Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 1, 2021, Pages. 4404 - 4410

Received 15 December 2020; Accepted 05 January 2021.

The Role of Cartilage Oligomer Matrix Protein (COPM) in Diagnostics of Early Cartilage Destruction in Reactive Arthritis

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ABSTRACT

The study enrolled 120 patients in the age of 36,9±12,3 classified into three groups according to the trigger factors and 20 healthy subjects. On the basis of the obtained data about early stages of ReA withChlamydia trachomatis etiology, long-lasting progression, and particularly rise ofcartilage oligomer matrix protein(COMP) in womenwe can make a conclusion about the initiation of early cartilage destruction in the structure of a joint. Besides that, it indicates activation of alteration in the articulate structure and development of secondary osteoarthritis in early stages of the disease.

KEYWORDS

Reactive Arthritis, Cartilage Oligomer Matrix Protein (COMP).

Introduction

Nowadays rheumatic diseases attract attention in all spheres of medicine. According to its prevalence reactive arthritis (ReA) occupies one of the leading places and according to various references it takes 4-40% [6,10,19].Moreover, it is characterized by progression accompanied by articular syndrome and damage of major joints. Itleads to invalidation ofyoung and middle-age patients, which has social significance and urgency.

According to recent data and various opinions [4, 12, 19], pathogenesis of ReA is based on immunologic disorders, and in 88-96% of the cases inadequate immune response to HLA-B27- antigen, in other words T-cellular cytostatic immune response. According to modern data [13, 16], development of the progress is triggered by infectious foci in intestinal or urogenital tracts. In relation to that it should be mentioned, that it was proven thatReA is initiated by Chlamydia trachomatis, Yersinia enterocolitica, Salmonella enteritidis, Shigella flexneri and Campylobacter jejuni infections acting as trigger factors [18] and it indicates complex etiopathogenesis of the disease. That is why it attracts attention of specialists from different spheres of medicine. In its turn, according to the criteria ofThe Assessment of SpondyloArthritis international Society (ASAS) diagnostic check-up should be initiated in case of articular syndrome, enthesistis, and pain in spine. Diagnostics includes polymerase chain reaction or microbiological test for the detection of the infection causing ReA, considered to be a “golden standard” [17].

It is known that,clinical presentation and articular syndrome of many rheumatologic diseases differ by specific morphologic alterations and inflammatory process. Rheumatic diseases, undoubtedly, cause certain alterations due to different progression and variety of underlying mechanisms. According to various opinions, the factors vary from unfavorable environmental effects [10] to profile of cytokines with negative effect on joints (TNF-α, IL-17, IL-23, IL-1, and IL-6)[14, 21]. Moreover, ReA is considered to be a disease with different progression, which means it has different clinical and x-ray alterations[14],and functionally heterogeneous pathology. According to the results of the performed study, articular lesions in ReA depend on its trigger factors. Especially urogenital ReA differs by active structural alterations and in33.3%of the cases secondary osteoarthritis develops within the first year of the disease. In its turn, it causes activation of structural alterations, which leads to deterioration of patients’ life quality. That is why, detection of early cartilage destructionin ReA has a practical importance.

Recently,according to the available data in literature [7], osseous erosions caused by proinflammatory cytokins in ReA immune response (IL-1, IL-6 andTNF-α)can serve the basis for degenerative alterations in cartilages. That process causes intensification of synthesis of collagenase and matrix metalloproteinase leading to splitting of 2 type of collagen [2, 8]. Results of the last scientific researches showed [1, 3], that cartilage oligomere matrix protein (COMP) provides important information about metabolic changes occurring in cartilage matrix under the influence ofthe aforesaid enzymes. Consequently, rise of COMP in blood serum can serve as a biomarker of early cartilage

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destruction in ReA. That is why, study of change of COMP in blood serum dependently on the clinical progression of the disease in patients with ReA has scientific and practical value.

