CARTILAGE OLIGOMERIC MATRIX PROTEIN (COMP) in EARLY DIAGNOSIS of OSTEOARTHRITIS

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Abstract. Sixty patients with radiologically determined 0-II stages of knee joint osteoarthritis aged 50.3±4.4 years old with average duration 5.4±3.6 years were enrolled in the study. At the same time ten healthy individuals (average age 47.5±7.1years old) of the age and gender compatible with the patients of OA group were also enrolled in the study.

According to the results of the study radiological stage of osteoarthritis, progression and duration are characterized by certain structural changes. Within pre-radiological stage rise of cartilage oligomeric matrix protein (COMP) in blood serum indicates early destruction of cartilage.

Keywords: osteoparthritis, cartilage oligomeric matrix protein, radiological alterations.

Introduction. Nowadays, the problems of skeletal-muscular system pathologies serve to be an urgent issue in several branches of medicine [4]. Particularly, osteoarthritis (OA) based on destruction of cartilage tissue, remodeling of bone structure, osteophytosis and inflammation processes, differs with certain clinic presentation and characteristics dependent on articulate anatomical physiological disorders, leading to invalidity especially in middle-aged patients, which determined its social importance and urgency [1,3]. In present time OA is considered to be multifactor disease. In other words, OA development pathogenesis is based on such important risk factors as age, overweight, heredity, defects in the development of skeletal system, including hyper mobility of joints, hormonal disorders, side-effects of drugs, traumas, co-morbid pathologies [2,13]. Negative social-economical effect of diseases of skeletal system, particularly OA, is quite significant. For example, according to W.Felts and E.Yelin (2013) only in the USA 5% of all patients in clinics, 10% of diagnosis and therapy, and 5% of visits to doctors are those of rheumatologic patients. In Canada the economical burden of pathologies of skeletal system can be compared to those spent on the therapy of oncologic patients. In relation to that, a in the modern medicine great scientific interest is paid to biomarkers allowing early diagnosis of OA and therapy monitoring due to great prevalence of OA, increasing unemployment rates of workable population and causing deterioration of life quality. In Biomarkers in OA consolidated project of the Foundation for the National Institutions of Health (FNIH) it is stated, that biomarkers provide urgent indications for certain measures and assist invention of

new therapeutic agents. Recent references [11,14] provide important information about metabolic alterations in cartilage oligomeric matrix protein (COMP) occurring under the influence of the aforesaid enzymes in cartilage matrix. Some scientific works [9,10] report, that there is correlation between serum COMP and clinical stage of OA and certain histological alterations. According to the data in other references [7, 12], osteoarthritis develops within initial stages of RA, and rise of cartilage oligomeric matrix protein (COMP) indicates early destruction of cartilage. Rise or drop of serum COMP, actually, indicate exacerbation or remission of the pathology. That is why, for coordination of cytokines, collagenase, and matrix metalloproteinases in the development of pathologic process it is correct to decrease COMP. It is known, that many rheumatic diseases differ by clinical presentation and articulate syndrome, with certain morphological alterations and specific inflammatory process. Certainly, differences in the development of rheumatic diseases and variety of underlying factors leads to specific alterations in joints. In compliance with various opinions, it can be explained by several factors from negative influence of environmental factors [8], to aggressive impact of cytokine profile (TNF-α, IL-1 and IL-6) on joints [5, 6]. Accordingly, OA is considered to be a disease with different progression, in other words with various clinical, radiological and functional changes. In its turn, it serves the basis for intensification of structural alterations in joints and causes deterioration of patients' life quality. That is why, definition of early destruction in cartilage has a practical significance.

The objective: was assessment of cartilage oligomeric maytrix protein (COMP) definition method in diagnosis of cartilage early destruction in patients with OA.

Materials and research methods. Sixty patients with radiologically determined 0-II stages of knee joint osteoarthritis aged from 42 to 57 years old (average 50.3±4.4 years old) with average duration 5.4±3.6 years were enrolled in the study. At the same time ten healthy individuals (average age 47.5±7.1years old) of the age and gender approximately compatible with the patients of OA group were also enrolled in the study.

All the patients with OA were classified into three groups (Table 1) according to definition of stages on the basis of x-ray images of knee joint in compliance with Kellgren-Lawrence criteria:

I group (n=18) included patients with radiological 0 stage of knee joint OA with average age 47.3±6.3.

II group (n=22) included patients with radiological I stage of knee joint OA with average age 49.2±5.1.

III group (n=20) included patients with radiological II stage of OA with average age 52.4±3.9.

