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Pattern of IgM and IgG changes depending on the pathological process duration in patients with autoimmune thyroiditis

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of the study was to find out the pattern of IgM and IgG changes in patients with autoimmune thyroiditis depending on the pathological process duration.

Materials and methods. A single-center cross-sectional study with randomization elements enrolled 170 patients with autoimmune thyroiditis, and 65 patients without thyroid pathology or other autoimmune diseases were assigned to sex- and age-matched comparison group (p = 0.6155 and p = 0.3093, respectively). The patients were classified according to thyroid status parameters into subclinical and manifest groups. All study participants were examined on IgM and IgG levels based not only on the clinical form of the disease, but also on the disease duration (up to 5 years and more than 5 years). The control group comprised 65 healthy individuals, including 26 men and 39 women (mean age 38.7 ± 10.8 years).

Results. A slight decrease in IgM levels was observed in patients with subclinical form and longer disease duration, which was 1.5 (1.5; 1.7) g/l with the disease duration of up to 5 years and 1.4 (1.2; 1.4) g/l with the disease duration of more than 5 years, while there were no differences in IgM levels in patients with manifest form with longer disease duration. IgG concentrations were statistically significantly higher in both clinical groups of patients with the disease duration of up to 5 years compared to those in patients with the disease duration of more than 5 years (13 (11; 14) g/l up to 5 years and 11 (10; 12) g/l more than 5 years in subclinical group, p < 0.05); 13 (12; 14) g/l up to 5 years and 12 (10; 15) g/l more than 5 years in manifest group, p < 0.05).

Conclusions. A downward trend in IgG concentrations is noted with the disease progression and longer duration, while IgM levels are uninformative.

Keywords: autoimmune thyroiditis, Hashimoto thyroiditis, autoantibodies, disease duration, IgM, IgG.

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Характер змін IgM та IgG у хворих на автоімунний тиреоїдит залежно від тривалості перебігу патологічного процесу

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Мета роботи – визначити характер змін IgM та IgG у хворих на автоімунний тиреоїдит залежно від тривалості патологічного процесу.

Матеріали і методи. Здійснили моноцентрове перехресне дослідження з елементами рандомізації, до якого залучили 170 пацієнтів з автоімунним тиреоїдитом, а також 65 осіб без патології щитоподібної залози або інших автоімунних захворювань, які сформували групу порівняння, зіставну за статтю та віком обстежених (p = 0,6155 і p = 0,3093 відповідно). За показниками тиреоїдного статусу пацієнтів поділили на субклінічну та маніфестну групи. У всіх учасників дослідження визначили вміст IgM і IgG не тільки залежно від клінічної форми захворювання, але й залежно від тривалості захворювання (до 5 років і понад 5 років). До контрольної групи залучили 65 умовно здорових осіб: 26 чоловіків і 39 жінок, середній вік – 38,7 ± 10,8 року.

Результати. У пацієнтів із субклінічною формою встановили незначне зниження IgM зі збільшенням тривалості захворювання: 1,5 (1,5; 1,7) г/л при тривалості захворювання до 5 років та 1,4 (1,2; 1,4) г/л, коли захворювання тривало понад 5 років. У хворих із маніфестною формою захворювання не виявили відмінностей за вмістом IgM зі збільшенням тривалості захворювання. Концентрація IgG в обох клінічних групах пацієнтів із тривалістю захворювання менше ніж 5 років статистично достовірно більша порівняно з хворими з тривалістю захворювання понад 5 років: 13 (11; 14) г/л – до 5 років, 11 (10; 12) г/л – понад 5 років у субклінічній групі, p < 0,05; 13 (12; 14) г/л – до 5 років, 12 (10; 15) г/л – понад 5 років у маніфестній групі, p < 0,05.

Висновки. З прогресуванням захворювання і збільшенням його тривалості визначають тенденцію до зниження концентрації IgG, а вміст IgM стає неінформативним.

Ключові слова: аутоімунний тиреоїдит, тиреоїдит Хашимото, аутоантитіла, IgM, IgG.

