Methodology of Early Detection of Thyroid Pathology in Patients with Rheumatoid Arthritis and Autoimmune Thyroiditis

Isamitdinova Nilufar Shakhobovna
Bukhara Regional Multidisciplinary Medical Center, Republic of Uzbekistan, Bukhara city
Email address: nelya--89@list.ru

Resume: Currently, RA is a chronic systemic inflammatory disease that affects not only the joint and periarticular tissues, but also the central and autonomic nervous system, endocrine systems and their interrelationships, and further complicates the course of the underlying disease. Clinicians are familiar with pathologies such as goitre, hypothyroidism, adrenal gland dysfunction, which are common pathologies of endocrine glands in patients with RA. The principles of treating patients with rheumatoid arthritis and autoimmune thyroiditis are one of the complex problems of modern rheumatology. Its relevance is the progression of two autoimmune diseases (RA and AIT), the severity of damage to the musculoskeletal system, the high number of injuries among the working population, early decline in functional ability, loss of professional and social skills, difficulty in physical and psychological adaptation in patients with loss of motor function, It is defined as a general medical and social problem that causes significant economic loss, ie disability.

Prolongation and acceleration of the duration of the main disease leads to the development of thyroid pathology, the addition of new joints and extra-articular systems to the pathological process, the formation of irreversible, permanent changes in the joints (destruction, half-extinction, contracture). All this leads to severe functional deficiency, disruption of all aspects of life and a decrease in the quality of life of patients.

Keywords: rheumatoid arthritis, autoimmune thyroiditis, thyroid gland, hyperthyroidism, hypothyroidism

Introduction. The high medical and social importance of RA and AIT among autoimmune diseases is due to its widespread and early disability and reduced life expectancy of patients [1-6]. The diagnosis of RA is still based on a set of clinical and laboratory indicators in the form of constantly changing classification criteria. The visceral manifestations of RA stand out because they determine not only the severity and outcome of the disease, but also its outcome. RA shortens patients' life expectancy by an average of 10 years, causes of death are generally similar to those in the general population, but early cardiovascular and renal disease, pulmonary and gastrointestinal infections are high among the causes of death [9-12]. Currently, RA is a chronic systemic inflammatory disease that affects not only joint and peri-articular tissues, but also central and autonomic nervous system, endocrine systems and their interrelationships and further complications of the course of the main disease [7,13,15]. Clinicians are familiar with pathologies such as goitre, hypothyroidism, adrenal gland dysfunction, which are common pathologies of endocrine glands in patients with RA. Thyroid hormones increase the activity of metabolic processes, stimulate lipogenesis, enhance glucose uptake by muscle and adipose tissue, and activate glucogenesis and glyconeogenolysis [8,16,18]. Thyroid hormones (triiodothyronine-T3, thyroxine-T4) enhance the resorption and synthesis of bone tissue, the production of connective tissue protein glycans and glycosomes. An increase in their amount increases the number of growing and active osteoclasts, accelerates the metabolism of bone tissue, and stimulates osteoblastic function, and this process increases bone tissue-forming markers in the blood [17,19,27].

In the absence of thyroid hormones, the amount of adenyl cyclase in the synovial membrane increases, fibroblasts increase the production of hyaluronic acid, which in turn leads to the accumulation of synovial fluid in the joints and causes synovitis [20-26]. In clinical practice, tests for TTG receptors and antiperoxidase antibodies are carried out in the tissue of thyroid gland [28,30].

