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RELATIONSHIP BETWEEN MATRIX METALLOPROTEINASE-3 LEVELS AND DISEASE ACTIVITY AND DESTRUCTIVE CHANGES IN JOINTS

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation and gradually progressive bone destruction. Matrix metalloproteinases (MMPs), a family of zinc-containing enzymes, have been found to play an important role in the degradation and remodeling of the extracellular matrix (ECM).

Keywords: rheumatoid arthritis, matrix metalloproteinase-3.

Matrix metalloproteinases (MMPs) are involved in cell proliferation, migration, inflammation, and cell metabolism. More and more people are paying attention to their function in inflammatory and immune diseases.

Introduction. In RA, the main role is played by 3 types of MMP: collagenases, stromelysins and gelatinases. The main role is assigned to MMP-3 (stromelysin -1), MMP-1 (fibroblast collagenase), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase-2) and MMP-13 (collagenase-3). Among them, the leading role in the destruction of articular cartilage belongs to MMP-3 [9-12]. It is produced by synovial cells [12], is found in synovial tissues in the form of a proenzyme and is activated by plasmin [13], after which it itself activates proenzymes of other MMPs [12,13].

In RA, the level of MMP-3 in the serum increases 7-8 times. Thus, Y. Ichikawa et al. [3], studying the concentration of MMP-3 in 60 patients with RA and 21 with systemic lupus erythematosus (SLE), noted a significant increase in the level of MMP-3 (436.8 ± 474.2 ng/m l) in the study group compared to the control (43.9 ± 15.2 ng/m l, p <0.0001). The enzyme matrix metalloproteinase-3 (MMP-3), also known as stromelysin-1, is encoded in humans by the MMP-3 gene, which is part of the MMP gene cluster located on chromosome 11q22.3. MMP family proteins are involved in the degradation of extracellular matrix proteins during tissue remodeling in normal physiological processes such as embryonic development and reproduction, as well as in disease processes such as arthritis and tumor metastasis. Most MMPs are secreted as inactive pre-proteins that are activated by cleavage by extracellular proteinases. MMP-3 is a proteinase synthesized and secreted by synovial fibroblasts and chondrocytes in joints. It is actively involved in joint destruction in patients with RA. The MMP-3 enzyme degrades collagen types II, III, IV, IX and X, proteoglycans, fibronectin, laminin and elastin. In addition, MMP-3 can also activate other MMPs such as MMP-1, MMP-7 and MMP-9, making MMP-3 a critical factor in connective tissue remodeling [12, 13]. MMP-3 and plasmin can affect inflamed synovial tissues and promote joint destruction [3]. Moreover, the higher the level of serum MMP-3, the greater the joint destruction, which was confirmed in the work of I. Chetverikov et al. [14], who examined RA patients with moderate and severe joint destruction. It turned out that the latter had a significantly higher level of MMP-3. This allowed us to conclude that serum MMP-3 is a prognostic factor for joint damage in the early stages of the disease. The implementation of MMP action is regulated at various stages, including gene activation, transcription, translation, and secretion of the enzyme with activation of its proenzyme. Once MMPs are produced and activated, their action and subsequent inactivation is controlled by tissue inhibitors of metalloproteinases (TIMPs) produced in the inflamed synovial tissue. MMPs are produced in response to the proinflammatory cytokines TNF-a and IL-1 [15] and are found in excess in the inflamed joint [1]. Degradation of articular

cartilage is one of the early features of diseases associated with increased activity of proteolytic systems [11]. Dysregulation of MMPs is manifested in RA, osteoarthritis (OA) and cancer [7, 12]. Progressive destruction of the extracellular matrix, including articular cartilage, bone, ligaments and tendons, is the main feature of arthritis, leading to impairment of the patient's functional capacity [10]. MMPs are involved in RA-associated bone destruction mainly through three mechanisms:

1) Adhesion to chondrocytes leading to collagen degradation and subsequent cartilage damage;

2) Regulation of inflammatory cytokines and chemokines leading to homeostasis imbalance in the affected joint and activation of inflammatory signaling pathways that promote osteoclast differentiation and bone resorption;

3) Stimulation of cell migration and invasive angiogenesis, initiating signals of osteoblast-osteoclast balance and accelerating bone destruction.