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The disturbance of the equilibrium between pathogen recognition and the prevention of self-attack, influenced by complex environmental and genetic factors, can give rise to autoimmune pathologies. Autoimmune pathologies may manifest in a systemic or organ-specific manner, affecting specific tissues or organs [1,2,3]. Autoimmune thyroiditis (AIT) or Hashimoto's thyroiditis (HT) is a prevalent autoimmune thyroid pathology characterized by lymphocytic infiltration of the thyroid parenchyma. The precise molecular mechanism underlying immune dysfunction and the subsequent destruction and/or overgrowth of hormone-producing zones of glandular tissue remains unclear. Consequently, the study on the pathogenesis of HT remains a pressing issue [4].

The presence of antibodies to thyroid tissue is a well-documented feature of HT. The disease is characterized by an increase in antibodies to thyroglobulin (Ab-TG) and peroxidase (Ab-TPO). Antibodies against TPO and

TG belong to the immunoglobulin G (IgG) class. Both antibodies have a high affinity to their respective antigens. In contrast to Ab-TG, Ab-TPO can activate complement and cause damage to thyroid cells through antibody-dependent cell-mediated cytotoxicity [5]. It is well established that T-cell-mediated cytotoxicity and the activation of apoptosis pathways influence the disease outcome [6]. Autoantibodies, which interact with follicular cells, cause their cytolysis. This is due to the binding of the antibodies to thyroglobulin and peroxidase, which prevents iodine uptake by these proteins. This disruption of iodine metabolism in the gland ultimately leads to impaired production of thyroid hormones [7].

In response to the influence of specific immunogens, B-cells differentiate into plasma cells, which are involved in the humoral immune response not only against bacteria, viruses, fungi, parasites, but also against endogenous cellular antigens [8,9]. The serum concentration of immunoglobulins is the result of an equilibrium between their synthesis and breakdown. Immunoglobulins fulfil two distinct functions. Firstly, they act as cell surface antigen receptors, which provide cell signaling and activation. Secondly, they serve as soluble effector molecules, which can bind and neutralize antigens at a distance [10]. As an integral component of the adaptive immune response, IgG may be involved in the pathogenesis of autoimmune diseases. IgG consists of four distinct subclasses, designated as IgG1-4. All IgG subclasses have the potential to contribute to the immunopathogenesis of autoimmune diseases by regulating the interaction between immunoglobulins, FcγR and complement [11].

Glycans present in the immunoglobulin molecule exert a profound influence on the binding affinity of the molecule for immune mediators and for receptors on effector cells. Aberrant glycosylation of immunoglobulins has been demonstrated to have deleterious consequences. For instance, patients afflicted with a plethora of autoimmune disorders have been observed to exhibit elevated levels of IgG devoid of sialic acid or galactose, in comparison to those in healthy individuals [12,13].

Immunoglobulin M (IgM) is the first immunoglobulin expressed during B-cell development. Naive B cells express monomeric IgM on their surface. Following maturation and antigenic stimulation, multimeric (typically pentameric, occasionally hexameric) IgM is secreted [14,15]. The function of IgM is to coat antigens for destruction and fixation by complement. Antibodies with relatively low affinity are also referred to as natural antibodies. Some of these natural antibodies not only participate as a first line of defense but also play a role in immunoregulation [16]. Despite numerous studies and research papers on immunoglobulins, their role and the character of alterations in various pathologies, there is no clear opinion in the known literature on the role of immunoglobulins M and G in autoimmune thyroiditis.

Aim

The aim of the study was to find out the pattern of IgM and IgG changes in patients with autoimmune thyroiditis depending on the pathological process duration.

Materials and methods

A single-center cross-sectional study with randomization elements enrolled 170 patients with autoimmune thyroiditis, and 65 patients without thyroid pathology or other autoimmune diseases were assigned to sex- and age-matched comparison group ($p = 0.6155$ and $p = 0.3093$, respectively). The blood of patients diagnosed with AIT was collected at two institutions: the Endocrinology Department of the Scientific Surgical Centre, named after acad. M. A. Topchubashev, and the Research Laboratory at the Biochemistry Department of Azerbaijan Medical University.

The inclusion criteria for this study were patients with a primary diagnosis of AIT and no concomitant allergic or other autoimmune severe somatic diseases. Exclusion criteria were occurrence of comorbid pathology associated with AIT by a single pathogenetic mechanism as a result of exacerbation of the autoimmune process; blood analyses with significant abnormalities; pregnancy and lactation; acute and chronic inflammatory processes affecting the immunological status of patients.