Patients suffering from rheumatological diseases tend to develop thyroid autoimmune pathology in a high frequency, which is explained by the presence of common immunological mechanisms in the development of the above diseases. This predetermines the need for screening evaluation of thyroid function in patients with rheumatological diseases. Autoimmune diseases are one of the most widespread and serious human diseases, including more than 80 nosological types. The frequency of autoimmune diseases among the population is 5-8%. Autoimmune diseases (AID) are one of the most common and clinically severe human diseases, with a prevalence of up to 10% of the population and include many different forms. The pathogenesis of these diseases is based on autoimmunity, which is characterized by a violation of immune tolerance against autoantigens, which leads to the development of an immune response against one's own tissues and organs [29,31] Patients with rheumatological diseases are prone to the development of thyroid autoimmune pathology at a high frequency, and these diseases are related to the above it is explained by the presence of common immunological mechanisms in its development. This predetermines the need for screening evaluation of thyroid function in patients with rheumatological diseases. Autoimmune diseases are one of the most widespread and serious human diseases, including more than 80 nosological types. The frequency of autoimmune diseases among the population is 5-8%. The basis of autoimmune diseases is autoimmunity, which is characterized by a violation of tolerance to one's own antigens and, supposedly, they are foreign to the body - leading to the development of an immune reaction against normal tissues. The immunological specificity of produced autoantibodies is based on organo-nonspecific (systemic) and organospecific division of autoimmune diseases [25,24] The main representatives of organospecific autoimmune diseases are endocrine diseases (Hashimoto's thyroiditis, Graves' disease, etc.). Organo-nonspecific autoimmune diseases include, first of all, systemic rheumatological diseases: systemic lupus erythematosus (SLE), RA, etc. [17,19]. Endocrine diseases play an important role in the occurrence and development of rheumatological diseases. The relationship between these two groups of diseases is unquestionable and significant, and it is evident between TG pathology on the one hand and RA, systemic lupus erythematosus on the other [20,1,5]. The problem of co-occurrence of RA with thyroid pathology is still receiving a lot of attention in domestic and foreign literature, which is explained by the frequent occurrence of these pathologies, immunogenetic predisposition, common mechanisms of immunopathogenesis, and hormonal disorders in these diseases. [12,13]. Patients with RA have a higher frequency of developing autoimmune thyroid diseases. According to O.V. Paramonova, the prevalence of thyroid gland pathology among patients with RA reaches 28% [25,18,4] and according to various other authors, Hashimoto's that the frequency of autoimmune thyroid pathology in RA is significantly higher than the population level (4-13.5 compared to 1-6%), [14,16], therefore, the main attention of patients with RA should be the dynamic status of the functional state of the thyroid should be directed to control. Hereditary predisposition plays an important role in the development of RA and autoimmune thyroid diseases - hyperthyroidism (Graves' disease) and chronic autoimmune thyroiditis (AIT).

D. Thomas et al. [15], according to their conclusions, despite the absence of any clinical and biochemical signs by TG, the detection of these antibodies reflects the initial stages of the pathology. Information about the processes of production of antibodies to thyroid hormones is very little covered in the existing literature. Therefore, it is considered that the detection of direct antibodies to thyroid hormones in RA patients can be a test in the diagnosis of autoimmune damage of the thyroid gland.

Thus, in rheumatic diseases, in particular, in RA, the course and prognosis of the thyroid gland pathology remains largely unexplored and relevant in arid regions.

According to the obtained data, the determination of the amount of antibodies to TPO and AT to TG of the thyroid gland showed that the titer was increased in the majority of patients with RA compared to the control group.

The high frequency of thyroid pathology (42.5%) in patients with RA prompted us to study in detail the processes of the formation of antibodies to thyroid hormones, which depend on the activity and form of RA.

Purpose: In patients with rheumatoid arthritis and autoimmune thyroiditis early detection of thyroid pathology and development of measures to prevent complications.

Research material and methods: The study was conducted on clinical, instrumental, laboratory analyzes of all patients with rheumatoid arthritis (RA) treated inpatient at BRMMC (Bukhara Regional Multidisciplinary Medical Center) rheumatology department during 2018 and 2020, and among them 82 RA patients (42 RA and 40 RA+AIT) patients were prospectively and 20 healthy controls were selected. The diagnosis of RA was made based on the diagnostic criteria based on the American Society of Rheumatology 2010 classification.

