



## Evaluation Of Structural Changes in The Joints of the Hands and The Rate of Progression of Rheumatoid Arthritis According to Sonography

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**Annotation** – to determine the value of ultrasound examination (ultrasound) in the diagnosis of early destructive changes in the joints of the hands and the rate of progression of rheumatoid arthritis (RA) in patients with different ages of disease onset.

**Keywords:** sonographic index of destruction, ultrasonography of the joints of the hand, rheumatoid arthritis, radiological progression of structural changes.

**Material and methods.** We examined 100 patients with a reliable diagnosis of RA (1987 ACR criteria), who were randomized into two groups: the first group consisted of patients (n=11) with early RA (RA; disease duration up to 2 years), the second (n=35) - patients with RA duration of more than 2 years (DtRA). Ultrasound of the hands (Logic F8, G.E.; linear transducer 4–13 MHz, gray scale mode) were performed at baseline and after 6 months of follow-up. To assess the progression of destruction, a sonographic index (US-Er-10) was proposed, based on a bilateral assessment of five articular areas: carpals, II–III metacarpophalangeal, and II–III proximal interphalangeal joints. Depending on the dynamics of US-Er-10, the rate of development of the destructive process was conditionally divided into three categories: 1 - slow rate of progression; 2 - average rate of progression;  $\geq 3$  - rapidly progressive course. The X-ray parameters of structural progression were assessed over a 12-month follow-up using the Sharp method in the van modification. der Heijde.

**Results.** The incidence of erosions on ultrasound compared with radiography was significantly higher for both PRA and DtRA ( $p < 0.05$ ). In patients with PRA who fell ill after 55 years, more significant initial and final destructive changes were observed according to the SHS total score ( $p < 0.05$ ) and UZER-10 index ( $p < 0.005$ ) than in individuals with RA onset at a younger age. In patients with RRA who had an increase in US-ER-10 by 3 points or more by 6 months of follow-up, the rate of radiographic progression by 12 months of follow-up was significantly higher than in patients with less pronounced negative dynamics of this index ( $\Delta$  of the total score SHS 13.5 [3; 23] and 0 [0; 0], respectively;  $p < 0.05$ ). In the DTRA group, there were no statistically significant relationships between the rate of progression of erosions according to ultrasound data, the dynamics of radiographic changes and clinical and laboratory data.



**Conclusion.** Ultrasound of the hands significantly more often detects early erosive changes in the joints than radiography, and a high rate of progression of destruction according to ultrasound data and the onset of the disease after 55 years of age are associated with a more severe course and poor prognosis in patients with RRA.

Among the urgent problems of modern rheumatology, rheumatoid arthritis (RA) occupies a special place due to its growing socio-economic significance and a clear trend towards early disability of patients. The main postulate of the modern concept of managing patients with RA is the earliest possible diagnosis and early initiation of active therapy aimed at preventing structural damage and maintaining a high quality of life for patients [1, 2]. The polymorphism of the clinical picture and the rate of progression determines the difficulties in diagnosing RA and the need for early verification of predictors of an unfavorable course of the disease [3]. Risk factors for rapid progression of RA include the age of the onset of the disease, high activity of the inflammatory process, the presence of rheumatoid factor (RF), antibodies to cyclic citrullinated peptide (ACCP), HLA-DRB1\*04 positivity, ineffectiveness of basic anti-inflammatory drugs (DMARDs) for 6 months and erosive changes on radiographs or according to magnetic resonance imaging (MRI) [4–8]. The question of which of the markers of poor prognosis are most closely related to radiological progression indicators remains open. According to some authors [9], structural damage to the joints occurs even with normal values of acute phase parameters. Other authors [10] noted that patients with a number of swollen joints (SPJ)  $\geq 1$ , regardless of laboratory data, have higher rates of radiological progression than those with high laboratory activity, but without clinically affected joints. It has also been shown that elevated ESR and the level of C-reactive protein (CRP) are the most significant predictors of degradation progression [11]. At the same time, the clinical assessment of the joints is quite subjective and not always reliable, since the results can vary widely depending on the experience of the researcher [12]. X-ray examination of the joints of the hands and feet is a traditional and well-standardized method for verifying the diagnosis of RA, monitoring the course of the disease, and the effectiveness of the therapy [13]. However, standard radiography has low sensitivity for diagnosing early structural changes in the joints [14, 15]. In recent years, the attention of clinicians has been drawn to "new" imaging tools, such as MRI and ultrasound (US), which can identify early signs of destruction [16, 17]. The use of MRI significantly expands the possibilities of early diagnosis of RA and prediction of a severe destructive process in the joints [18]. But the high cost and the presence of contraindications (foreign metal bodies, pacemakers, artificial heart valves, magnet-activated insulin pumps, etc.) may limit its use in a certain category of patients. At the same time, the modernization of equipment, the expansion of educational programs and the affordability of ultrasound provide favorable conditions for the widespread introduction of this method into clinical practice. The purpose of the work is to determine the value of ultrasound in the diagnosis of early destructive changes in the joints of the hands and the rate of progression of RA in patients with different ages of onset of the disease.

