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Cartilage Glycoprotein-39 in Patients with Osteoarthritis in Combination with Cardiovascular Pathology

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Abstract – The article studies lipid parameters and inflammatory markers of OA without comorbidity, OA in combination with IHD, AH in conjunction with clinical symptoms of the disease. 110 patients with OA combined with IHD, AH, 30 patients with OA without comorbidity treated at the rheumatology department of the NOSMA clinics, and 30 healthy volunteers of identical gender and age were examined. The clinical parameters of gonarthritis, CGP-39, CRP, ESR, lipid profile (cholesterol, LDL, HDL, triglycerides, CA), and UDE results were analyzed. A significant increase in CGP-39 was observed in all the patients. The highest rates of CGP-39 were found in patients with the third stage of gonarthritis. Reliable direct correlations were found between CGP-39 and clinical indices of gonarthritis severity, CCA IMC thickness, the lipid spectrum, CRP, and ESR. CGP-39 can reflect OA severity. It can be regarded as a risk factor for OA and atherosclerosis development.

Key words – glycoprotein, osteoarthritis, cardiovascular pathology

I. INTRODUCTION

Osteoarthritis (OA) is one of the most common diseases of the RNO-Alania causing disability. The cardiovascular pathology is widespread [1, 2]. Factors of cardiovascular diseases can affect the progression of OA. The cardiovascular continuum affects the subchondral parts of the tubular bones causing ischemia, inflammation, lipid impregnation [3, 4] and remodeling [5, 6]. The main role is assigned to the subchondral bone which is involved in the OA pathogenesis [7, 8]. Lipids are able to accumulate in articular cartilage [9, 10]. Other sources identified the direct effect of dyslipidemia on the remodeling of the subchondral bone at the initial stages of OA [11]. W. de Munter et al. suggested that correction of the lipid spectrum can affect OA development [12]. It is difficult to assess the lipid status of patients with OA. Thus, the clinical and pathogenetic significance of atherosclerosis and dyslipidemia in osteoarthritis requires further study.

Under the influence of local inflammatory mediators that develop in OA, endothelial dysfunction is formed which can cause the disease [13]. Inflammatory agents play an important role in the development and progression of atherosclerosis and OA. The biological response of in vivo inflammation is regulated by the cytokines including a large group of interleukins, tumor necrosis factor α (TNF-α), cartilage glycoprotein-39 (CGP-39), growth factors, and interferons [14, 15]. The increased concentration of CGP-39 is due to inflammatory diseases and processes of active tissue restructuring. The correlation of elevated concentrations of CGP-39 with various tumors and cardiovascular diseases has been thoroughly studied. CGP-39 is a highly specific protein

product of cartilage chondrocytes. CGP-39 is a marker of chondrocyte activation and a sign of progressive OA [16, 17].

In vitro studies aimed at detecting biomarkers of atherosclerosis identified an increase in the CGP-39 level in macrophages after LDL oxidation which imitates the formation of foam cells and indicates the role of this cytokine in the formation of atherosclerotic plaques [6]. In addition, several in vivo studies found that there is CGP-39 in the adventitia of the vascular wall and in macrophages of various tissues where the inflammatory remodeling of the extracellular matrix is focused [7,18]. CGP-39 is closely related to the level of interleukin-6 which can stimulate the synthesis of all proteins in the acute inflammation phase. It also releases monocyte chemoattractant protein 1 and matrix metalloproteinase 9 (MMP-9) from macrophages which can cause degradation of all components of the extracellular matrix due to its catalytic activity and degradation of collagen fibers of the fibrous cap of the atherosclerotic plaque causing its thinning and rupture [19,20].

Thus, CGP-39 plays a role in the pathogenesis of endothelial dysfunction, atherosclerosis, and abnormal angiogenesis by enhancing chemotaxis, reorganizing and reconstructing vascular wall tissues in response to the endothelium damage [15]. CGP-39 is a very promising marker for a wide range of nosologies.