Table 1

Classification of the patients enrolled in the study

Groups		Gender		Mean age of the patients
		Male	Female	
I group (n =18)	abs	7	11	47.3±6.3

	%	38.9	61.1	
II group (n=22)	abs	9	13	49.2±5.1
	%	40.9	59.1	
III group (n=20)	abs	8	12	52.4±3.9
	%	40	60	

The study included pain visual analogue scale (VAS), Lequesne index of joint activity assessment, and common clinical and biochemical blood analysis.

Cartilage oligomeric matrix protein (COMP) and female sexual hormones were identified using immunoassay (ELISA, Russia).

Exclusion criteria for the study were the following:

1) patients with no OA diagnosed according to EULAR/ACR criteria;
2) no surgical treatment of OA before or during the study;
3) severe concomitant pathology (renal, hepatic, cardiac failure, uncontrollable high AH, decompensated diabetes mellitus, etc), traumas;
4) malignant tumors, consumption of alcohol, psychic diseases, including dementia and cognitive impairments;
5) secondary OA.

Statistical processing of the obtained results was done using Microsoft Office Excel 2013 software and standard statistical methods.

Results and discussion. The greater part of the patients enrolled in the study were women (60%) (Table 1). According to the results of history analysis, mean age of the patients at the time of appearance of OA initial symptoms was 47.2±2.1. Average time period from the appearance of initial symptoms till the diagnosis was 1.9 months.

Table 2

Clinical laboratory values of the patients with OS enrolled in the study

Parameters	I group (n =18)	II group (n =22)	III group (n =20)
Duration of the disease, years	1.9±1.1	2.8±1.8	3.2±1.4
Pain VAS, mm	35.4±4.7	55.4±5.9*	69.4±8.7$^{\&}$
Duration of morning stiffness, minutes	4.1±1.9	8.6±1.8*	10.9±2.5$^{\&}$
Synovitis, %	5.6	59.1*	75$^{\&\nabla}$
Lequesne index	7.1±1.8	7.9±1.6	9.3±2.1$^{\nabla}$
Functional failure of joints			
I class	83.3	18.2*	10$^{\&\nabla}$
II class	11.1	54.5	30$^{\&\nabla}$
III class	5.6	27.3	60$^{\&\nabla}$
Laboratory results			
C-reactive protein, mg/L	6.5±1.2	8.2±1.4	9.9±1.6$^{\&}$
Erythrocyte sedimentation rate (Westegren) mm/s	16.2±3.8	18.2±4.3	17.9±3.2

BMI			
18-24.9 (%)	11.1	4.5	5
25-29.9 (%)	16.7	36.4	10
30-34.9 (%)	22.2	13.6	45
35-39.9 (%)	27.8	27.3	30
Above 40 (%)	22.2	18.2	10

Note: difference reliability $p<0.05$: * - between I and II groups; $^{\&}$ - between I and III groups. $^{\nabla}$ - between II and III groups.

According to the results clinical presentation of the disease was different in three groups (table 2). Dysfunctions in joints can be linked to dynamic changes in typical x-ray images of degenerative process in cartilage. In the Table 2 it is seen, that indicators of articulate functional failures were reliably ($p<0.05$) different; in other words, the greater were radiological differences the more limited functionally the joint became.

At the same time, comparison of the groups showed, that structural alterations in joints were based on pain syndrome. Pain VAS and morning stiffness indicators were reliably different between the groups ($p<0.05$).

The data in table 2 show, that most part of the patients were those with overweight and 1-3 stages of obesity.

It is known, that in arthritis joint structure undergoes some changes. For example, progression of OA with alterations on different levels cause bone erosion and incongruence of the joint surface. That process, in its turn, is linked with the change in characteristics of cartilage morphologic substrate. Thus, the results show, that rise of serum COMP indicate metabolic changes in the cartilage [9]. It should be noted, that COMP varied greatly among the patients enrolled in the study. As it is depicted in figure 1, in compison to the control group patients of all three groups had reliable total COMP rise ($p<0.05$).