In the early stages of RA, fibrosis and absence of proteoglycans are observed on the cartilage surface, even in the absence of pannus tissue (Cabral-Pacheco et al., 2020). Under various stimuli, chondrocytes are able to express various proteases, including MMP-1, 2, 3, 7, 8, 9, 10, 13, 14 and other types, which directly initiate cartilage destruction. Evidence suggests that FLS are involved in both synovial inflammation and bone erosion in RA through the production of various factors such as IL-1β, TNFα, IL-6, IL-8, MMP-1, and MMP-13 (Wang et al., 2002 ; Mu et al., 2016). IL-1β is able to induce various MMPs including MMP-1, 3, 8, 13, 14, 29 and activate osteoclasts to degrade cartilage matrix (Amarasekara et al., 2018). MMP-13 activity is required for cartilage erosion (Ericsson et al., 2019). MMP activation is required for cell migration as the ECM must be remodeled to allow cellular movement (Little et al., 2009). MMP-12 has been shown to play an invasive role in macrophage penetration across the repaired basement membrane (Shipley et al., 1996).

Despite the acceptable diagnostic value of ACCP (anti-cyclic citrullinated peptide antibodies) and RF (rheumatoid factor), there is still a need to identify

additional markers to further improve the diagnosis of RA. One of them is MMP-3. In this regard, several recent reviews of RA biomarkers have not even mentioned MMP-3 [11], [12], [13], [15]. However, since the introduction of the multiple biomarker disease activity (MDA) for RA in 2016 [2], more objective indices have been introduced, increasing the subjectivity of conventional indices. The pathology of RA involves various joint cells, such as chondrocytes, T cells, fibroblast-like synoviocytes and macrophages, especially. Among them, fibroblast-like synoviocytes are considered as key components in RA [5,6], and they are known to express MMP-3, which is associated with their ability to cleave aggrecan, collagen type II, IX, X binding proteins and others in the joint [7,8]. In addition, MMP-3 can activate other MMPs such as pro-MMP-1, pro-MMP-8, pro-MMP-9 and pro-MMP-13 [9–12], and therefore MMP-3 is considered an important pathological mediator of RA.

The purpose of our study was to establish the relationship between the level of matrix metalloproteinase-3 and disease activity and destructive changes in the joints.

Materials and research methods. We examined 50 patients with RA undergoing inpatient treatment in the rheumatology department of the multidisciplinary clinic of the Tashkent Medical Academy for the period from 2022 to 2024. Among the patients we examined, there were 91 women, which made up 91%. There were 9 men, or 9%. The following indicators served as criteria for patient selection: persons of both sexes aged 30-75 years with RA of varying activity. General examination of patients was conducted according to the plan adopted in the clinic.

The average age of the examined patients was 46.5 ± 4.5 years.

When making a diagnosis, the following criteria were taken into account:

- articular syndrome occurring in the form of mono or oligo arthritis, unilateral or bilateral sacroiliitis;

- history of clinical complaints about the general condition of the liver;

- age and duration of RA;

- presence of extra-articular manifestations of RA.

The course of RA was divided into acute (duration of the disease up to 6 months), protracted (from 6 months to a year) and chronic (more than 1 year).

RA activity was determined by the intensity of pain, the presence of effusion in the joint cavity, the presence of joint dysfunction, an increase in ESR and CRP and ACPA. The stage of synovitis was determined using X-ray examination. The duration of the anamnesis of the examined patients ranged from 6 months to 8 years. Depending on the duration of the disease, RA patients were divided into patients with an anamnesis duration of up to 6 months (12% of patients), up to 1 year (14%), from one year to 5 years (37%) and more than 5 years (37%). The largest number of patients had an anamnesis duration of 1 to 10 years. A general assessment of health status was carried out using a visual analogue scale (VAS), on which the patient marks a score from one to ten, corresponding to the severity of pain and general condition. The results of the analogue scale were interpreted as follows: no pain – 0 points; mild pain – 1-2 points; moderate pain – 2-4 points; severe pain – 4-6 points; 6-8 points – severe pain; and 9-10 points – unbearable pain.