II. MATERIAL AND METHODS

We examined 110 patients (68 women and 42 men) with knee joint OA who were treated at the rheumatology department of the NOSMA clinics in 2014-2016 and signed informed consent to participate in the study. The average age of patients was 64.2 ± 0.98 years, the average disease duration was 6.12 ± 0.37 years. The diagnosis was made according to the diagnostic criteria of the American College of Rheumatology (ACR, 1991). The coronary heart disease (CHD) was diagnosed in accordance with the WHO criteria (1979) and supplements of the All-Union Cardiological Scientific Center (AECSC, Moscow, 1984). The arterial hypertension (AH) was diagnosed in accordance with the criteria of WHO / ISH (2008). Dyslipidemia was diagnosed according to the following criteria: total cholesterol level> 5.0 mmol / l; LDL> 3.0 mmol / l; HDL <1.0 mmol / l; triglycerides> 1.7 mmol / l. CCA IMC was carried out using LOGIQ F6. Normally, the normal CCA thickness is 0.5–0.8 mm. Clinical and ultrasound signs of synovitis were observed in 72 patients with OA.

The criteria for inclusion in the study were as follows: intensity of pain in the target joint ≥40 mm on a visual analogue scale (VAS), body mass index ≤40 kg / m^2, the absence of malignant neoplasms and other rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, reactive arthritis, etc.).

Contraindications for inclusion were as follows: IV Kellgren X-ray OA of the knee joint, uncontrolled hypertension, congestive heart failure, cerebral strokes, diabetes, peptic ulcer and / or duodenal ulcer in the acute stage, the presence of secondary OA.

The clinical OA parameters were assessed in all patients: severity of joint damage according to the alko-functional Leken index, points; strength of pain syndrome according to the VAS at rest and when walking, mm; functional joint insufficiency, stiffness and pain according to the WOMAC scale, mm. The data characterizing these indicators depending on the X-ray stage of OA are presented in Table 1.

TABLE I. CLINICAL PARAMETERS OF OA, DEPENDING ON ITS RADIOGRAPHIC STAGE

Clinical parameters	I stage (n=22)	II stage (n=42)	III stage (n=46)
Leken index, points	6.41±0.22	7.88±0.20; p=0.0025[a]	11.69±0.23; p=0.0000[a]
WOMAC (pain), mm	26.05±0.76	29.63±0.85 p=0.13275	41.42±0.76 p=0.0000[a]
WOMAC (stiffness), mm	9.23±0.32	11.03±0.42 p=0.0605	15.81±0.38 p=0.0000[a]
WOMAC (functional insufficiency), mm	118.86±2.87	120.97±2.54 p=0.31	151.44±1.72 p=0.0000[a]
WOMAC (global) mm	154.14±3.51	161.53±3.30 p=0.0298[a]	208.47±2.19 p=0.0000[a]
Pain at rest according to the VAS mm	48.95±1.85	52.44±1.04 p=0.1858	65.36±1.13 p=0.0000[a]
Pain while walking according to the VAS, mm	57.73±1.79	61.25±1.21 p=0.14335	73.17±1.06 p=0.0000 [a]

[a.] [a] Reliability of differences with indices at the first X-ray stage of OA

Blood was taken in the morning on an empty stomach from 8^{30} to 8^{40}, before treatment.

The study of the content of CGP-39 in the serum was carried out by the enzyme-linked immunosorbent assay (ELISA). The ELISA was carried out in a microplate format (reference values in the range of 24–125 ng/ml). The CRP content was studied by immunoturbidimetry (reference values in the range of 0.0–5.0 mg/l). Triglyceride levels (reference values in the range of 0.4–2.3 mmol/l), cholesterol (cholesterol) (reference values in the range of 2.9–5.2 mmol/l), low lipoproteins (LDL) (reference values in range 0–3.4 mmol/l) and high density (HDL) (reference values in the range of 0–1.5 mmol/l) were studied by enzymatic photometric testing. The atherogenic coefficient (AC) was calculated using the formula AC = (total cholesterol – HDL) / HDL.