The objective: Study of dynamic changes of cartilage oligomere matrix protein (COMP) level in patients with ReA dependent on its clinical presentation for the definition of early cartilage destruction.

Materials and Research Methods

The study enrolled randomly selected 120 patients with average term of ReA equal to3.8±1.7 years aged 18-50 (36.9±12.3) years old. The major part of these patients were women, 70 (58.3%). For the study patients were classified to three groups according to etiological factors. The I group (n=60) had Chlamydia trachomatisetiology; the II group (n=30) had Sinia enterocolitica, and the III group (n=30) had Campylobacter jejuneas an etiological factor. The control group involved 20 healthy subjects(average age 37.5±6.2 years old) with age and sex approximately compatible to patients with ReA (Table 1).

For the detection of trigger infections we used immunologic (detection of antibodies to infectious antigen in blod serum), molecular-biological (polymerase chain reaction), and bacteriological tests. We had detection of infections causing ReA in all patients, after which they were examined by urologist, gynecologist (taking smear from urethra and vagina), and oculist.

For the assessment of the progression and activity of ReA we applied visual analogue scale (VAS), DASand parameters of the acute stage of inflammation. Functional capabilities of the patients were assessed according to functional classes (FC), Health Assessment Questionnaire (HAQ) and Ritchie index. Laboratory tests included common blood analysis and biochemical blood tests. All patients had x-ray imaging of the joints.Cartilage oligomer matrix protein (COMP) were detected using enzyme immunoassay(«Human COMP ELISA Kit»).

Table 1. Clinical characteristics of patients with ReA (n = 120)

Groups		Sex		Average age	Average term of the disease (years)
		Male	Female		
Igroup (n =60)	abs.	25	35	32.9±11.1	2.9±1.8
	%	41.7	58.3		
IIgroup(n=30)	abs.	13	17	36.4±6.8	3.1±1.9
	%	43.3	56.7		
IIIgroup (n =30)	abs.	12	18	34.1±7.3	2.8±1.9
	%	40	60		

Exclusion criteria were as follows:

1) Patients with no confirmed diagnosis ofReA according to EULAR/ACR;
2) Patients under 18;
3) No surgical treatment of ReA within and before the period of study;
4) Severe concomitant pathology (renal, hepatic, cardiac failure, high uncontrolable AH, decompensated diabetes mellitus, etc.); injures;
5) Dangerous tumors, drinking of alcohol, psychic diseases, such as dementia and mental impairments;
6) Tpatients with BMI below 29.

Statistical processing of the results was performedusing Microsoft Office Excel 2013 software and standard statistical method.

Results and Discussion

Majority of the patients were30-40 years old(69.1%) and women (58.3%). On the basis of the analysis of anamnesis morbid the average age of patients at the moment of appearance of initial symptoms of ReA was 30.1±4.5 years old. Average time from the moment of appearance of initial symptoms till the diagnosis was 3.7 months.
The data in Table 1 show that, according to the form of the disease and etiological factors clinical presentation of

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ReA differs in three groups. There is reliable ($p<0.05$) difference of long-lasting progression of the pathology among the patients of the I group compared to other forms (Table 1). At the same time, in 31.6%of the cases we could observe recurrent progression of urogenital ReA.

Dysfunction of joints can be linked with certain alterations relevant to inflammatory process. Indicators of acute stage, duration of morning stiffness and the number of inflamed joints in the patients of the I group (Table 1) caused limitation of functional capabilities of the joints. In their turn, patients of the II and III groups suffered monoarthritis, while the patients of the I group there were more cases of oligoarthritis and polyarthritis. It should be noted that, 100% of all patients in all three groups had synovitis, which was mostly singular and sometimes accompanied periarthritis manifested by tendinitis or bursitis.