All patients underwent the following laboratory and instrumental studies: complete blood count, biochemical blood test, immunofluorescence analysis of MMP-3, IgM.

SPSS for Windows, 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical processing of the obtained data. Quantitative variables were compared using the Student t test and the Mann-Whitney test, and qualitative variables were compared using Fisher's exact method. Survival was analyzed using the Kaplan-Meier method. The difference was considered statistically significant at $p < 0.05$.

Research results and their discussion. The level of MMP-3 in the group of patients with early and advanced RA was significantly higher compared to healthy donors: 46.7 (15.5-64.5) ng/ml; 35.0 (12.5-66.5) ng/ml and 7.8 (5.5-11.8) ng/ml, respectively, $p<0.05$.

An elevated level of this indicator was recorded in 64.4% of patients.

In the group of patients with early RA, a positive correlation was found between the basal level of MMP-3 and disease activity indicators, including DAS 28 (r=0.55, p<0.05), SDAI (r=0.45, p<0.05), CDAI (r=0.35, p<0.05), ESR (r=0.46, p<0.05), CRP level (r=0.66, p<0.05), and IgM RF concentration (r=0.32, p=0.03). In the group of patients with advanced RA, a positive correlation was observed between the MMP-3 level and ESR (r=0.4, p=0.01) and the concentration of CRP (r=0.4, p=0.001) in the blood. 24 weeks after the start of therapy, the correlation between the MMP-3 level and the concentration of CRP (r=0.52, p=0.0003) and IgM RF (r=0.45, p=0.004) was maintained. To identify the relationship between the serum MMP-3 level and disease activity, all patients were divided into two subgroups depending on the MMP-3 level. Among patients with elevated MMP-3 concentrations before the start of therapy, there was a significantly higher initial disease activity, level of acute phase indices and autoantibodies compared to the group of patients with normal MMP-3 levels (Table 31).

Table 31. Clinical and laboratory parameters in patient groups depending on the level of MMP-3 in the blood serum Me (IR)

Indicator	**Elevated MMP-3 (>19.4 ng/ml) (n=50)**	**Normal MMP-3 level (<19.4 ng/ml) (n=20)**
DAS 28, points	6,02 (5,4-6,5)	4,99 (4,2-5,5)
SDAI, points	38,4 (26,6-47,2)	24,1 (18,04-39,2)
ESR, mm/h	36,0 (20,0-50,0)	20,0 (10,0-31,0)
CRP, mg/l	42,2 (18,8-77,4)	11,2 (1,7-25,6)
IgM RF, IU/ml	151,0 (66,8-429,0)	58,7 (19,6-212,0)

Note: p<0.05 between groups in all cases.

Before the start of therapy, the median total Sharp score in the group of patients with early RA was 67 (27-85), the number of erosions was 2 (0-4), and the number of narrowings was 59 (27-85). In 17 patients, erosive joint lesions were not detected during standard X-ray examination, while the rest had erosions of small joints of the hands and feet. One year after the start of therapy, radiographic progression was recorded in 8 patients (20.5%), and in 4 of them (9.8%) it was assessed as rapid (change in the total Sharp score>5). In the group of patients with advanced RA, the median initial value of the total Sharp score was 78 (46-122), the number of erosions

was 10.5 (2-35), and the number of stenosis was 67 (42-98). By the 48th week of treatment, radiographic progression was noted in 9 patients (22.5%), the appearance of one or more new erosions was observed in 10% of patients, and 7 patients (17.5%) had rapid rates of radiographic progression. A positive correlation was found between the basal level of MMP-3 and the number of erosions before the start of therapy (r=0.47, p=0.002) and after 12 months of treatment (r=0.34, p=0.03) (Figure 17), as well as a greater number of erosions among patients with an elevated level of MMP-3 in the blood serum before the start of therapy (n=29) compared to patients with a normal level of this indicator (n=16): 2 (1-5) and 0 (0-2), p<0.05, respectively. Among patients with advanced RA, no correlation was observed between the level of MMP-3 and destructive changes in the joints according to X-ray examination data.