Microsoft Excel 2007 and Statistica 10.0 were used for statistical processing of the data. The following values were calculated using standard methods of variation statistics of a biomedical profile: arithmetic mean (M), arithmetic mean error (m). To establish the difference in mean values in the

compared groups, the t-test was used (Student's test). Differences were significant with an error probability of p <0.05. To assess the difference of non-parametric criteria, the Mann-Whitney criterion was used. For statistical identification of dependencies, Pearson's correlation studies were carried out. Pearson's chi2 was used to assess the statistical significance of differences in relative indicators. The correlation coefficient was checked for statistical accuracy. When assessing the value of the correlation coefficient r, the generally accepted criteria were used: when r <0.4, the bond is weak, when 0.6 <r <0.8, the degree of coupling is average; when r is in the range from 0.8 to 0.95, the degree of coupling is strong. Using KRelRisk 1.1, the relative risk index was calculated.

III. Results

CGP-39 was determined in all patients and healthy volunteers. A significant increase in CGP-39 was observed in patients with OAX (p <0.001). This indicator increased both in the group of patients with OA combined with IHD, AH (p <0.001), and in the group of patients with OA without comorbidity (p <0.001). With an increase in the degree of severity of OAXc, concentration of CGP-39 in the serum increased. The highest level of CGP-39 was in patients with the third stage gonarthrosis accompanied by reactive synovitis (Figure 1.2).

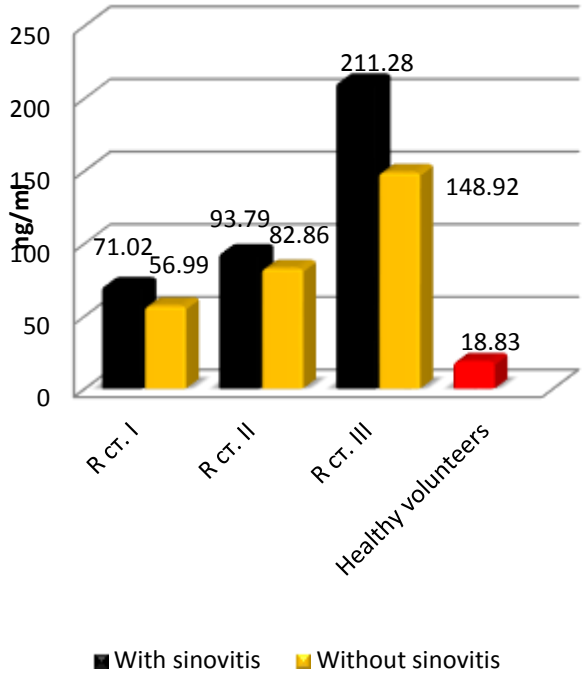

Fig. 1. CGP-39 in patients with OA combined with IHD, AH, depending on the stage of the disease and joint inflammation

In order to identify the relationship between the level of CGP-39 and the main clinical and functional indicators of patients with OA combined with the coronary artery disease, hypertension, the correlation analysis was carried out. There was a correlation between CGP-39 and WOMAC severity of pain (r =, 7676, p =, 000), CGP-39 and WOMAC stiffness (r =, 7037, p =, 000), CGP-39 and WOMAC functional insufficiency (r =, 7623, p =, 000), CCGP-39 and WOMAC global (r =, 8049, p =, 000), CCGP-39 and YOUR rest pain (r =, 7373, p =, 000), GP -39 and VAS pain when walking (r =, 7118, p =, 000). The most intense relationship was established between the Leken index and CGP-39 (r =, 8876; p =, 000).

