gland autoreactive lymphocytes existence with characterized, a nti

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- r T T G, tir e operoxidase and thyr e oglobulin tolerance to the violation they believed that they would help.

Pesheva E. D. and common [19] at present Graves disease 3 methods of treatment It is believed that there are: thyrostatic drugs are long term application, surgery treatment with radioactive iodine treatment (radio iodine therapy-R Y T). R Y T is preferred in A QSh seen, Europe, Latin America and Osi or the first in line conservative cure is ordered. Graves disease the first of treatment line choose according to doctors between continue is going disagreement treatment "gold standard" existence about to speak possibility does not give.

According to WHO, 750 million people suffer from QB pathology in the world. 64-84% of people develop nodular formations. The lack of a tendency to decrease in the number of patients is due to the presence of endemic areas, where the incidence rate is from 1.2 to 9.0 per 100 thousand population. It is clear that there is a need to increase the effectiveness of measures for the prevention and treatment of QB diseases in Uzbekistan [2,3].

2. Materials and Methods

The diagnosis of hypothyroidism involves the determination of TTG and T4 levels, where the detection of an isolated increase in TTG indicates subclinical hypothyroidism, and at the same time an increase in TTG and a decrease in the level of T4 indicate obvious or manifest hypothyroidism. The American Association of Clinical Endocrinologists (2012) does not support general screening for hypothyroidism in adults, pointing out that it is more common in people over 60 years of age, and believes that it is appropriate only in them. According to the author, hypothyroidism is a viable indication for prescribing thyroid hormone preparations [19].

The analysis of the parameters of the immune status of 92 children aged 8-12 years with subclinical hypothyroidism showed that most of the children had depression in the cellular link of immunity, and activated the humoral link. These data testify to the stress of immunological homeostasis in children with this pathology. Therefore, for the early diagnosis of AIT, immunological monitoring of children with subclinical hypothyroidism is necessary, which allows to diagnose AIT at the preclinical stage and to differentiate it from other causes of QB hypofunction. The author Antibodies to TG in AIT healthy in children too high in titers observed [1].

Nodular colloidal goiter, adenomas, "pseudo-nodules" in chronic autoimmune thyroiditis, various morphological variants of cancer of the prostate gland, and their combinations are considered under the term "nodular derivatives of the thyroid gland". In France, per 1000 people, the average number of QB node derivatives was 35%, in the USA it was 4-7%, and in Japan it was 19%. On average, 10% of focal pathology occurred in Uzbekistan. The number of focal derivatives of QB increased with age [2,3].

Ismailov S.I. According to [12], the incidence of nodular euthyroid diseases ranges from 10% to 62%.

Hanna J. et al. (2015) proved that environmental factors cause QB autoimmune diseases against the background of genetic predisposition. Immunoregulatory genes predisposed to this pathology (FOXP3, CD25, CD40, CTLA-4, HLA, PTPN22 genes) have been shown to play a crucial role in the development of effective immune response, autotolerance, cell-mediated and humoral immunity. Understanding the functional and mechanistic consequences of these susceptibility gene variants is essential for the development of new preventive treatments for this pathology [16].

Morphological characteristics of thyrocytes of QB follicles and phenotypic composition of intrathyroidal lymphocytes were studied in 58 women with Graves' disease. In this disease, tissue-specific autoimmune inflammation and long-term thyrostatic treatment resulted in remodeling of the thyroid epithelium with histological signs of chronic autoimmune thyroiditis, which was evident in the recurrence of the disease. In the group of patients with Graves' disease relapse, compared to patients diagnosed for the first time, the percentage of T-lymphocytes with CD3+CD4+CD127 LowCD25High phenotype and V1-memory cells increased, the content of T-activated and cytotoxic activated T-cells, the population of V1-lymphocytes decreased [7].

by the authors for the presence of antibodies to 21-hydroxylase (21-ON), IAA, ICA, GAD, IA2, ZnT8, AGA, Anti-tTG, PCA, IF, rheumatoid factor, antiovarian antibodies, plasma glucose levels were studied. The authors found that patients with this pathology have a high risk of developing APS type 3, a complicated heredity of autoimmune diseases [18].

At present, it has been proven that pathological changes in the immune system play an important role in the formation of most diseases of QB. It is known that the development and progression of autoimmune pathology in QB is accompanied by disturbances at the humoral and cellular levels of immunity. The main mechanisms of cellular autoimmunity are: anergy of the thymus, tolerance of the thymus due to the destruction of autoreactive T-lymphocytes in the thymus; clonal non-recognition due to a physical or immunological barrier to antigen recognition; peripheral tolerance due to anergy or apoptosis of T-lymphocytes due to the expression of class II HLA molecules in non-professional antigen-presenting cells; with the support of specific cytokines, active suppression due to immunological shift due to mutual suppression of type 1 T-helpers (Th1) and type 2 T-helpers (Th2) is observed [5].