In the first empirical stage, only patients with rheumatoid arthritis, autoimmune thyroiditis and a healthy control group matched for age and gender were selected. A total of 82 patients were included in the study, including 42 patients with rheumatoid arthritis alone, 40 patients with rheumatoid arthritis and autoimmune thyroiditis, and 20 healthy controls. The course of patients' main disease, concomitant disease, as well as drug anamnesis and pharmacotherapy were evaluated. All patients underwent complex hematological, biochemical, thyroid hormones and anti-antibodies, thyroid ultrasound examination, and densitometry examinations that evaluated all manifestations of RA and AIT accepted in comprehensive rheumatological clinical practice. Hemoglobin, general urinalysis, serum creatinine, calcium, phosphorus, urea, albumin, ALT, AST, T3, T4, TSG(thyroid stimulating hormone), antiTPO, antiTG were performed laboratory tests.

Table-1

Description of the rheumatoid arthritis and control group selected for the study

Indicator	RA (n-82)	Control group (n-20)	R
Gender (female %)	76(92.6%)	16(82%)	0.62
Age	50.58±1.6	48.45 ± 2.1	0.6
Villagers	55(67%)	13(65%)	0.7
Hypertension	37(46%)	9 (43%)	0.04
Duration of illness, year.	8.82±1.12	-	-
Type 2 diabetes	6(7%)	1(5%)	0.05
Type of therapy:	82 (100%)	-	-
Methotrexate	76 (92.6%)	-	-
Glucocorticoids	28 (35.2%)	-	-
Leflunomide	13 (15.7%)	-	-
NSAIDs	80 (97.2%)	-	-
GEBT	3 (3.7%)	-	-
Combined therapy	45 (54.9%)	-	-

During the study, 76 (92.6 %) and 16 (82 %) women, 55 (67 %) and 13 (65 %) rural residents, and 37 (46 %) hypertensive patients in the 82 RA patients and 20 control groups, respectively. and 9 (43%), type 2 diabetes was 6 (7%) and 1 (5%). 76 (92.6 %) of patients with RA received methotrexate, 28 (35.2 %) glucocorticosteroids, 13 (15.7 %) leflunomide, 80 (97.2 %) NSAIDS, 3 (3 %) GEBT (genetic engineering basic therapy), 45 (54, 9 %) received combination therapy. Thus, during the study, the majority of patients with rheumatoid arthritis were taking NSAIDS and methotrexate drugs continuously.

At the next stage of the study, 82 patients with rheumatoid arthritis were divided into two groups - 42 with only rheumatoid arthritis and 40 with rheumatoid arthritis combined with autoimmune thyroiditis, based on the results of questionnaires, clinical and laboratory-instrumental examinations.

Table 2
Description of RA and RA+AIT patients

Indicator	RA (n=42)	RA+AIT (n=40)	n-82(100%)
Women, n (%)	38(90.4%)	38(95.0%)	76(92.6%)
Men, n (%)	4(9.5%)	2(5.0%)	6(7.4%)
Average age , years	50.73±1.30 let	53.62±1.48	51.6±1.34
Body mass index , kg/m2	25.56±0.24	25.34±0.28	25.46±0.25
Duration of rheumatoid arthritis , years .	8.77±1.12	9.0±1.10	8.88±1.12
RF (+), n (%)	35 (83%)	32 (80%)	67(81.7%)
ACCP (+), n (%)	11 (26.6%)	22 (55%)	33(40.2%)
DAS-28, scores	5.4±0.15	5.68±0.15	5.55±
Process activity : Level I (low) Level II (medium) Level III (higher)	 10(23.8%) 22(52.3%) 10(23.8%)	 5 (12.5 %) 20(50%) 1 5 (37.5 %)	 15 (18.3 %) 42(51.2%) 25 (30.5 %)
Functional class , n (%) I II IIII V	 2 (4.8%) 8 (19.0%) 30 (71.4%) 2 (4.8%)	 4 (10.7%) 7 (17.5%) 28 (70.0%) 1 (2.5%)	 6(7.4%) 15(18.3%) 58(70.7%) 3(3.6%)
X-ray stages (according to Steinbroker), n (%) I II III IV	 4(12%) 24 (57.1 %) 12 (26.2 %) 2 (4.7%)	 3 (7.5%) 1 6 (45%) 17 (42.5%) 4 (5%)	 7 (8.5 %) 40 (4 8.7 %) 29 (35.3 %) 6 (7.5 %)
The presence of extra-articular (systemic) symptoms, n (%)	6 (14.3%)	7 (17.5%)	13(17.0%)
Patients receiving basic therapy, n (%)	42(100%)	40(100%)	82(100%)