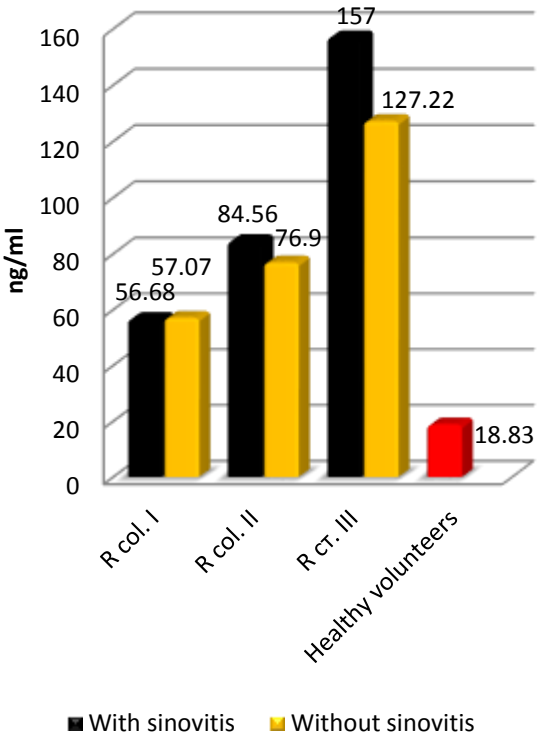

Fig. 2. CGP-39 in patients with OA without comorbidity, depending on the stage of the disease and joint inflammation

The correlation analysis was carried out between CGP-39 and the parameters studied in patients with OA without comorbidity. Direct reliable correlations between CGP-39 and WOMAC pain severity (r=, 8191, p =, 000), CGP-39 and WOMAC stiffness (r =, 7692, p =, 000), CGP-39 and WOMAC functional deficiency (r =, 8293, p =, 000), CCGP-39 and WOMAC global (r =, 8659, p =, 000), CGP-39 and VAS rest pain (r =, 7897, p =, 000), CGP-39 and VAS pain when walking (r =, 8289, p =, 000) were identified. The strongest correlations were found between CGP-39 and the Leken index (r =, 9240; p =, 000), as well as between CGP-39 and the third stage of the PACS (r =, 9210; p =, 000). These results suggest that CGP-39 may reflect KNOA severity.

Table 2 shows the results of the lipid spectrum of patients with OA combined with IHD and AH.

Patients with the second stage gonarthritis showed a statistically significant increase in some lipid profile parameters, in particular total cholesterol (p = 0.0026), LDL (p = 0.0000), and triglycerides (p = 0.0013). Patients with the third stage revealed a significant change in all indicators of the lipid spectrum which indicates the presence of dyslipidemia.

Lipid homeostasis dysregulation was observed in patients with OA in combination with IHD and AH. It is one of the leading pathophysiological mechanisms for the development of OA and atherosclerosis.

Table 3 presents the results of the lipid spectrum of patients with OA without comorbidity.

In patients with the second radiological stage of gonarthritis, changes in the lipid spectrum were not reliable. Only in patients with synovitis triglycerides (p = 0.0111) and CA (p = 0.0078), the lipid spectrum increased. Table 3 shows how cholesterol (p = 0.0159), triglycerides (p = 0.0027), and CA (p = 0.0148) in patients with the third stage of gonarthrosis increased compared with patients with the first stage of gonarthritis, regardless of synovitis, which may indicate the presence of dyslipidemia. When analyzing the blood lipid spectrum by OA stages without comorbidity, the indicator of total cholesterol, triglycerides and CA significantly increased in patients with the third stage of gonarthritis, which suggests that dyslipidemia influences the OA pathogenesis violating cellular metabolism in the cartilage.

Table 4 presents the measurements of the CCA IMC thickness in patients with OA combined with IHD, AH.