Zdor V. V. and common [9] Graves in illness one row of ts itokins at the current level TGFβ1 deficiency identified the changes in the background and against the background of treatment with thiamazol, IFNg and IL-2 levels osh gan, this Tregs dysfunction show me The persistence of high levels of IL-10 against the background of thyrotoxicosis treatment for 6 months indicated a negative role of the cytokine due to the induction of differentiation of Treg into Th17-cells, which subsequently decreased the number of Tregs. In addition to the study of QB hormones, TTG, and thyroid autoantibodies, IL-2, IFN γ, IL-6, sIL-6R, IL-17,

and TGF β 1 in the serum are used to control the autoimmune process, predict disease recurrence, and decide on radical treatment. it is recommended to control the level.

Jung JH et al. [12] proved that DTB is inextricably linked with the disorder of the immune system, thyroid-stimulating antibodies, excessive production of QB hormones with the formation of an imbalance in the cytokine regulation system, which play a key role in the pathogenesis of DTB, which is expressed in the increase in their production, the violation of the ratio of pro-inflammatory and anti-inflammatory cytokines in the body.

Russian researchers Zdor V.V. and h amm ual. [9] one row there was DTB in his works in patients ts itokin of the body the answer state ni learned sh gan. IL -8 is healthy persons 3-4 times their indicators osh gan, increase of IL -1a observed at the beginning of the disease and of thyrotoxicosis to the weight directly proportional was.

Motylewska E. et al al., (2017) at work T - and B lymphocytes increase and differentiation for in charge has been of IL -7 concentration decline control in the group as well in remission patients with DTB manifest form in comparison has been of patients blood in serum it was determined.

A number of studies have identified the relationship between TNF- α gene polymorphism and DTB. In the experiment Makai B. et al. (2017) found an increase in TNF- α in the blood serum of rats in a state of drug-induced thyrotoxicosis. The authors note that the increase in TNF- α levels is due to the activity of the autoimmune process directed at the target organ, not the level of thyroid hormones. It was believed that TNF- α is directly involved in the production of autoantibodies.

Saprina T.V. According to [5], the levels of TNF- α, IL-2, and IL-4 in patients with DTB were not significantly different in thyrotoxicosis and euthyroidism.

Russian researchers Gryaznova M.A., Khamnueva L.Yu., [5] demonstrated the existence of an inflammatory process in QB hyperfunction with manifestation of the nephrocardial continuum, subsequent damage to the cardiovascular system and kidneys, and showed an increase in pro-inflammatory cytokines in patients with DTB.

Yersinia enterocolitica, which has the ability to complex with TTG, can be the initiator of the formation of antibodies to QB, *Mycoplasma spp, which can complex with TTG, which initiates the formation of antibodies to TTG receptors*, can contribute to the formation of antibodies to TTG receptors. These bacteria are able to cooperate with TTG receptors and initiate the formation of appropriate antibodies with the participation of macrophages and lymphokines. Thyrocytes are able to express immunologically active molecules, adhesive factors and ICAM-1, IL-6, IL-8 in response to immune attack and cytokines [20].

Bifidobacterium bifidum in serum of patients with QB autoimmune diseases The frequency of antibodies to *791* and *Lactobacillus plantarum V-01* was 71% and 63%, which is 2 times higher than healthy subjects. On the surface of microbial cells, there is evidence of the presence of components that selectively affect thyroperoxidase and thyroglobulin with autoantibodies, compete for the binding of these immunoglobulins to thyroantigens, and interact with thyroperoxidase. Data *Bifidobacterium* and It has been shown that *Lactobacillus* genera are involved in the pathogenesis of QB autoimmune diseases by the mechanism of molecular mimicry [13].

In another study, evidence of Treg deficiency was obtained in both manifest autoimmune thyrotoxicosis and several months after radioiodine therapy. *Mycobacterium tuberculosis* and *Escherichia coli* Experimentally inducing NTI-syndrome ("nonthyroidal illness") by administering *LPS* extracts to animals, the authors were unable to induce thyroid dysfunction associated with reduced mast cell numbers in mice with mutations in the KitW/KitW-v genes, and after introducing donor mast cell cultures into these animals, they had Fc γ R3, TLR2, TLR4, TLR9 receptors were successfully developed NTI-syndrome [15].

3. Result and Discussion

Disruption of Th17 and Treg cell homeostasis plays an important role in the development of autoimmunity and inflammation. The quantitative change of Th17/Treg cells is one of the key links in the pathogenesis of Graves' disease. Treg cells are important in preventing autoimmune reactions, CD4+-helper cells with redox properties are more resistant to cells and pro-apoptotic effects of N_2 O_2 [16,17].