The diagnosis of AIT was made based on anamnesis, clinical and palpatory data, evaluation of the thyroid gland functional state, thyroid panel status, results of thyroid ultrasound examination, and the presence of antibodies to thyroid antigens.

According to thyroid status data, the patients were divided into two groups. Group I included 74 patients with the manifest form of the disease, while Group II consisted of 96 patients with the subclinical form of the disease. IgG and IgM levels were measured in all study participants.

The study on immunoglobulins in HT patients was carried out depending on both the clinical form of the disease and the duration. The patients were divided into two subgroups. The first subgroup included 106 HT patients with a disease duration of between one and five years. The second subgroup comprised 64 patients with a disease duration of between five and ten years. In the group with a manifest form of the disease, a disease duration of more than five years was in a significant proportion of patients (57 patients). There were only 17 patients with a relatively short disease duration defined as 1 to 5 years. In contrast, a disease duration of 1 to 5 years was in the majority of patients in the subclinical AIT group (89 individuals), while a disease duration of 5 to 10 years was only in 7 patients.

The concentration of immunoglobulins of classes M and G was measured by a turbidimetric technique using a semi-automatic Stat Fax photometer and polyclonal anti-immunoglobulin antibodies on a biochemical analyzer Cobas Integra 400 Plus Roche (Switzerland) using IgM and IgG detection reagents for the analyzer (Germany). The statistical analysis of the study results was performed using the software package Statsoft Statistica 12.

Medians and upper and lower quartiles were calculated to represent quantitative parameters. Data were presented as Me (Q25; Q75). Differences were considered statistically significant if "p" did not reach the null hypothesis significance level (alpha) of 0.05. The Groups were compared using Kruskal–Wallis one-way analysis of variance followed by pairwise comparison using the Mann–Whitney test.

Ethics approval of the study. The present study was approved by the Ethics Committee of Azerbaijan Medical University (Ref. no: AMU/IEC/№12/07.02.2020).

Table 1. The levels of immunoglobulin M, immunoglobulin G and specific antibodies in patients with HT, Me (Q25; Q75)

Parameter, units of measurement	Control group, n = 65	HT, n = 170	Subclinical form, n = 96	Manifest form, n = 74
Ab-TG, IU/ml	16 (13; 30)	458 (381; 544)*	456 (395; 544)*	470 (381; 527)*
Ab-TPO, IU/ml	20 (13; 25)	525 (458; 568)*	523 (464; 568)*	531 (458; 566)*
IgM, g/l	1.5 (1.2; 1.6)	1.5 (1.4; 1.7)	1.7 (1.1; 1.8)	1.8 (1.3; 2.2)
IgG, g/l	11.4 (9.5; 13.0)	13.0 (11.0; 14.0)*	12.6 (10.4; 15.1)	16.9 (12.6; 21.8)*

*: statistically significant difference compared to the control group at a level of $p < 0.05$;
#: statistically significant difference compared to the subclinical group at a level of $p < 0.05$.

Results

The values of autoantibodies to thyroglobulin and thyroperoxidase in patients randomized into subclinical and manifest groups are shown in *Table 1*.

Notwithstanding the level of antibodies to thyroglobulin and thyroperoxidase in the total cohort of patients was approximately 30 times higher than the control values, no significant differences were observed in the antibody levels between the studied clinical groups. In the case of immunoglobulins, an intriguing pattern was revealed. There was no significant difference in IgM levels between the entire patient group and the control group. However, the mean values in the manifest patient group were 20 % higher than those in the control group. The entire patient group showed an increase of nearly 20 % in IgG, while the manifest patient group demonstrated an elevation of around 50 % above the control values.

The study on immunoglobulins in AIT patients was carried out not only depending on the clinical form of the disease, but also on the disease duration *(Fig. 1)*.

The study on IgM and IgG concentrations in patients with different clinical forms and the disease duration yielded the following results. While a slight decrease in IgM was observed in patients with subclinical form and longer disease duration, which was 1.5 (1.5; 1.7) g/l for the disease duration of up to 5 years and 1.4 (1.2; 1.4) g/l for the disease duration of more than 5 years, no differences in IgM levels were found in patients with manifest form of the disease and longer duration. IgG concentrations were statistically higher in patients with subclinical course of the pathology with the disease duration of up to 5 years as compared to the group of subclinical patients with the disease duration of more than 5 years, 13 (11; 14) g/l and 11 (10; 12) g/l, respectively $p < 0.05$. In patients with manifest form of the disease, being in a hypothyroid state, there was also revealed a decrease in the studied immunoglobulin levels with longer duration of the pathology amounting to 13 (12; 14) g/l for the disease duration of up to 5 years and 12 (10; 15) g/l for the disease duration of more than 5 years, $p < 0.05$.