Table 2. Clinical presentation of patients with ReA

Symptoms	**I group (n=60)**		**II group (n=30)**		**III group (n=30)**	
	abs.	**%**	**abs.**	**%**	**abs.**	**%**
According to progression						
Acute	7	11.7	19	63.3	16	53.3
Long-lasting	24	40	5	16.7	3	10
Chronic	10	16.7	3	10	7	23.3
Recurrent	19	31.6	3	10	4	13.4
Articular syndrome						
Monoarthritis	4	6.6	16	53.3	14	46.7
Oligoarthritis	34	56.7	10	33.4	13	43.3
Polyarthritis	22	36.7	4	13.3	3	10
Sacroiliitis	53	88.3	26	86.7	4	13.3
Spondylitis	40	66.7	4	13.3	13	43.3
Dactylitis	6	10	5	16.7	6	20
Dysfunctionof joints						
Iclass	12	20	18	60	15	50
IIclass	29	48.3	8	26.7	11	36.7
IIIclass	19	31.7	4	13.3	4	13.3
Articular index and laboratory results						
Duration of morning stiffness, minutes	31.3±5.9		19.1±6.1		17.3±8.5	
Pain, VAS, mm	79.5±12.8		67.5±12.8		53.5±11.4	
Number of painful joints	8.2±3.7		4.1±0.7		4.1±0.7	
Number of swelling joints	5.6±0.6		2.5±2.6		2.1±0.9	
C-reactive protein, mg/L	19.8±3.9		12.8±1.9		11.8±1.7	
Erythrocyte sedimentation rate, mm/s	25.3±3.9		18.3±3.6		19.3±5.5	

It is known that, diseases proceeding with arthritis are characterized by certain alterations in joint structure. Immunologic alterations in ReA are based on synovial inflammation, disorders in its structure and development of fibrosis [5]. The aforesaid processes proceed with various alterations providing the possibility of bone erosion and articular surface discongruence. Perhaps, these transformations are linked with change in characteristics of cartilage morphologic substrate. So, rise of COMP in blood serum of the patients with ReA indicate metabolic changes in cartilage [9]. It should be noted that, changes of COMP level among the patients enrolled in the study varied greatly. As it is seen in Table 2, when compared to the control group, all male and female patients had a tendency for the rise of COMP, but the values were not statistically significant ($p>0.05$). however, in the I group the part of those who had rise of COMP reference values (1000ng/mL>) was equal to 53.3% (Fig. 1).

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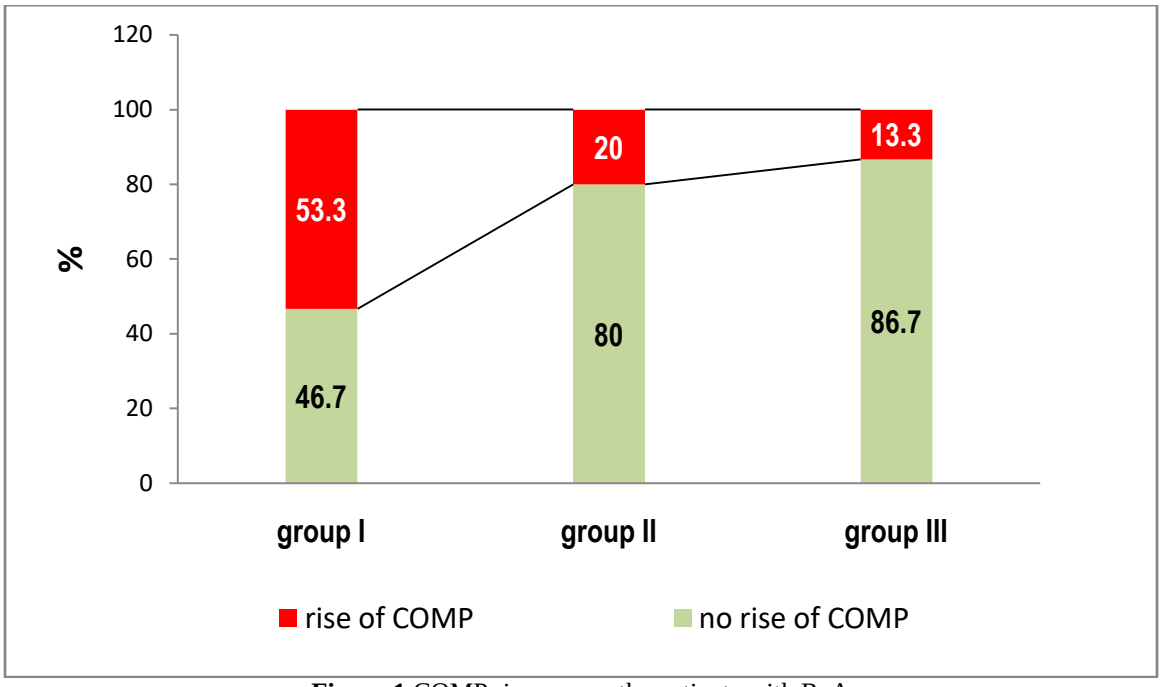