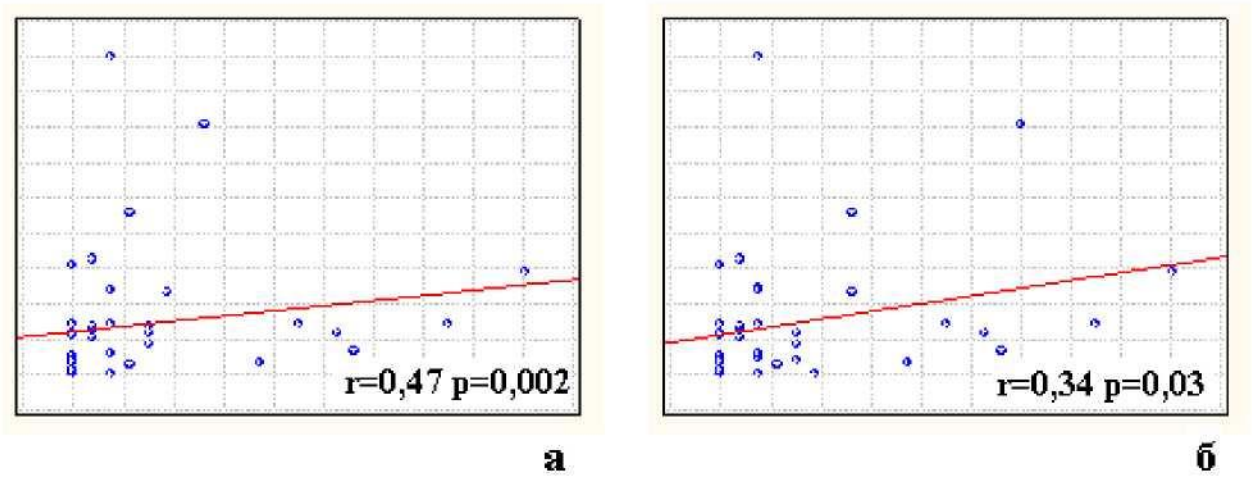

Figure 17. Correlation relationship between the basal level of MMP-3 and the number of erosions before the start of therapy (a) and after 12 months of therapy (b)

Among patients with early RA who showed progression of joint destruction after 52 weeks (n=8), there was a tendency for higher levels of MMP-3 after 12 weeks of MT therapy compared to patients without progression of destructive changes (n=31) (35.5 (15.5¬105.3) ng/ml and 17.5 (1.4-44.5) ng/ml, respectively, p=0.05). There were no significant differences between these groups in disease activity, acute phase response parameters, and autoantibodies, p>0.05.

Among patients with early RA, ROC analysis showed that MMP-3 levels greater than 34.3 ng/ml by week 12 of MT therapy were associated with progression

of destructive changes in the joints after 52 weeks (AUC=0.7; 95% CI 0.46-0.93) (Figure 18).