**Material And Methods** We examined 100 patients (86 women and 14 men) with a reliable diagnosis of RA (criteria of the American College of Rheumatology - ACR - 1987), who were

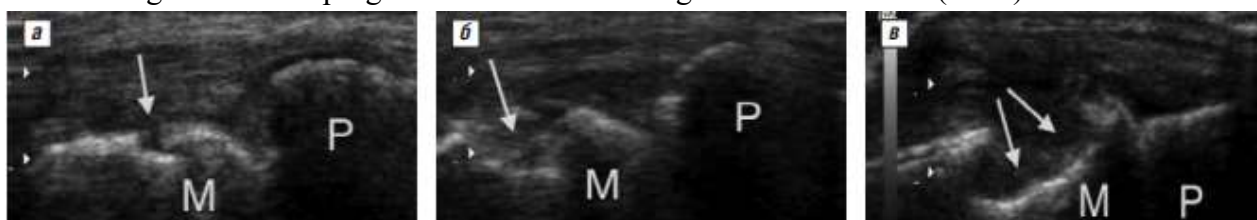


consecutively admitted to the Federal State Budgetary Institution "NIIR" of the Russian Academy of Medical Sciences in 2009–2011. The age of the patients was 53 [45; 58] years (median [25th; 75th percentile]), duration of illness - 84 [46; 162] months. Most patients were seropositive for RF (82%), ACCP (87%) and had high RA activity (median DAS28-CRP 6 [5.5; 7]) (Table 1). Due to the insufficient effectiveness of previous DMARD therapy, all patients received genetically engineered biological drugs (GEBPs): tocilizumab (TCZ; Actemra) - humanized monoclonal antibodies (mAbs) to IL6 receptors (n=44); infliximab (Remicade) - chimeric mAbs to tumor necrosis factor  $\alpha$  (TNF $\alpha$ ; n=7); rituximab (MabThera) - chimeric mAbs to CD20 antigen of B-lymphocytes (n=27); abatacept (Orencia), an inhibitor of costimulation of T-lymphocytes (n=22). Depending on the duration of the disease, the patients were randomized into two groups: the first group (n=17) consisted of patients with early RA (RA; disease duration up to 2 years), the second group (n=83) - patients with long-term current RA (DtRA; duration more than 2 years). The clinical study included the calculation of HR and HR, assessment of morning stiffness, determination of the Ritchie index, general assessment of the patient's state of health (PHA) and the severity of pain on a visual analogue scale (VAS, cm). The activity of the inflammatory process was determined using the DAS28-CRP index. Serum concentration of CRP and RF IgM was measured by immunonephelometric method (BN ProSpec, Siemens, Germany), ACCP content was measured by immunochemiluminescent method (COBAS e 411 Hitachi, Roche). Ultrasound of the hands (Logic F8, GE; multifrequency linear transducer 4–13 MHz) was performed in the gray scale mode at baseline and after 6 months of follow-up to monitor destructive changes in the joints. A bone tissue defect visualized in two perpendicular scan projections, more than 2 mm wide and more than 1 mm deep, was regarded as erosion (see figure) [19]. For the convenience of dynamic assessment of structural changes, we proposed a sonographic index (US-Er-10) of the most commonly affected joints of the hand, including a bilateral assessment of the cortical layer of five articular areas: wrists (wrist and intercarpal joints), II–III metacarpophalangeal (PFJ) and II–III proximal interphalangeal joints (PMJJ). Erosive changes were assessed in points according to the number of affected joints (0–10 points). An increase in the US-Er-10 score by 1 point or more by 6 months of observation indicated the progression of destruction. Depending on the dynamics of US-Er-10, the rate of development of the destructive process was conditionally divided into three categories: 1 - low rate of progression; 2 - average rate of progression;  $\geq 3$  - rapidly progressive course. X-rays of the hands and feet were performed in direct projection with Steinbrocker stage assessment and determination of structural progression indicators (total erosion count and total joint radiographic progression index) using the Sharp method modified by van der Heijde (SHS; 1989) [20] for 12 months of follow-up. The obtained data were statistically processed using the Statistica 8.0 software package. Variables were presented as a median with the upper and lower quartiles indicated in brackets [25th; 75th percentile]. The significance of changes within the groups was determined using the Wilcoxon test, when comparing groups, the Student's t-test, Mann-Whitney test were used. Results were considered significant at  $p < 0.05$ .