Figure 1.COMP rise among the patients with ReA

Thus, in some cases of ReA we can observe activation of structural alterations. The results show reliable difference in etiological factors, progression, and duration of the disease.

Table 3. Parameters of cartilage oligomere matrix protein (COMP) in patients with ReA

Groups	COMP ng/mL		p
	Male	Female	
Control(n=20)	814.7±52.2	912.2±112.2	-
I group(n=60)	2746.2±393.5	3051.2±165.5	$p^э<0.02;p^а<0.001$
IIgroup(n=30)	1003.7±119.1	1132.5±302.7	$p^э>0.05;p^а>0.05$
III group(n=30)	987.2±715.2	1089.9±955.7	$p^э>0.05;p^а>0.05$
Total(n=120)	1343.2±1101.2	1359.2±1002.8	$p^э>0.05;p^а>0.05$

Note: $p^э$–male and $p^а$– female reliable parameters compared to the control group.

In its turn, analysis of the etiological factor showed that, exactly in the I group (with Chlamydia trachomatis etiology)both male and female patients had reliable ($p<0.02;p<0.001$, respectively) rise COMP in blood serum compared to the control group.At the same time, we determinedthat, progression of the pathology in these patients was relevant to structural alterations in cartilages. Figure 2 demonstrates that, long-lasting progression of the disease was reliably ($p<0.01$) accompanied by the rise of COMP. It was particularly expressed in women, who had 3672.8±176.6 ng/mL, which was 2.5 fold ($p<0.05$)higher than in men (1421.8±412.3 ng/mL). These data certainly indicate presence of gender differences in the progression of the disease and probable involvement of sexual hormones in its genesis.

The study of COMP level in blood serum of the patients suffering ReA showed characteristic dynamic changes occurring with the prolongation of the term of disease. Table 3 shows that, in the I group COMP started rising within initial stages of the disease ($p<0.05$) and intensified with the prolongation of the term of the disease. So, on the basis of the obtained results, we can make a conclusion about long-lasting progression and start of early destruction of cartilage in the structure of joint, especially in women, within initial stages of Chlamydia trachomatis ReA. Besides that, it can indicate intensification of structural changes in joints and development of secondary osteoarthritis in initial stages of the disease.