TABLE II. EVALUATION OF THE LIPID SPECTRUM IN PATIENTS WITH KNEE OSTEOARTHRITIS IN COMBINATION WITH CORONARY ARTERY DISEASE, HYPERTENSION[A]

Indicator	Cholesterol	LDL	HDL	Triglycerides	CA
I stage	5.03±0.10	3.43±0.03	1.26±0.01	1.71±0.17	2.94±0.10
I stage with synovitis	5.35±0.06	3.50±0.00	1.24±0.02	2.26±0.06	3.23±0.08
I stage without synovitis	4.57±0.10	3.32±0.05	1.28±0.01	0.92±0.19	2.53±0.10
II stage	5.34±0.07	3.55±0.01	1.24±0.01	12.32±0.05	3.22±0.12
	p=0.0026[a]	p=0.0000[a]	p=0.0871	p=0.0013[a]	p=0.0732
II stage with synovitis	5.64±0.07	3.59±0.01	1.21±0.01	2.49±0.03	3.65±0.06
	p=0.0049[a]	p=0.0000[a]	p=0.0886	p=0.0025[a]	p=0.0002[a]
II stage without synovitis	5.10±0.08	3.52±0.01	1.26±0.01	2.19±0.07	2.89±0.16
	p=0.0003[a]	p=0.0000[a]	p=0.0856	p=0.0000[a]	p=0.1461
III stage	6.61±0.08	3.84±0.03	1.20±0.01	2.66±0.03	4.51±0.08
	p=0.0000[a]	p=0.0000[a]	p=0.0043[a]	p=0.0000[a]	p=0.0000[a]
III stage with synovitis	6.80±0.07	3.92±0.04	1.20±0.01	2.75±0.03	4.70±0.07
	p=0.0000[a]	p=0.0000[a]	p=0.008[a]	p=0.0000[a]	p=0.0000[a]
III stage without synovitis	6.19±0.13	3.66±0.03	1.21±0.01	2.44±0.04	4.09±0.11
	p=0.0000[a]	p=0.0000[a]	p=0.0005[a]	p=0.0000[a]	p=0.0000[a]

[b.] [a] Reliability of differences with indices at the first X-ray stage of OA

TABLE III. EVALUATION OF THE LIPID SPECTRUM IN PATIENTS WITH KNEE JOINT OSTEOARTHRITIS WITHOUT COMORBIDITY IN COMBINATION WITH THE CORONARY ARTERY DISEASE, HYPERTENSION [A].

Indicator	Cholesterol	LDL	HDL	Triglycerides	CA
I stage	5.34±0.14	3.37±0.25	1.27±0.02	1.31±0.12	3.19±0.12
I stage with synovitis	5.48±0.07	3.58±0.04	1.28±0.01	1.34±0.02	3.32±0.06
I stage without synovitis	5.20±0.21	3.15±0.45	1.27±0.02	1.27±0.17	3.07±0.18
II stage	5.56±0.11	3.72±0.13	1.21±0.02	1.79±0.12	3.60±0.07
	p=0.4417	p=0.4775	p=0.0804	p=0.17725	p=0.0732
II stage with synovitis	5.70±0.10	3.65±0.16	1.24±0.02	1.87±0.14	3.60±0.06
	p=0.1386	p=0.7452	p=0.1580	p=0.0111[a]	p=0.0078[a]
II stage without synovitis	5.09±0.22	3.98±0.10	1.11±0.04	1.53±0.28	3.60±0.29
	p=0.07449	p=0.2128	p=0.0029	p=0.3323	p=0.1368
III stage	6.55±0.12	4.18±0.28	1.18±0.03	2.36±0.14	4.60±0.21
	p=0.0159[a]	p=0.1711	p=0.3736	p=0.0027[a]	p=0.0148[a]
III stage with synovitis	6.72±0.10	4.02±0.06	1.15±0.03	2.35±0.20	4.89±0.20
	p=0.0000[a]	p=0.0000[a]	p=0.0030[a]	p=0.0002[a]	p=0.0000[a]
III stage without synovitis	5.09±0.22	4.62±0.06	1.26±0.01	2.38±0.16	3.83±0.08
	p=0.0317[a]	p=0.0737	p=0.7441	p=0.0052[a]	p=0.0295[a]

[c.] [a] Reliability of differences with indices at the first X-ray stage of OA

The CCA IMC thickness in patients of the main group significantly increased depending on the stage of gonarthritis. The highest rates were observed in patients with the third stage of OA which confirms the clinical and pathogenetic relationship of osteoarthritis and atherosclerosis (Table 4).