Based on the analysis of the table, it was found that there was almost no difference between rheumatoid arthritis (82) and control group (20) by age, gender, comorbidities and region of residence. 82 patients, 76 women (92.6%) and 6 men (7.4%) treated with RA in the rheumatology department of the Bukhara regional multidisciplinary medical center were examined. Among them, patients with rheumatoid arthritis, 55 women (72.4%) and 4 men (25%) belonged to the socially active population, and their age group exceeded 55 to 60 years, respectively. Thus, it was found that the majority of patients with RA were of working age, 50 (61%). The average age of the patients was 50.58 ± 1.34 years. The average duration of the disease was 8.88±1.12 years.

In addition, during the study, all patients filled out a questionnaire identifying thyroiditis and hypothyroidism. Application of questionnaires plays an important role for early diagnosis of the disease and prevention of complications.

Table 3
Questionnaire for the diagnosis of hypothyroidism

Symbol	Yes, there is	It lasts a long time	No
Unexplained disorders of gastrointestinal functions (mainly constipation)	+40	+6	-5
Weight gain	+25	+5	-3

Abnormal drying of the skin (without cosmetics, climate change)	+30	+6	-15
Fatigue, weakness	+4	+3	-13
Daytime sleepiness	+26	+5	-6
Increased hair loss	+20	+5	-3
Frequent occurrence of swelling (in the previous drinking mode)	+20	+4	-19
Decreased voice timbre, hoarseness (in non-smokers, respiratory system diseases are excluded).	+39	+4	-6

Any total score greater than 7 points from the questionnaire will serve as a basis for referral to an endocrinologist.

Table 4
Symptoms identified on the basis of questionnaires

Symptoms _	RA+AIT		RA	
	N (40)	%	N (42)	%
Increase in swelling	30	75	14	33
Drowsiness	24	60	1 1	26
Delayed reaction	30	75	20	54
Increased fatigue	28	70	13	30
Memory impairment	2 2	55	19	45
Apathy and low mood	15	38	12	29
Bradycardia	12	30	8	20
Weight gain	35	30	7	18
Hair loss	28	70	13	32
Skin dryness	30	75	13	30
Constipation	30	75	6	15

The analysis of the questionnaires showed that before the examination of the thyroid status, it is possible to identify the symptoms of thyroid gland pathology in patients early and to make a plan for further targeted examination of patients.

As a result of the study, rheumatoid arthritis patients with autoimmune thyroiditis had dry skin in 30 (75%), constipation, slowed reaction, increased fatigue in 28 (70%), increased body weight, drowsiness in 24 (60%), memory impairment in 22 (55%) It was found that only those with rheumatoid arthritis had a relatively high percentage of the mentioned symptoms.

RA was diagnosed according to the American College of Rheumatology (ACR) 1987 diagnostic criteria and the 2010 ACR/EULAR classification [33]. Pain intensity was assessed using a 100 mm visual analog scale (VAS). The DAS-28 index was used to evaluate RA activity according to modern EULAR recommendations. RA is in disease remission when the DAS-28 index is <2.6, moderately active when the DAS-28 is <3.2 (3.2 <DAS-28 <5.1), and disease active when the DAS-28 index is >5.1 was rated as high. The functional class was evaluated based on the following criteria: I - self-service, professional and non-professional activity ability is maintained; II - the ability to self-service, professional activity is preserved; there is limited non-professional activity; III - self-service ability is preserved, non-professional and professional activities are limited; IV - self-service, professional and non-professional activities are limited.