A number of clinical studies have shown that Treg levels are reduced in Graves' disease, which is consistent with data from animal models. An increase in the number of CD4+ CD25hi or CD4+CD25+int-hi CD127+lo Tregs was found in older patients with active Graves' disease, while no significant deficiency in Tregs was detected. This disparity was due to different identification markers for Treg cells [11].

Troshina E.A., Senyushkina E.S. [18] found increased levels of IL-17 in blood serum in patients with an active stage of Graves' ophthalmopathy. A positive correlation has been shown between the amount of Th17 and the severity of Graves' ophthalmopathy. This proved that Th17 cells and cytokines are involved in the pathogenesis of orbital connective tissue, extraocular muscle inflammation.

In 1974, the Canadian scientist Volpe R. was the first to establish the theory of autoimmune genesis of DTB, according to which the control over the number and activity of autoreactive cells is disturbed in this pathology due to the deficiency of organ-specific T-suppressors. In individuals with a genetic predisposition, immunological control is weakened under the influence of environmental factors, and clones of "forbidden" T-lymphocytes survive and stimulate the production of thyroid antibodies such as V-lymphocytes, thyroid-stimulating antibodies, antibodies to thyroglobulin, peroxidase, nuclear substance, etc. [14]. A decrease in SD8+-, CD16+-, CD56+-cells in the blood, and an increase in spontaneous proliferation of QB lymphocytes belonging to the CD4+-cell population were observed.

Saprina T.V. showed that Th1 (IL-2) and Th2 (IL-4) lymphocytes are involved in DTB immunopathogenesis. According to the author, the differences in the course of the disease are related to the interaction of the Th1/Th2 immune response. Of the synthesized thyroid antibodies, antibodies to the AT-rTTG receptor are of primary importance, they mimic the effect of thyroid-stimulating hormone and are found in 89-98% of DTB cases.

There is evidence that the increase in the synthesis of QB hormones leads to the activation of inflammatory cytokines and TNF- α, IL-1, IL-8-prooncogenes [21,22].

Kodirov A. E. and common [14] organ -specific autoimmune process based on antigen - specific T cells target tissues i with mutually effect It is believed that it lies e.g autoreactive cells select it and clonal leading to expansion will come Authors stated that CCL21 's in plasma level DTB li in patients high has been and negative TRAb in plasma, TRAb and OPN, with CCL21 in correlated patients was in the normal range. Recombinant OPN time i and increased CCL21 expression in a dose - dependent manner. These results are DTB and clinical correlation between CCL21 in plasma show that CCL21 is a novel candidate for Graves' disease marker and positive TRAb which is DTB li patients treatment for possible has been as a target view can.

To research the first verified Graves' disease tash h isi with 18 from the age 55 under the age of has been 26 a woman included. Patients diagnosed with this disease in the blood in neutrophils respiratory distress intensity eat it Neutrophils in the onset of Graves' disease and QB with hormones respiratory burst indicators between However, there are no correlations hemil yu mines cent reaction and anti-TPO concentration between dependence occurred [6].

Prostaglandins and with NO conducted in experience aseptic inflammation of thyro ts in dogs reaction time development and by them IL-1 a, IL-1 b, IL-2, IL -4, IL -6, IL -8, IL -10, IL -12, IL -13, IL -14, TNF - a i IFN - gone with g separation. This does not contradict the data that the severity of thyrotoxicosis in Graves' disease has a direct correlation with the level of pro-inflammatory cytokines and IL-10. Cytokines have also been implicated in the functional activity of intrathyroidal immunocytes and the inability of immunoregulatory T-lymphocytes to control it [8,11].

The authors believed that L-3, IL-10, IL-4, IL-33 can appear as cofactors determining differentiation, proliferation and granule formation in mast cells. When mast cells are activated, they can release a certain profile of mediators and other factors: histamine, tryptase, chymase, A-carboxypeptidase, proteoglycans, TNF- α, IL-13, IL-3, GM-CSF, IL-5, GM-CSF, CXCL8/IL -8, CCL3/MIP-1 a, VEGF-A, VEGF-B, VEGF-C and VEGF-D, lipid mediators [9,13].

II MNS and CD86 molecules on the surface of mast cells gave them the ability to surface as APK for Th2 cells. MNS class II antigens MS expression was noted in animals with normal QB. It is reliably increased during the development of spontaneous AIT in rats and before the appearance of circulating thyroid autoantibodies and QB mononuclear cell infiltration [8,9].

Popova V.A. and all. The research conducted by [21] recorded stress phenomena of humoral immunity in 340 children aged 4 to 7 years living in different regions of the Rostov region of the Russian Federation, obvious pathological changes were noted in children living in the region with a high level of man-made pollution. Children from environmentally disadvantaged areas had lower levels of selenium and zinc, and increased levels of lead in morning urine, which correlated with lower levels of eT4 and eT3 in the blood.