Table 5 presents the measurements of the CCA IMC thickness in patients with OA without comorbidity.

The thickness of the right and left CCA IMC in patients with OA without comorbidity increased depending on the

stage of gonarthritis. The highest rates were observed in patients with the third stage of OA (Table 5).

The main group and the OA group without comorbidity were compared.

TABLE IV. EVALUATION OF CCA IMC THICKNESS IN PATIENTS WITH OA IN COMBINATION WITH IHD, AH

Indicator	Right CCA IMC	Left CCA IMC
I stage	0.7±0.03	0.75±0.03
I stage with synovitis	0.71±0.03	0.76±0.03
I stage without synovitis	0.68±0.04	0.73±0.04
II stage	0.81±0.03 **p=0.0123**	0.87±0.03 **p=0.0067**
II stage with synovitis	0.86±0.04 **p=0.0063**	0.93±0.04 **p=0.0024**
II stage without synovitis	0.77±0.03 p=0.0844	0.82±0.03 p=0.0844
III stage	1.06±0.03 **p=0.0001**	1.13±0.03 **p=0.0001**
III stage with synovitis	1.11±0.04 **p=0.0001**	1.2±0.04 **p=0.0001**
III stage without synovitis	0.94±0.02 **p=0.00002**	0.98±0.03 **p=0.0001**

TABLE V. EVALUATION OF CCA IMC THICKNESS IN PATIENTS WITH OA WITHOUT COMORBIDITY

Indicator	Right CCA IMC	Left CCA IMC
I stage	0.61±0.03	0.67±0.03
I stage with synovitis	0.65±0.05	0.7±0.10
I stage without synovitis	0.60±0.04	0.66±0.04
II stage	0.77±0.01 p=**0.000036**	0.83±0.02 p=**0.0002**
II stage with synovitis	0.77±0.02 p=**0.044135**	0.82±0.02 p=0.2604
II stage without synovitis	0.78±0.03 p=**0.006982**	0.85±0.03 **p=0.0052**
III stage	0.89±0.02 p=**0.00001**	0.95±0.02 **p=0.0000**
III stage with synovitis	0.90±0.02 **p=0.0024**	0.96±0.02 **p=0.0381**
III stage without synovitis	0.87±0.03 **p=0.001**	0.9±0.01 **p=0.0006**

In patients of the main group, the symptoms of gonarthritis were more pronounced, and the indicators of CGP-39, CRP, CA, IMC were higher which indicates the clinical and pathogenetic relationship of osteoarthritis and atherosclerosis (Table 6).

To identify the relationship between the content of CGP-39 and laboratory parameters in patients with OA without comorbidity, a correlation analysis was performed. A significant direct correlation was observed between CGP-39 and CRP (r =, 8622, p =, 000), CGP-39 and ESR (r =, 7375, p =, 000), CGP-39 and cholesterol (r =, 7827 , p =, 000), CGP-39 and CA (r =, 8356, p =, 000), right CCA IMC thickness (r =, 8024, p =, 000), left CCA IMC thickness (r =, 7822, p =, 000).

