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Pathogenetic associations of galectin-3 levels with chronic heart failure severity parameters in patients with osteoarthritis

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Chronic heart failure (CHF) is a disease that negatively affects the prognosis of patients. The presence of aggravating (comorbid) conditions, in particular connective tissue disorders, can aggravate the course of heart failure (HF). Modern immunologic markers can be used for additional assessment of the severity of the CHF course.
The aim of the study was to investigate possible associations of galectin-3 with laboratory and instrumental parameters in patients with CHF and osteoarthritis (OA).
Methods. A one-stage cross-sectional study was performed in 115 patients with CHF who were undergoing outpatient follow-up: 65 patients — the study group with CHF and knee OA and 50 patients — the group with CHF without OA. A comparative analysis of laboratory and instrumental parameters reflecting the severity of OA progression and galectin-3 in both groups was performed, as well as the search for possible associations of galectin-3 with parameters reflecting the severity of CHF. The results of the comparative analysis are presented as median (Me) with first (Q1) and third (Q3) quartiles based on the Mann-Whitney test. The method of linear regression analysis was used to analyze the characteristics of the analyzed associations between several parameters. The critical level of significance of the statistical hypotheses evaluated was $p<0.05$. Comparison of frequency differences in the analyzed groups was performed using the χ^2-Pearson test.
Results. Significant differences in creatinine levels, glomerular filtration rate (GFR), changes in lipidogram parameters were found between the studied groups. Higher rate of left ventricular hypertrophy (LVH), higher values of left ventricular myocardial mass index and ratio of transmitral flow parameters were found in the studied group (CHF and OA) compared to patients with CHF without OA. A statistically significant increased level of galectin-3 was found in the group of patients with CHF and OA compared to patients without OA: 39.4 (30.3 — 68.2) and 19.1 (15.5 — 8.4) ng/mL, respectively. Also in the group of patients with

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CHF and OA, a logistic regression model was constructed with galectin-3 levels and parameters reflecting the severity of the CHF course.

Conclusion. Chronic low-intensity inflammatory process, as exemplified by OA, may significantly worsen the course of CHF. The increased level of galectin-3 and its association with parameters reflecting the severity of the HF course in the group of patients with CHF and OA may indicate more pronounced myocardial fibrosis and a higher risk of adverse outcomes compared to patients without OA.

Keywords: chronic heart failure, osteoarthritis, comorbidity, galectin-3

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Introduction

In recent years, a substantial amount of data has accumulated in the literature regarding the pathogenetic aggravating associations of cardiovascular diseases (CVD) with osteoarthritis (OA). According to meta-analyses including 15 studies with 32,278,744 participants, the prevalence of cardiovascular pathology in patients with OA ranges from 24 % to 39 %. These patients have been reported to have an increased risk of CVD, including coronary heart disease (CHD), arterial hypertension (AH), and chronic heart failure (CHF) [1–3]. The increased risk of CVD development with the background of OA is caused by a number of factors: chronic non-infectious inflammation of low severity, which leads to a progression of endothelial dysfunction and development of atherosclerosis; constant intake of painkillers — non-steroidal anti-inflammatory drugs, leading to deterioration of renal function, fluid retention in the body; decreased physical activity [4]. These factors lead to the development of AH or worsen the course of existing one [5]. The presence of CVD and OA in patients is often associated with the presence of obesity [6].

The study of the progression of CHF in patients with OA is currently trending. The role of chronic inflammation in the development of CHF is actively discussed. According to the available data, proinflammatory cytokines may play a leading role in the development and progression of CHF. Patients with CHF with preserved left ventricular ejection fraction (LVEF) in the setting of pre-existing rheumatic pathology, particularly OA, should be considered as a distinct risk group [7, 8]. Immunologic cytokines, in particular galectin-3, a marker of myocardial fibrosis involved in the regulation of reactions such as cell differentiation, cell cycle and apoptosis, may provide additional information about the severity and prognosis of such patients. The study of its properties in patients with CHF and OA may be valuable for determining additional clinical data and prognosis [9, 10].

The aim of the study was to perform a comparative analysis of laboratory and instrumental parameters of CHF in patients with and without OA, including the myocardial fibrosis marker galectin-3, and its possible associations with CHF severity parameters.

Methods

The study included 65 patients with CHF and OA; 50 patients with CHF and without OA. Examination and enrollment into the study were carried out in the therapeutic and rheumatological departments of the Irkutsk City Clinical Hospital No. 1. When patients were included in the study, individual consultations were conducted in accordance with the ethical principles required by the Declaration of Helsinki of the World Medical Association, revised in 2013. The work was approved by the protocol of the local ethics committee of the above-mentioned hospital, on the basis of structural subdivisions where the inclusion of patients was carried out (protocol dated 05.10.2013). When agreeing to participate in the study, patients signed a voluntary informed consent.