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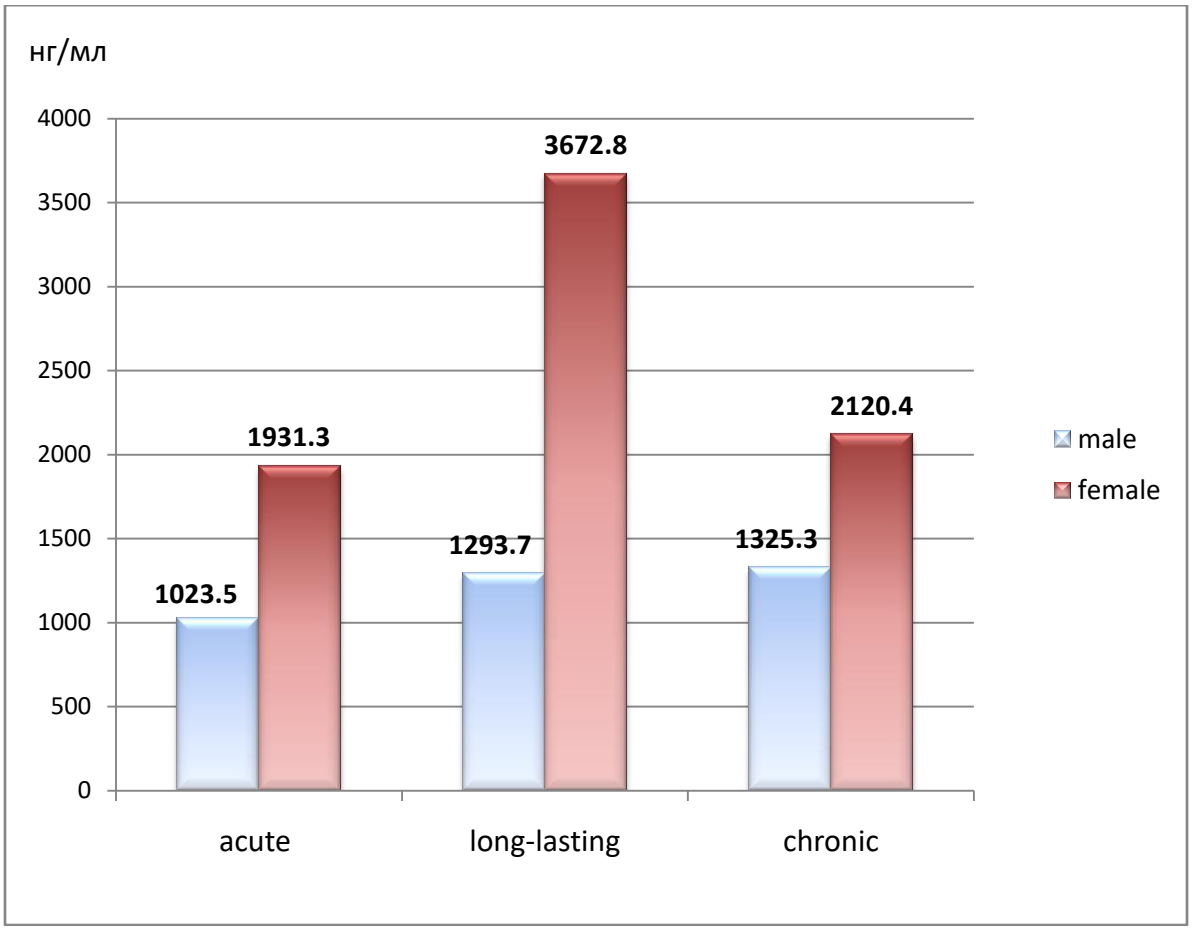

Figure 2. Change of COMP level in patients with ReA dependently on the progression of the disease.

It is worth mentioning, that x-ray images of knee joint of the patients with Rea showed development of secondary osteoarthritis within initial years of the disease in 20% of the patients. Figure 3 demonstrates that, alterations develop with the progression of the disease. In 23.4% of the cases in thirty six months from the start of ReAwe could observe III and IV stages of osteoarthritis, in other words there was need of endoprosthetics.