**Results** When analyzing the clinical characteristics of patients with RRA and DrRA, no



statistically significant differences in clinical and laboratory markers of inflammation were found. In the RRA group, the CRP level was slightly higher than in the DtRA group (50 [25; 79] and 28 [14; 55] mg/l, respectively;  $p > 0.05$ ), but these differences were not significant (see Table 1). Bone erosions were diagnosed in 87% of cases on X-ray examination, and in 99% of cases on ultrasound examination ( $p < 0.001$ ). The frequency of detection of erosions according to sonography, in comparison with radiography, was significantly higher as in PRA: 94% ( $n=16$ ) and 59% ( $n=10$ ), respectively ( $p < 0.05$ ). In ultrasonography, destructive changes were observed in 97% of cases in the joints of the wrists, in 96% in the PFS, and only in 70% in the PMFS. The topical predominance of the destructive process was established in PFS II and PMFS III (82 and 47.9%). The dynamics of the progression index is shown in Table. 2. So, in the general group of patients after 6 months of observation, a statistically significant increase in the number of erosions from 5 [3.5; 7] to 7 [5; 9] ( $p < 0.001$ ). In general, US-ER-10 monitoring showed the progression of erosive changes in 78% of cases ( $n=78$ ).



months, c – 228 months). M - head of the metacarpal bone; P - base of the proximal phalanx; arrows indicate bone erosion

At the same time, a low rate of progression ( $\Delta US-Er_{10}=1$ ) was observed in 26 (33%) patients, an average rate ( $\Delta US-Er_{10}=2$ ) in 29 (37.2%), and rapidly progressive progression was observed in 23 (29.5%) patients. current ( $\Delta US-Er_{10} \geq 3$ ). In 36 patients treated with TCZ for 6 months, a separate X-ray assessment of structural changes in the joints was performed using the SHS method. According to the erosion count, the progression of destruction was recorded in 13 cases, when analyzing the total SHS count, in 15 cases (the median delta of the erosion count was 0 [0; 3] and 0 [0; 13.5], respectively). In PRA, patients with the onset of the disease after 55 years of age had significantly more pronounced initial and final destructive changes according to the results of determining the total SHS score and US-Er-10 than those with RA onset at a younger age (Table 3). At the same time, most of them showed a rapid progression of destruction according to sonography, as evidenced by an increase in US-Er-10 by 3 [2; 4] points for 6 months of observation. No such differences were observed in the DtRA group. Of particular interest is a subgroup of patients with rapid progression of destruction and, presumably, a poor prognosis of the disease. A rapidly progressive course of RA in the first group was observed in 10 patients, in the second - in 13 patients. Patients with RRA who had an increase in US-ER-10 by 3 points or more by 6 months of follow-up had significantly faster rates of radiographic progression of destruction by 12 months ( $p < 0.0001$ ).

**Discussion** One of the main pathological signs of RA is bone erosion, the presence of which is taken into account in the diagnosis, monitoring and prognosis. Early development of erosive changes in the joints is associated with a high risk of progression and a poor prognosis of the disease [1, 7, 21]. Patients at high risk for RA progression usually require more aggressive