Inclusion criteria for the study were:

— Age between 50 and 70 years;

— presence of CHF confirmed on the basis of current clinical guidelines;

— CHF developed with the background of CHD and/or hypertension;

— presence of OA confirmed on the basis of current clinical guidelines;

Exclusion criteria for the study were:

— severe course of CHF (Functional classes (FC) III and IV CHF according to NYHA);

— non-ischemic etiology of CHF;

— secondary (posttraumatic) knee OA;

— diabetes mellitus;

— GFR less than 30 mL/min/1.73m^2.

The diagnosis of CHF was confirmed based on clinical guidelines [11, 12]. The general characterization of patients is presented in Table 1.

Table 1. **Characteristics of patients**

Parameter	Groups		p	χ^2
	CHF and OA (n=65)	CHF with no OA (n=50)		
Age, years; Me (Q1 — Q3)	58 (52–65)	56 (50–63)	0.07	
CHF course duration, years; Me (Q1 — Q3)	6 (4–8)	5 (5–10)	0.08	
Patients with CHD, n (%)	65 (100%)	50 (100%)	0.1	0.01
Patients with AH and CHD, n (%)	57 (88%)	42 (84%)	0.09	0.05

Comparative analysis of the therapy taken by the patients is presented in Table 2.

Table 2. **Drug therapy taken**

Medications	Groups		p	χ^2
	CHF and OA (n=65)	CHF with no OA (n=50)		
ACE inhibitors	14 (22%)	13 (25%)	0.07	2.1
ARBs	30 (46%)	20 (40%)	0.06	1.9
Beta-blockers	65 (100%)	50 (100%)	0.1	1
MRAs	11 (17%)	10 (21%)	0.09	1.4
Statins	55 (85%)	42 (84%)	0.08	1.3

Standard laboratory and instrumental tests were performed in the study groups. The serum concentration of galectin-3 was analyzed. The obtained data were analyzed using the software STATISTICA 10.0. Evaluation of data distribution characteristics was performed using Shapiro-Wilk test. The results of comparative analysis are presented as medians (Me) with indication of first (Q1) and third (Q3) quartiles on the basis of Mann-Whitney U-test. The method of linear regression analysis was used to assess the associations of several parameters. The critical level of significance of the evaluated statistical hypotheses was $p < 0.05$. Comparison of frequency differences in the analyzed groups was performed using χ^2-Pearson test [13].

Results

The comparative analysis of echocardiographic (EchoCG) parameters showed no significant differences in the parameters compared, except for the increase in left ventricular mass index (LVMI) and the ratio of early to late mitral velocity, which was found in the group of patients with CHF and OA (Table 3).

Table 3. **Comparative analysis of morphologic parameters of myocardium**

Parameter	CHF and OA (n=65)	CHF with no OA (n=50)	p
EDD, cm; Me (Q1 –Q3)	4.44 (4.4–5.8)	4.7 (4.2–5.6)	0.5
ESD, cm; Me (Q1–Q3)	3.3 (2.4–4.2)	3.2 (2.2–4.1)	0.2
LVPW, cm; Me (Q1–Q3)	1.2 (1.1–1.4)	1.15 (1–1.3)	0.6
IVST, cm; Me (Q1–Q3)	1.2 (1.15–1.3)	1.1 (1.12–1.18)	0.2
LVMI, g/m^2, Me (Q1–Q3)	127.4 (107.8–134.3)	118.5 (104.1–125.6)	0.03
LVEF, %, Me (Q1–Q3)	45.05 (42.4–51.7)	44.2 (41.3–52.1)	0.09
E/A, Me (Q1–Q3)	1.1 (0.9–1.2)	0.9 (0.7–1.0)	0.02
LVH, n (%)	61 (95%)	46 (93%)	0.004 (χ^2 = 10.7)

Comparative analysis of the levels of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) showed no statistically significant differences between the groups studied (Fig. 1).