Table 4. Change of COMP level dependently on the term of disease

Groups	**COMP ng/mL**		
Control(n=20)	865,5±82,2		
Term	I group (n=60)	II group(n=30)	III group (n=30)
0-12 mo	1348.1±97.9*	901.7±95.2	843±231.4
12-24 mo	2293.5±223.2*	913.3±118.8	909±219.2
24-36mo	2870.2±191.3*	1055.8±342.1	891±105.8
36-48 mo	3012.6±234.2*	1456.5±201.2*	1132± 124.3
More than 48 mo	3144.1±301.5*	2011.4±121.9*	1897±100.8*

Note: * - $p<0.05$ reliability of the data compared to the control.

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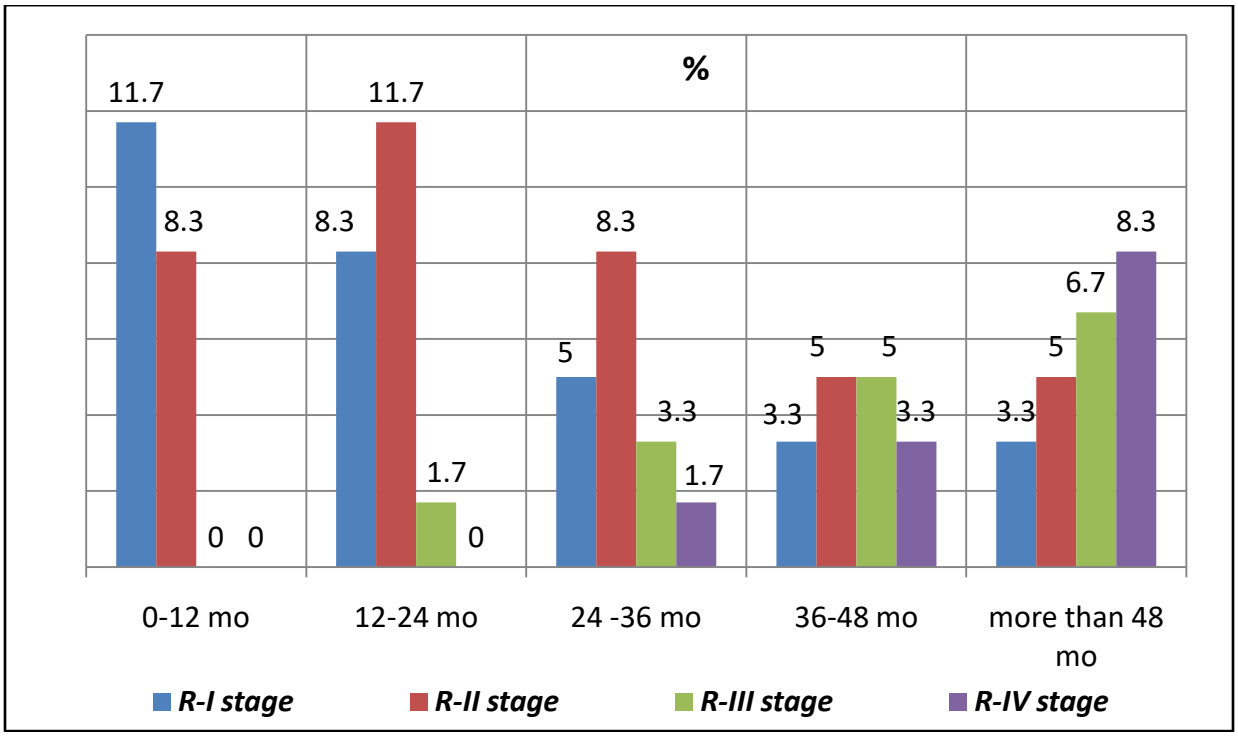

Figure 3. Development of secondary osteoarthritis in ReA patients of the I group (Chlamydia trachomatis etiology).

Conclusion

Thus, secondary osteoarthritis develops within initial stages of ReA and rise of cartilage oligomer matrix protein (COMP) indicates early destruction of cartilage. ReA with Chlamydia trachomatis etiology and long-lasting progression is characterized by intensification of structural alterations in joints.

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