TABLE VI. PAIN SYNDROME, INDICATORS OF INFLAMMATION, LIPID SPECTRUM, CCA IMC THICKNESS

Indicator	OA with comorbidity (main group)	OA without comorbidity (control group)	p
Rest pain VAS	56.76±1.05 (n=110)	51.045±1.18 (n=30)	**p=0.0004**
Walking pain VAS	65.16±1.02 (n=110)	59.5±1.09 (n=30)	**p=0.0002**
WOMAC index	178.50±3.10 (n=110)	163.29±4.00 (n=30)	**p=0.003**
Leken index	9.04±0.27 (n=110)	7.9±0.3 (n=30)	**p=0.005**
ESR	16.94±0.41 (n=110)	17.46±0.47 (n=30)	p=0.4
CRP	5.78±0.09 (n=110)	5.4±0.07 (n=30)	**p=0.0011**
CGP-39	124.01±6.56 (n=110)	90.7±5.57 (n=30)	**p=0.0002**
CA	3.67±0.09 (n=110)	3.15±0.13 (n=30)	**p=0.0013**
Right CCA IMC	0.88±0.02 (n=110)	0.77±0.02 (n=30)	**p=0.0001**
Left CCA IMC	0.94±0.02 (n=110)	0.82±0.02 (n=30)	**p=0.0001**

To identify the relationship between CGP-39 levels with other parameters in patients with OA in combination with IHD and AH, a correlation analysis was performed. A significant direct correlation was observed between the content of CGP-39 and the levels of CRP (r =, 8949, p =, 000), ESR (r =, 6925, p =, 000), XC (r =, 8970, p =, 000) and CA (r =, 8269, p =, 000), thi right CCA IMC thickness (r =, 6974, p =, 000), left CCA IMC thickness (r =, 7122, p =, 000).

IV. DISCUSSION

Increased blood levels of CGP-39 are associated with inflammatory diseases and active tissue remodeling such as tumors, asthma, rheumatoid arthritis, osteoarthritis and

atherosclerosis. As a rule, the CGP-39 level is a sign of poor disease prognosis [14, 21, 22]. CGP-39 is a very promising prognostic marker for a wide range of diseases.

One study examined the level of CGP-39 as a death prognostic factor in patients with CVD. The study was conducted to assess the risk of CVD death in people over 50. 369 people aged from 50 to 89 years were examined (the laboratory screening, including general and biochemical blood tests, urinalysis, lipid spectrum analysis, highly sensitive CRP analysis, natriuretic peptide and creatinine analysis, and CGP-39 analysis). The median of the observation period was 5 (0.17–5.28) years. It was found that in patients with elevated levels of CGP-39 without diabetes mellitus and CVD, the relative death risk was 1.57 (95 % confidence interval 1.12–2.23, p = 0.009). The analysis confirmed that CGP-39 is an independent predictor of mortality and an unfavorable prognostic factor in a population over 50 [15].

The study showed that in people with OA, the CGP-39 level is high. In patients with the third radiological stage of OA, the CGP-39 content was significantly higher than in patients with the first and second stages of OA. The highest level of CGP-39 is associated with synovitis.

The correlation between CGP-39 and clinical gonarthrosis parameters (VAS rest and walking pain), Leken index and global WOMAC allow for conclusion that the CGP-39 level may reflect OA severity.

The direct correlation between CGP-39 and ESR, CRP, XC, CA, and CCA IMC thickness was identified. The most pronounced dependence was established between CRP, cholesterol and CGP-39 which reflect the presence of inflammation which is an integral component of atherosclerosis pathogenesis and OA.

V. Conclusion

The concentration of CGP-39 is closely related to the severity of pain and functional insufficiency, reflects the severity of OA and can be a marker of the disease. The synovitis is characterized by an increase in the concentration of CGP-39 which confirms its proinflammatory activity. The highest rates of CGP-39 were found in patients with OA in combination with IHD, AH which indicates the participation of this protein in articular pathology and atherogenesis. The concentration of CGP-39 can be regarded as a risk factor and progression of atherosclerosis which is confirmed by the reliable correlation with the atherogenic coefficient and the CCA IMC thickness. An increase in the concentration of CGP-39 is a result of catabolic processes in the cardiovascular and musculoskeletal systems. The age of the patients and comorbidity suggest that these diseases have common pathogenetic mechanisms that are able to induce progression of both cardiovascular and articular pathologies.

This study is relevant for our republic, as it makes it possible to prevent comorbid conditions.

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