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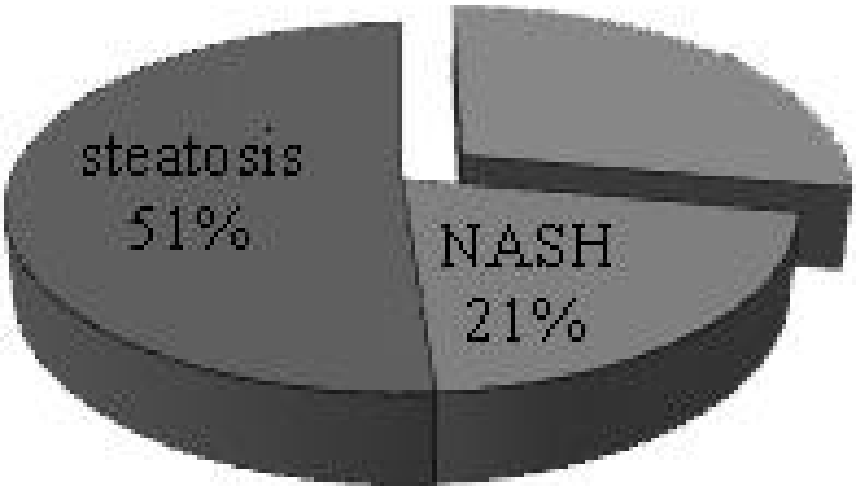

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RESEARCH ARTICLE

THE PROGNOSTIC VALUE FOR DETERMINING OF GALECTIN-3' LEVEL IN PATIENTS WITH METABOLIC SYNDROME AND NONALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

Aims: To evaluate the level of galectin-3 in patients with metabolic syndrome (MetS).
Methods: The research of level of galectin-3 has included 76 patients, 43 patients with MetS, 72, 1% (31 out of 43) from them - with nonalcoholic fatty liver disease (NAFLD), 33 patients without MetS and NAFLD.
Results: An average level of galectin-3 in the group with MetS was reliably higher compared with the group without MetS, p=0,006. Positive correlation was revealed between the level of galectin-3 and 1) Left ventricle hypertrophy - LVH (r=0,30), 2)Chronic heart failure - CHF (r=0,35), 3) Coronary heart disease (r=0,34), 4) Fraction of fibrosis of the heart (r=0,24) 5) Hepatic (r=0,43) and pancreatic (r=0,24) steatosis, 6) NAFLD fibrosis score (r=0,30), 7) The level of leptin, p<0,05.
Conclusions. The research revealed the relationship between the level of galectin-3 and the diseases, closely associated with MetS, namely LVH, CHF, fraction of fibrosis in the heart, NAFLD, pancreatic steatosis. The level of galectin-3 was higher in patients with MetS, which can be seen as evidence of more distinct fibrosis of the heart and liver in this group of patients. The galectin-3 can be used as an additional criterion for the diagnosis of cardiovascular diseases and NAFLD.

INTRODUCTION

Metabolic syndrome (MetS) is a complex of metabolic, hormonal and clinical disorders, which are risk factors of the cardiovascular and liver diseases. High prevalence of metabolic syndrome among the population older than 30 years, as well as high mortality from its complications, dictates the need for careful monitoring of such patients with a mandatory comprehensive examination and treatment. Three key moments play the most important role in further growth of MetS: inflammation, insulin resistance and as a consequence the replacement of the normal connective tissue with the formation of fibrosis.

In order to assess the degree of fibrosis in clinical practice, it is possible to use two groups of research methods: invasive and noninvasive. Noninvasive methods, namely serum markers of fibrosis, are more attractive, as fairly dynamic indicators for assessing the severity and prognosis of the disease and treatment. Investigations are underway with regard to the role and peculiarity of action of galectin-3, the amount of which increases during the process of fibrosis of various organs and tissues. At present, study is performed, to determine the role of galectin-3 as a potential marker of fibrosis of various organs, including the heart and liver.

Galectins are beta-galactoside-binding proteins with evolutionarily conserved carbohydrate-recognition domains (CRD).Each has an individual galectin active center that binds specific carbohydrates (carbohydrate specificity).Galectin-3can be localised in the cytosol and nucleus, as well as detected extracellularly.

Ligands for galectins can be extracellular matrix proteins such as laminin, fibronectin, elastin, and surface glycoproteins of cells, including integrins, cancer-embryonic antigen (CEA) and bacterial lipopolysaccharide, receptors for growth factors (epidermal fibroblast growth factor, insulin-like and platelet-derived growth factors). In addition, galectin can interact with receptors of immune cells (eg, T-cells, neutrophils, macrophages).

Among the 15 types of galectins, galectin-3 exerts pleiotropic biological functions, playing a key role in many physiological as well as pathological processes. It is involved in the development of biological events such as embryogenesis, adhesion, cell proliferation, apoptosis, mRNA splicing, bacterial colonization, modulation of the immune response, proliferation of myofibroblasts, fibrogenesis and remodeling of blood vessels and the heart (Dumic J.*et al*. 2006), Liu F. *et al*. 2002, Cooper D. 2002), as well as in the processes of fibrosis in the liver (Henderson N. *et al*. 2006).

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Main features of the structure and mechanism of action of galectin-3.The galectin-3 has a unique structure among galectins. Galectin-3 contains a «nonlectin domain», through which it aggregates into oligomers, and a single CRD, fused to an N-terminal sequence. This galectin is called «chimera type galectin». The galectin-3 revealed opposite effects on cells depending on its localization: intracellular he protects cells from apoptosis (Hoyer K. *et al*. 2004), extracellular can cause cell death (Rubinstein N. *et al*. 2004). Located outside the cell it can stimulate cell death, for example, acting on T-cells (Dumic J.*et al*. 2006).