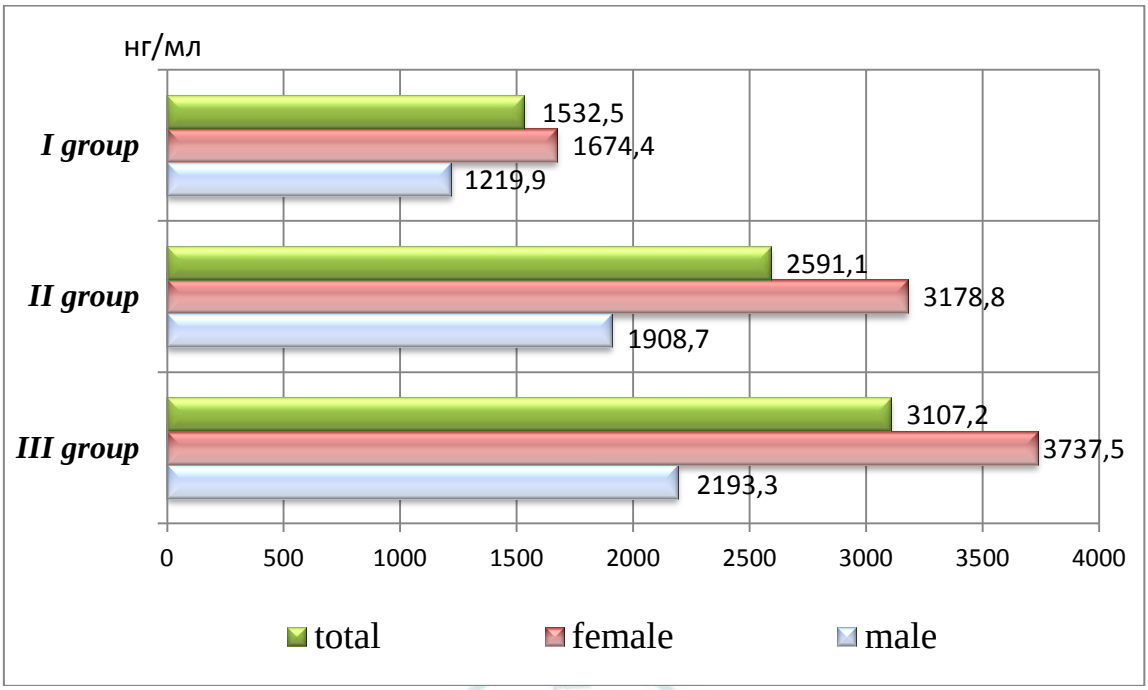

Figure 2. COMP change according to OA radiologic stage.

At the same time, analysis of COMP in the groups showed reliable differences therein ($p<0.05$), and as figure 2 illustrates, the total value in the I group was 1532.5±113.1ng/mL, in the II group it was 2591.1±96.5 ng/mL, and in the II group it was 3107.2±102.6 ng/mL. So, in patients with OA intensification of cartilage destruction in joint is accompanied by rise of COMP.

Moreover, according to our results, there are definite differences in roentgenologic stages and duration of disease between the genders. Particularly, compared to men it was more expressed in the women ($p<0.05$). Surely, that confirms the link between the way of disease progression and the gender and probability that hormonal disorders serve the basis for its genesis.

Table 3

Change in COMP according to radiologic stage of OA

Groups			
Control group (n=10)		836.5±62.4	
Duration	I group (n=18)	II group (n=22)	III group (n=20)
0-12 months	1354±91.3*	1909.6±117.1*	2789.1±96.8*
12-24 months	1695±119.2*	2240.3±109.25*	3290.6±129.4*
24-36 months	1860,1±95.8*	2955.8±102.1*	3969.2±182.4*

*Note: * - $p<0.05$ reliability in comparison with the control group.*

The study of serum COMP in the patients with OA showed specific dynamics with the progression of the disease. Table 3 shows, that in the I group within initial stage of the disease that value reliably increased ($p<0.05$) and continued growing with progression of the disease.

It is known, that cartilage destruction in OA can be linked with specific alterations in case of joint inflammation. In this case irreversible bone erosions appearing as an immune response to aggressive impact of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α maintain degenerative alterations in cartilage [3]. The study of COMP changes related to inflammation process in OA was based on the analysis of correlation between the values.

The analysis showed negative feedback between COMP and CRP and ESR and positive correlation with Lequesne index in the control group. In its turn, in patients with OA, particularly in the III group, rise of serum COMP conditioned negative feedback. Figure 2 illustrates, that the graph based on the results of correlation of the parameters of acute stage of inflammation and VAS with COMP in the control group is horizontal pentagon, while in the I, II, and III groups i8t is vertical. Correlation between IL-6 and COMP in the control group had positive r=0.44, but intensification of radiological changes led to formation of negative feedback (I group r=-0.58, II group r=-0.7 and III group r=-0.61; $p<0.05$).