Russian scientists Potutkin D.S. and all. [22] studied 100 men and 206 women aged 22 to 75 years without endocrine and immune system diseases who lived in the Arctic zone of the Russian Federation. Dopamine concentration in blood plasma, thyrotropin hormone (TTG), thyroglobulin (TG), thyroperoxidase (TPO-AT) and antibodies to thyroglobulin (TG-AT) were determined in blood serum. Higher concentrations of TTG and TG and lower concentrations of TG-AT and TPO-AT have been shown to increase dopamine levels. The authors explained this by the effect of dopamine on α-adrenergic receptors of antibody-producing cells and changes in the secretion of TG-AT and TPO-AT, which are IgG subclasses. The emergence of a concentration of autoantibodies different from the zero value has been associated with the negative effects of northern conditions.

The level of antibodies to QB tissues in the inhabitants of the Arctic zone of the Russian Federation, their correlation with thyroid hormones and TG was determined in 208 healthy euthyroid men and women. Circulating antibodies to QB tissues were detected in 20% of the population. This level of antibodies to QB was accompanied by high functional activity of QB in women. The results showed a correlation between parameters of QB function and QB antibodies, which determined the clinical value of the investigation of antibodies to QB and the monitoring of autoimmune diseases [4].

Savchenko A.A. and all. [13] The immunopathogenesis of Graves' disease was characterized by a negative correlation of TPO-AT levels with indicators of V- and T-cell immunity.

Other authors found that the value of the leukocyte migration index in the presence of QB tissue antigen reflects its morphological changes, which can be used as a predictor of its pathology. As a confirmation of this, the correlation between the QB echographic image and the level of anti-TPO was calculated in patients with Hashimoto's thyroiditis [10].

Selezneva T.D. and all. [21] compared to the control group, the changes in the cellular and humoral relations of immune defense in patients with QB and mammary PMSR in the form of a decrease in the total number of lymphocytes, CD3+-, CD4+-, CD16+ -lymphocytes, immunoregulatory index (IRI), immunoglobulins.

The authors showed that the effect of cytokines on the proliferative and functional activity of the QB in autoimmune thyropathies has the opposite direction, which is explained by the polyfunctional effect of cytokines, the characteristic of the subpopulation composition of lymphocytes

infiltrating the QB tissues, and the functional properties of autoantibodies [15].

4. Conclusions

Taking into account the research and creation of immunobiological preparations based on monoclonal antibodies to correct the imbalance of Th17, Treg cells in various autoimmune diseases, attempts are being made to use some of them in autoimmune thyropathies. In this regard, Troshina E.A. and all. [21] believed that further studies are needed to confirm the efficacy of this treatment in QB autoimmune diseases.

Savchenko A.A. and common As established in [22] studies, patients in the blood Treg and total number of activated T - helpers V- lymphocytes, V 2 - cells and simple V- lymphocytes with positive dependence determine, QB tissues i da e sa, Treg activated V- lymphocytes with dependence from the system out thrown away In patients with Graves' disease not only Treg decrease, but they are functionally active l i g violation too available that calculated.

It was found that the number of fat cells was the maximum on the 2nd day of the study under conditions of interruption of lactation in rats. Later (3-7 days), the proliferation density of these cells was minimally reduced on the 7th day of observation. After the 14th day, their number increased, then decreased on the 21st day of the test. These changes occurred synchronously with the dynamics of gland morphofunctional activity [17].

The dynamics of fibronectin content in plasma, its cryoprecipitating activity and the effect of this glycoprotein on hormonal (thyroxine, thymalin) and immune connections during surgical treatment in patients with DTB, nodular gout and chronic AIT were studied. The ability of thyroxine to modify the lymphocyte receptor site and block the immunomodulatory effect of thymalin has been determined [16].

Zueva O.M., Malakhova Yu.I. [2013] found a decrease in IL-1α synthesis in hypothyroidism, which they believed to be associated with activation of lipid peroxidation processes and subsequent cholesterol accumulation. Thyroid hormone deficiency has been proven to cause a sharp decrease in blood complement activity, a decrease in the level of properdin and lysozyme, an increase in the number of circulating immune complexes, and a decrease in phagocytic activity.

Thus, according to the analysis of scientific sources, the incidence rate of QB diseases, clinical features in poly- and comorbidity, the role of the immune system in the pathogenesis of diseases have been studied. However, the comparative parameters of innate, adaptive, humoral immunity indicators in QB diseases have not been sufficiently studied, immunological monitoring of the disease, diagnostic and prognostic criteria have not been developed.

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