Table-5
Clinical manifestations of symptoms of all examined patients

Symptoms	RA+AIT n=40		RA n=42	
	n	%	n	%
Swollen joints	40	100	31	75
Painful joints	40	100	35	84
Deformation of joints	24	60	16	40
Morning effort	40	100	42	100
Weight gain	28	70	13	30
Dry skin	22	55	19	45
Symptoms of hypothyroidism	9	22	0	0
Bradycardia	12	30	8	2 0

Table 6
Social characteristics of the examined groups

Indicator	Gender (E / A , %)	Age	Functional class	Disability , n (%)
RA (n=42)	4/39 (8%-92%)	50.83±1.60 years old	I: 1 (3%) II: 11 (28%) III: 29 (66%) IV: 1 (3%)	13 (16%)
RA+AIT (n=40)	2/37 (9%-91%)	52.92±1.60 years	I: 0 (0 %) II: 4 (11%) III: 34 (85%) IV: 2 (4%)	36 (90%)

According to the table, patients in both groups participating in the study did not differ from each other in terms of gender, age and functional classes of the disease. At the time of inclusion in the study, the number of disabled patients associated with rheumatoid arthritis and autoimmune thyroiditis was several times higher than those with only rheumatoid arthritis ($r > 0.05$). If the II-radiological stage predominates only in patients with RA, destructive processes and ankylosis of joints, characteristic of reliable stages III-IV, were observed in patients with RA combined with AIT.

Only in patients with RA, a significant decrease in functional activity was rarely noted, and most patients continued their professional activities and led an active lifestyle, while patients with RA associated with autoimmune thyroiditis became unable to work in the early stages of the disease.

Table 7 shows data on the disability of both groups of patients

Table 7
The structure of disability

Indicator	disability , n (%)	Group I disability , n (%)	Group II disability , n (%)	Group III disability , n (%)
RA (n=42)	13(31 %)	1 (2 %)	1 2 (2 9%)	0 (0%)
RA+AIT (n=40)	14(35 %)	2(5%)	12 (30 %)	0 (0%)

In both groups of patients, mainly II disabilities were recorded, but in patients with rheumatoid arthritis and autoimmune thyroiditis, the number of I disabilities was 2 times higher than in patients with only rheumatoid arthritis.

The level of activity of the pathological process was determined using diagnostic criteria, working classification and DAS 28 (Disease Activity Score) index. 9 (11.1%) patients had a score of 3.2 or less on the DAS 28 index, corresponding to the I activity level of RA, and 44 patients with a DAS 28 index of 3.2 to 5.1 (activity level II) 53.7%) patients and DAS 28 index higher than 5.1 (level of activity III) – 29 (35.2%) patients. According to the DAS-28 index, similar activity levels were found in the patients, and in both groups this indicator showed higher than average RA activity level results. Seropositive RA was detected in 67 patients, and seronegative - in 15 patients. In RA with AIT, the seropositive type was reliably detected more often (81.7%, compared to 18.3% in the control group), and in most cases it was severe.

Summary

The principles of treatment of patients with rheumatoid arthritis and autoimmune thyroiditis are one of the complex problems of modern rheumatology. Its relevance is the progression of two autoimmune diseases (RA and AIT), the severity of damage to the musculoskeletal system, the high number of injuries among the working population, early decline in functional ability, loss of professional and social skills, difficulty in physical and psychological adaptation in patients with loss of motor function. It is defined as a general medical and social problem that causes significant economic loss, i.e. disability.

Prolongation and acceleration of the duration of the main disease leads to the development of thyroid pathology, the addition of new joints and extra-articular systems to the pathological process, the formation of irreversible, permanent changes in the joints (destruction, half-extinction, contracture). All this leads to severe functional deficiency, disruption of all aspects of life and a decrease in the quality of life of patients.Given the above reasons and the high prevalence of thyroid gland damage in RA patients, it is reasonable to introduce active detection of signs of subclinical thyroid damage. The use of questionnaires in determining thyroid pathology in patients with RA and AIT will provide practical help to general practitioners, endocrinologists and rheumatologists in making a prognosis of the course of the underlying disease.

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