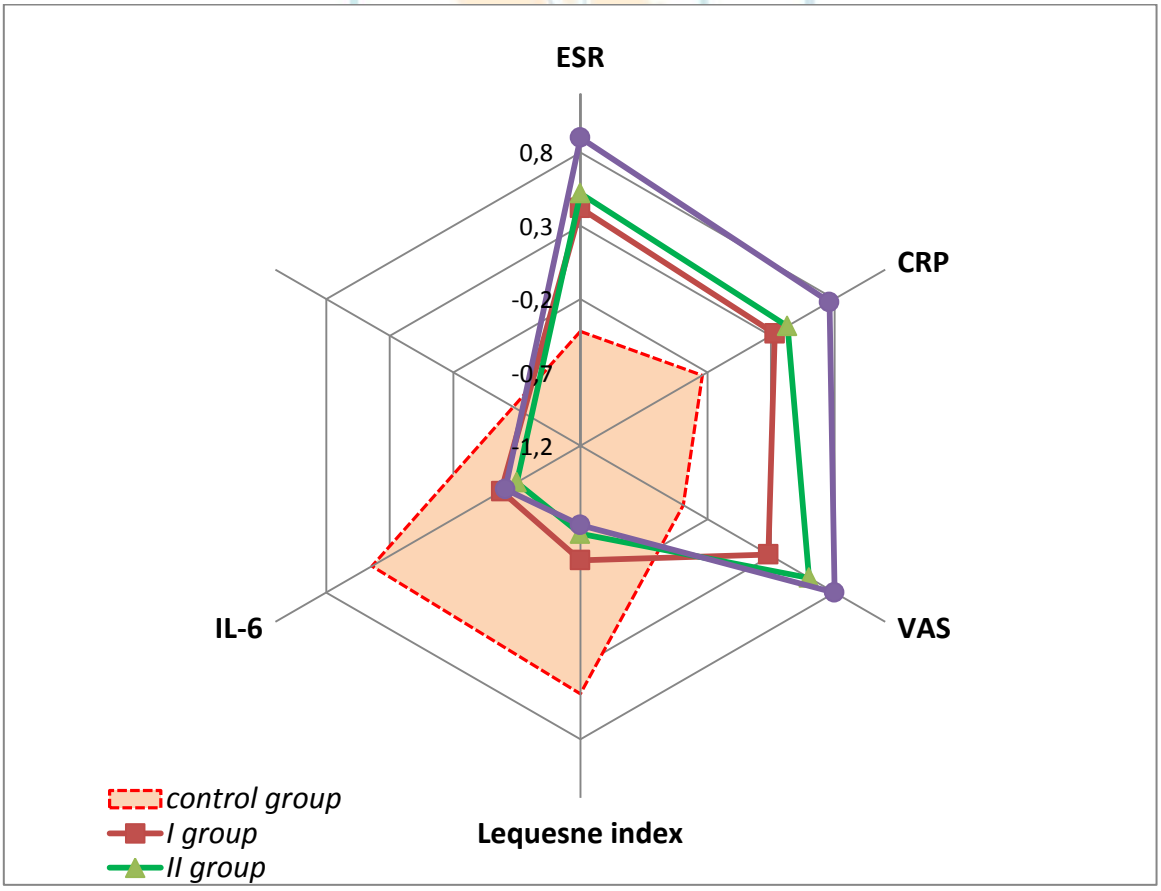

Figure 3. Correlation of COMP with inflammation process.

Thus, immune inflammatory process in OA, or pro-inflammatory cytokine IL-6 aggression is linked with the rise of COMP.

According to the obtained results, we can say that on the basis of OA of knee joint inflammatory markers and COMP amount indicating destruction of cartilage structures, and taking into account clinical radiological stage of OA, its progression can be classified into three variants (table 5):

1. variant with no clear clinical manifestations and relatively low COMP in blood (1500<2000 ng/mL) and normal ESR and CRP (A variant).
2. Low expression of CRP and ESR, clinical manifestations and high COMP (<2000 ng/mL) (B variant).
3. Simultaneous rise of CRP, ESR and COMP (<2000 ng/mL) with expressed destruction of cartilage (C variant).

Table 5

Variants of OA clinical presentation based on the obtained results

	A variant	B variant	C variant
I group (n=18)	4	8	6
II group (n=22)	2	10	10
III group (n=20)	2	7	11
% of clinical variants	13.3%	41.7%	45%

According to the results of the study prevalence of knee synovitis in cases of OA C variant was higher than in A and B variants. Thus, among the patients enrolled in the study there were 47 cases with synovitis, and 30 out of them corresponded to C variants of OA clinical form.

Conclusion. Radiological stage of OA, progression and duration are characterized by certain specific structural alterations in joints. Rise of serum cartilage oligomeric matrix protein (COMP) within pre-roentgenologic stage of OA indicates early destruction of cartilage.

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