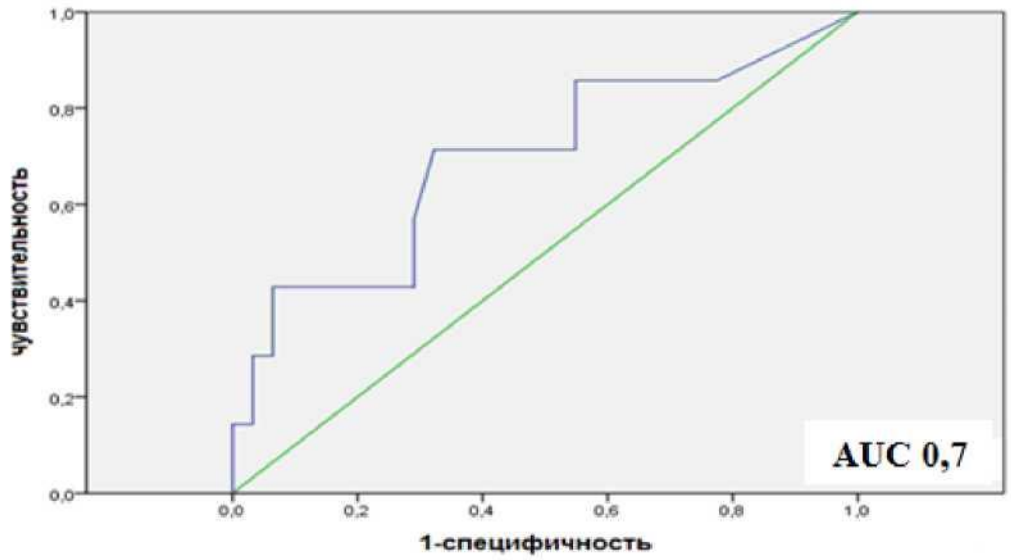

Figure 18. ROC curve reflecting the informativeness of determining the level of MMP-3 after 12 weeks of MT therapy for predicting the progression of joint destruction in early RA

In patients with advanced RA, a basal MMP-3 level of <51.3 ng/ml was associated with the absence of radiographic progression after 52 weeks (AUC=0.587; 95% CI 0.33-0.84) (Figure 19a). A relationship was also found between normalization of MMP-3 levels (<12.2 ng/ml) by the 24th week of therapy and the absence of progression of destructive joint changes after 1 year (AUC=0.597; 95% CI 0.32-0.88) (Figure 19b).

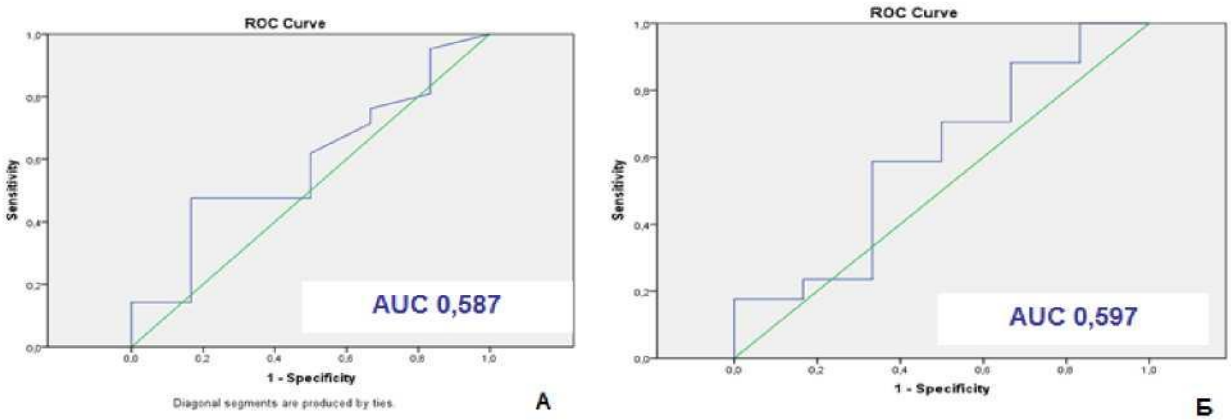

Figure 19. ROC curve reflecting the information content of determining the level of MMP-3 initially (a) and after 24 weeks of therapy (b) for predicting joint destruction in advanced RA

Conclusions. Thus, a close relationship was found between the level of MMP-3 in the blood serum, disease activity and destructive changes in joints in RA. The concentration of MMP-3 significantly correlates with the level of acute phase indicators; an elevated level of this marker in the blood serum is associated with higher inflammatory activity and the level of IgM RF. A correlation was noted between the MMP-3 level and the number of erosions before therapy and after 12 months of treatment in early RA, as well as a higher MMP-3 level in patients with radiographic progression after 1 year. Persistent elevated MMP-3 levels after 12 weeks of MT therapy can be considered as a prognostic marker of joint destruction.

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