The analysis of laboratory parameters in the studied groups revealed statistically significant differences in erythrocyte sedimentation rate and C-reactive

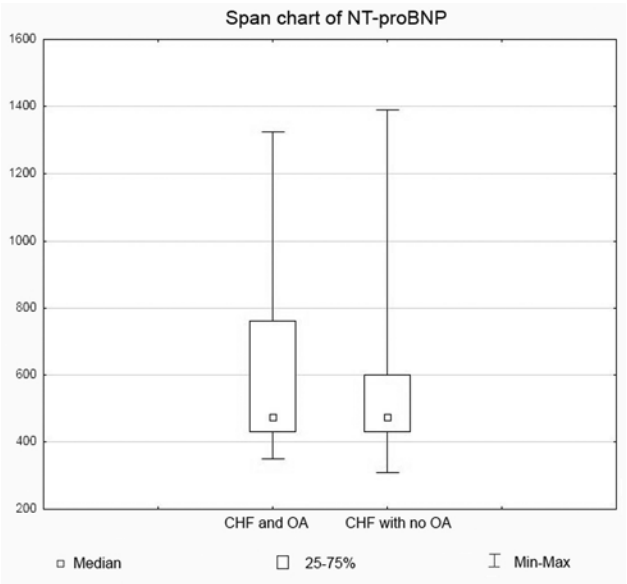

Fig. 1. Comparative analysis of NT-proBNP levels, pg/mL

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Table 4. **Comparative analysis of laboratory parameters**

Parameter	CHF and OA (n=65)	CHF with no OA (n=50)	p
Hemoglobin, g/l	112.1 (95.06 –129.2)	130.9 (119 –139.4)	0.008
Erythrocytes, 10^{12}/L	3.3 (2.05–3.9)	4.4 (3.4–4.9)	0.009
Thrombocytes, 10^{9}/L	385.9 (256.6–456.8)	372.1 (282.3–411.5)	0.07
Erythrocyte sedimentation rate, mm/h	33.6 (14.8–45.8)	7.1 (3.3–10.4)	0.001
Glucose, mmol/L	5.1 (3.7–6.1)	5.6 (4.2–6)	0.3
Glycated hemoglobin, %	5.4 (3.3–6.1)	5.3 (3.9–5.8)	0.2
Total protein, g/L	79.6 (59.01–88.4)	77.6 (56.05–85.6)	0.06
Creatinine, μmol/L	98.3 (72.5–133.2)	74.2 (65.2–111.4)	0.001
GFR, ml/min	63.2 (54.2–80.2)	74.8 (64.5–90.1)	0.004
C-reactive protein, mg/L	34.01 (14.4–54.01)	2.1 (0.3–3.2)	0.06
Potassium, mmol/L	3.9 (3.3–5.2)	4.2 (3.2–5.09)	0.09
Sodium, mmol/L	120.2 (112.9–145.2)	138.5 (114.5–142.8)	0.2
Calcium, mmol/L	2.1 (1.9–2.4)	1.9 (1.5–2.1)	0.05
Aspartate aminotransferase, IU/L	22.9 (15.5–26.5)	20.7 (16.9–28.9)	0.1
Alanine aminotransferase, IU/L	22.1 (13.09–26.3)	21.7 (14.5–25.8)	0.5
Total cholesterol, mmol/L	5.5 (4.1–6.1)	4.2 (3.4–5.1)	0.04
Triglycerides, mmol/L	2.04 (0.9–2.5)	1.5 (0.7–2.1)	0.001
LDL, mmol/L	2.4 (1.1–2.9)	1.9 (0.6–2.1)	0.04
HDL, mmol/L	0.9 (0.3–1.1)	1.3 (0.4–1.5)	0.03
Atherogenicity coefficient	5.2 (4.1–5.6)	3.3 (2.9–4.5)	0.001
Systolic BP	143.5 (132–155)	136.5 (124–149)	0.04
Diastolic BP	90.5 (70–111)	80 (65–95)	0.02

protein levels in the OA group. Significantly increased creatinine level and decreased glomerular filtration rate (GFR) were also found in the OA group. These findings are probably due to the presence of chronic inflammatory process as well as regular intake of non-steroidal anti-inflammatory drugs (NSAIDs). Changes in lipidogram parameters and higher levels of mean blood pressure (BP) were also found in the CHF and OA group (Table 4).

A significant increase in galectin-3 levels was found in the group of patients with CHF and OA compared to patients without OA (Fig. 2).

When building a regression model with the level of galectin-3 and earlier found parameters having statistically significant differences, a statistical association was obtained indicating the deterioration of these indicators with a background of increasing galectin-3 concentration (Table 5, Fig. 3).