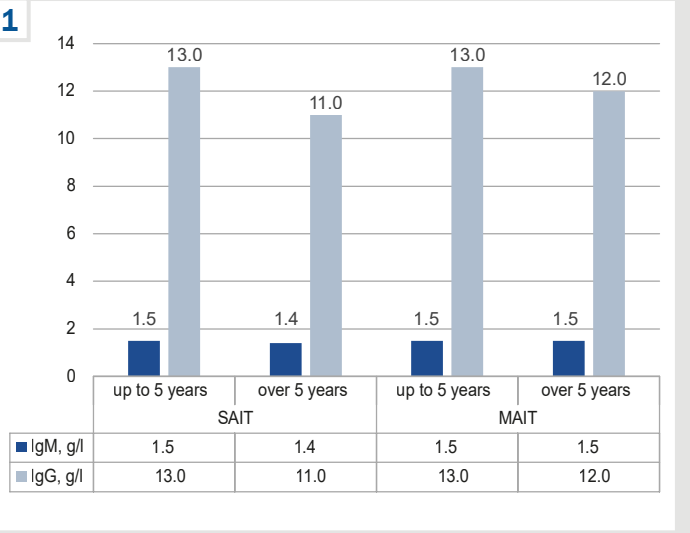

Fig. 1. Characteristics of immunoglobulin levels in patients with AIT depending on the disease duration (years). **SAIT:** subclinical autoimmune thyroiditis; **MAIT:** manifest autoimmune thyroiditis.

Discussion

The findings of our study indicate that patients with AIT and disease duration exceeding five years demonstrate a tendency towards a decline in the humoral immunity indicators, in this case IgM and IgG, and the changes in IgM are insignificant in contrast to IgG. In the cohort of patients with manifest disease, there were no changes in IgM levels depending on the disease stage. The literature data on the humoral immunity state in AIT patients are not entirely unambiguous, but clearly noted that there is a specific increase in serum immunoglobulins of the class G in AIT patients at the initial stages of the disease [17].

Oligosaccharides, which regulate the effector functions of the IgG molecule, account for 15 % of its molecular mass. Given that N-glycans influence the secretion, structure and half-life of the IgG molecule, remodeling of N-oligosaccharides may contribute to the development of pathological changes that ultimately contribute to autoimmunity. A recently published S. Trzos et al. study has indicated that the pathology of autoimmune thyroid diseases, including TH, was accompanied by changes in the composition of IgG N-glycans [18].

As stated in the paper C. Fahlquist–Hagert et al., the primary role of B-lymphocytes in the pathogenesis of autoimmune diseases is not the production of autoantibodies or antibody formation in general, but rather their involvement in alternative functions, primarily in the presentation of autoantigens to T-lymphocytes [19].

Other authors have observed that in individuals with AIT, there were alterations in the composition of not only thyroid hormones and autoantibodies, but also serum immunoglobulins. These changes were more prontounced in patients with a positive family history. However, as the disease progressed, serum levels of free IgG decreased due to binding to antigenic complexes of lipoproteins and participation in the formation of circulating immune complexes [20]. This is also in line with the findings of Marta Ząbczyńska et al., who concluded that there were no significant changes in IgM levels despite the observed changes in IgG and IgA [21].

Conclusions

1. In the initial stages of the disease (up to five years), the levels of IgM and IgG are elevated in patients with HT, 1.5 g/l and 13 g/l, respectively.

2. With longer disease duration and the pathological process development, there is a downward trend in humoral immunity indicators. In this case, IgM levels are 1.5 g/l for the disease duration of up to 5 years and 1.4 g/l – of more than 5 years. IgG levels are 13 g/l for the disease duration of up to 5 years and 11 g/l – of more than 5 years.

3. In the manifest stage, IgM levels are limited in informative value.

Perspectives of further scientific research include the study on IgM and IgG, both diagnostically and prognostically, in the dynamics of AIT.

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