therapy. For the treatment of this category of patients, GEBA's can be successfully used, which can effectively suppress clinical activity and slow down the development of structural changes in the joints [22]. Modern sonodiagnosics, having sufficient sensitivity and specificity in assessing the initial erosive process, can become one of the available methods for early verification of patients with a poor prognosis of the disease requiring active therapy [14, 23, 24]. The importance of ultrasound in the diagnosis of bone erosions in RA has been known since 1988 [25]. A decade later, R. Wakefield et al. [16], using MRI as the "gold standard" in the study of 100 patients with RA (40% of whom had a disease duration), showed that, compared with standard radiography, sonography reveals 6.5 times more erosions in the early stages of RA and in 3.4 times - with a disease duration of more than 2 years. The authors found that the sensitivity of X-ray diagnostics, ultrasound and MRI was 19%, 42% and 68%, and the specificity of these methods was 100%, 91% and 96%, respectively. In our study, when examining 100 patients with active RA showed a significant superiority of ultrasound in the verification of the destructive process in the joints of the hands. In patients with RRA, ultrasound revealed erosive changes almost twice as often as radiography (in 94 and 59%, respectively;  $p < 0.05$ ).

Probably, the variability of the results of studies regarding the incidence of erosions in RA may be due to the selection of the examined groups with different clinical and demographic characteristics and serological status. Sonographic assessment of the erosive process in our cohort of patients demonstrated the development of destruction in II PFJ and III PMJ already at an early stage of the disease, which confirms the need to study these structures to assess erosive changes according to US-Er-10. Despite the active work of expert rheumatologists from the committee of musculoskeletal sonography of the European Antirheumatic League (EULAR), there is no single standardized system for assessing structural joint damage detected by ultrasound. Various methods for quantitative and semi-quantitative assessment of the registration of erosive changes have been proposed [26–29]. There are also sonographic indices, including various combinations of joints (from 1 to 78) [29–33], which are aimed primarily at assessing the inflammatory substrate, the dynamics of therapy, and verifying the criteria for RA remission. The value of ultrasound for monitoring the erosive process and predicting radiological changes has not yet been fully studied.

#### Dynamics of Sonographic Indices of Structural Progression of Joint Destruction

UZ-ER-10	General group (n=100)	RPA (n=17)	DtRA (n=83)	Mann-Whitney test
Initially	5 [3.5; 7]	3 [3; 4]	6 [4; 8]	$p < 0.01$
After 6 months	7 [5; 9]	7 [5; 9]	7 [5; 9]	$p > 0.05$
Delta	2 [1; 2]*	3 [2; 4]*	eleven; 2]*	$p < 0.001$

Note. US-ER-10 - sonographic index of erosions of the dominant hand. \*  $p < 0.001$ , Wilcoxon test.

In this work, we tried to determine the relationship between the dynamics of sonographic and radiographic signs of structural damage. The index we propose is based on a quantitative





assessment of the results of ultrasound examination of seven areas ( German US7 score ) of the dominant hand and foot (carpal joints, II-III PFS, II-III PMFS and II, V metatarsophalangeal joints - PFS ), reflecting the activity of the disease and the effectiveness of therapy in patients with inflammatory arthropathies [29]. The results of the assessment of the development of structural disorders according to US-ER-10 closely correlated with the dynamics of radiological changes in patients with RRA. The results obtained allow us to consider an increase in US-R-10  $\geq 3$  as a potential marker of an unfavorable prognosis of the disease. Correlations between measures of structural progression diagnosed by both imaging modalities indicate the ability of sonography to detect early destructive changes. Thus, hand ultrasonography performed within the first 6 months of illness may help identify patients in need of a more aggressive therapeutic strategy. Similar data on the possibilities of monitoring the destructive process in the joints using ultrasound and the relationship of its results with indicators of radiographic progression were demonstrated in a number of works by foreign authors [34, 35], in particular, in a multicenter French study [35], which studied the information content of the sonographic index based on a study of 6 joints (II, V PFJ and V PPJ on both sides) in patients with early arthritis (126 from the ESPOIR cohort, with a disease duration of 103 days). A significant factor influencing the progression of destruction in our patients was the age of onset of RA. Our results confirm the fact that the onset of RA in old age is one of the predictors of poor prognosis of the disease. Our observations are consistent with the data of a study by Russian rheumatologists [36], conducted back in the 80s of the last century, where it was shown that early erosive changes during the first year of the disease develop in 80% of patients with RA onset in old age. Conclusion Thus, the study shows that ultrasound of the hands significantly more often detects early erosive changes in the joints than radiography, the onset of the disease after 55 years is associated with rapid progression of destruction, a more severe course and poor prognosis in patients with RRA. It is likely that the use of a quantitative assessment of destructive changes using ultrasound may become one of the available methods for early verification in patients with a rapidly progressive course of RA who require aggressive therapy.

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