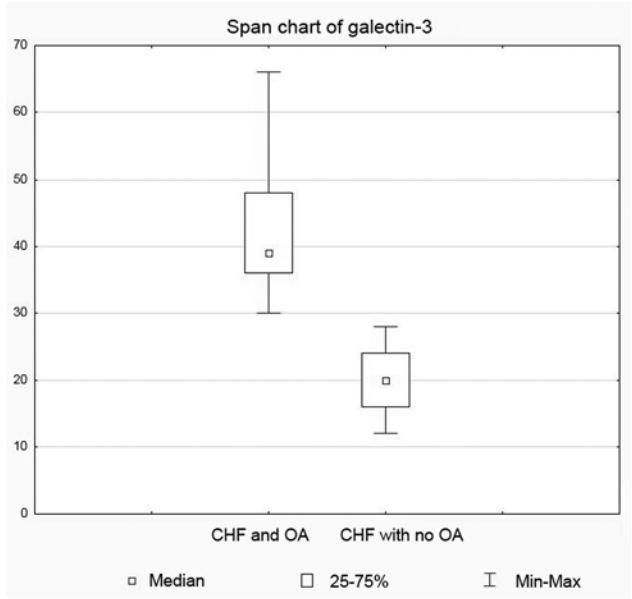

Fig. 2. Galectin-3 levels

Table 5. **Results of linear regression analysis**

Parameters	Galectin-3: Me (Q — Q3) 39.4 (30.3 — 68.2); t=2.14; p=0.043			
	r	r2	beta	p
C-reactive protein, mg/L	0.34	0.24	0.34	0.04
NT-proBNP, pg/l	0.28	0.29	0.35	0.008
Total cholesterol, mmol/L	0.3	0.4	0.44	0.006
LDL, mmol/L	0.41	0.31	0.2	0.001
LVH	0.2	0.3	0.3	0.03
LVMI, g/m^2	0.2	0.25	0.4	0.01

Discussion

Low-level chronic inflammation is thought to be a major factor in the development and progression of CHF [14]. The presence of OA in patients with CHF is a serious aggravating factor. The results of this study are consistent with this hypothesis, namely the statistically significant increased levels of galectin-3, LVMI, E/A and incidence rate of LVH compared to patients without OA. The absence of significant differences in

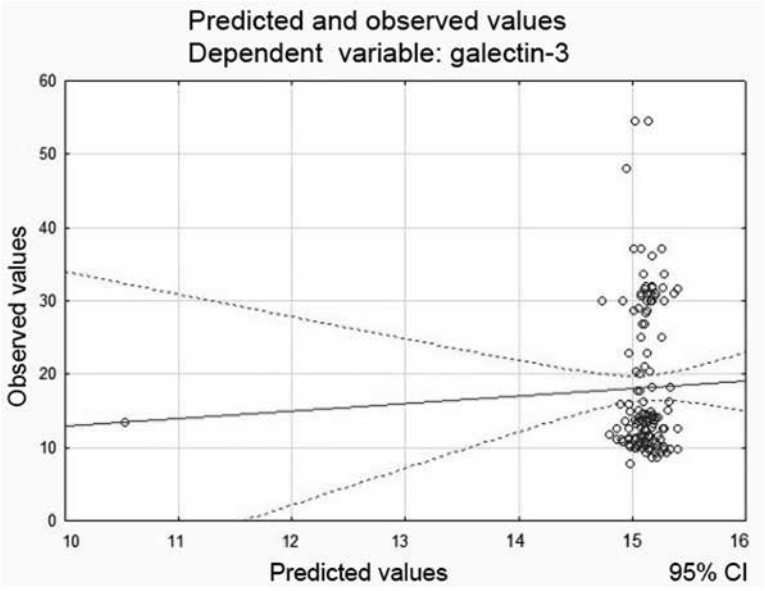

Fig. 3. Linear regression of galectin-3 with the studied parameters

NT-proBNP levels between groups may indicate the absence of clinical manifestations of CHF in the presence of the above changes.

In our opinion, the found statistically significant differences in BP levels are noteworthy. The reasons for such changes may be, on the one hand, sodium retention, constant intake of NSAIDs, as well as changes in the state of the vascular wall with the background of more pronounced changes in lipidogram parameters. This hypothesis is in accordance with the opinion of other authors working in this field. The combination of dyslipidemia, hypertension and chronic low-intensity inflammation is the most important pathogenetic comorbid combination that significantly worsens the prognosis of patients [15, 16].

For CHF patients with preserved and moderately reduced LVEF with OA, determining the prognosis is an important and open question. Given the lack of differences in many echocardiographic parameters and NT-proBNP levels, the use of immunologic markers is likely to be a relevant direction. The obtained regression model of galectin-3 with parameters such as NT-proBNP, LVH, LVMI confirms this hypothesis. However, it should be considered that this study was conducted as a single-stage cross-sectional study. Prospective studies are needed to determine the efficacy of this marker.

Conclusion

In addition to the traditional RFs of CHF decompensation, current data suggest that OA should be considered as an additional one. The presence of chronic, low-intensity, non-infectious inflammation in patients with CHF and OA leads to more pronounced myocardial fibrosis. In the present study, this hypothesis is supported by higher levels of galectin-3, LVMI and LVH. In this group of patients, galectin-3 should be considered as an additional marker for the assessment of CHF progression, according to the authors.

Conflict of interests: none declared.

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