Most of the features described for galectin-3reinforce rather than reduce the inflammatory process. These conclusions are supported by the fact that elevated levels of galectin-3 are accompanied by a variety of inflammatory diseases such as rheumatoid arthritis, Behcet's disease (autoimmune damage to small blood vessels). In addition, studies have indicated increased levels of galectin-3 in patients with obesity and MetS (Weigert J.*et al*. 2010), as well as in patients with diabetes (Yilmas H. *et al*. 2014).

Cardiovascular system and galectin-3. Cardiovascular disease and, in particular, heart failureremain the most common and complex problems in the health-care system. Traditional risk factors include: age, smoking, diabetes mellitus, and also recently began to include NAFLD. During last years, interest in the relationship of NAFLD and cardiovascular diseasessignificantly increased. According to the literature there is a direct correlation between NAFLD and the degree of left ventricle hypertrophy (Fallo F. *et al*. 2009) and occurrence of atherosclerosis, including coronary arteries (Mawatari S.*et al*. 2011), as well as the higher risk of developing coronary heart disease (Assy N. *et al*. 2010). Fibrosis is a process characterized by uniform similar arrangements, regardless of the affected organ. Therefore, fibrosis of the heart and liver are often combined. It well can be that fibrosis is a connecting pathogenetic link between chronic heart failure (CHF) and steatosis/steatohepatitis. In the light of above, role of galectin-3 as a marker of the fibrosis, is very important.

Experimental and clinical data demonstrate a correlation between the expression of galectin-3 and proliferation of myofibroblasts, fibrogenesis, tissue repair, inflammation, vascular and heart remodeling, and the severity of heart failure (Dumic J.*et al*. 2006, Liu F. *et al*. 2002, Cooper D. 2002). Increased levels of galectin-3 are associated with a higher risk of death from acute decompensation in acute and chronic heart failure (Henderson N., Sethi T. 2009). Since 2013, the galectin-3 has been included by American Heart Association as an additional marker to stratify patients into the group of high risk of adverse cardiovascular outcomes (death, rehospitalization) (Yancy C.*et al*. 2013). Thus, we can conclude that galectin-3 participates in the development of heart failure and fibrosis of the heart.

Liver and galectin-3. The fibrogenesis in the liver is a complex nonlinear dynamic process, mediated by inflammatory reactions, activation of stellate cells of the liver, destruction of hepatocytes with proliferation of connective tissue that can be observed in nonalcoholic fatty liver disease (NAFLD). In patients with MetS the probability of formation of NAFLD is assessed as high. In patients with NAFLD with subclinical inflammation in liver tissue risk of fibrosis is increased. Based on the results of some population studies, we can assume that in 60-80% of cases of "cryptogenic" cirrhosis of the liver are the outcome of NASH (Anstee Q., Day C. 2012).

According to (N. Henderson *et al*. 2006), galectin-3 may be involved in the development and regulation of liver fibrosis. In this paper, the possible activation of myofibroblasts and collagen synthesis in experimental models of liver fibrosis mutant rodents, has been described (Henderson N. *et al*. 2006), as well as the role of galectin-3 in the regulation and activation of stellate cells in vitro and in vivo. It was found that expression of galectin-3 was minimal in normal liver tissue and sharply increased at the stage of cirrhosis, regardless to the liver fibrosis' etiological factor (viral hepatitis B or C, autoimmune hepatitis, excessive accumulation of copper or iron in the body, primary biliary cirrhosis, alcoholic liver damage). This fact suggests that galectin-3 participates in the regulation of fibrosis in the liver, regardless of the initiating agent, or the stage of the disease (Henderson N. *et al*. 2006).
In another study, those mice that have been deficient for the gene of galectin-3 (detected during liver biopsy),demonstrated a decrease in signs of inflammation, damage of hepatocytes and fibrosis, decreased synthesis and deposition of fat in the liver, decreasing oxidative stress and insulin resistance were less likely to develop NASH (Iacobini C *et al*. 2011). Thus, we can conclude that galectin-3 participates in the development of NAFLD and fibrosis in the liver. In turn, NAFLD is an aggravating factor of cardiovascular diseases.

All these data, as well as interest in fibrosis in the cardiovascular system and liver in patients with metabolic syndrome, was the starting point for this study.

MATERIALS AND METHODS

This work is based on the analysis of observation results of 76 patients who were examined in Department of cardiology of University clinical hospital N 2 (I.M. Sechenov First Moscow State Medical University, Mosco w, Russia).

Out of the 76 patients included in the study, 43 patients had metabolic syndrome (MetS), of which, 72,1% were diagnosed with nonalcoholic fatty liver disease (NAFLD); 33 patients without MetS and NAFLD (control group). The average age of the 76 patients was 62,7±10,3 years in the group with MetS, and 60±14,7 years in the control group. Inclusion of patients in the group with MetS was made on the basis of IDF'main criteria (International Diabetes Federation), 2005 (http://www.idf.org/metabolic-syndrome).

All patients passed a comprehensive examination including collection of complaints, study of the history, physical examination, anthropometric measurements, laboratory tests, ECG, ultrasound of abdominal organs, echocardiography with assessment of diastolic function. The diagnosis of NAFLD was

established on the basis of exclusion of other possible causes of liver disease. Identification of markers of viral hepatitis B (HBsAg and HBeAg, anti-HBs and anti-HBe, anti-HBcorIgG and anti-HBcorIgM) and antibodies to viral hepatitis C (anti-HCV) was conducted as part of the study. In order to exclude any other possible causes of liver disease, careful assessment of the medicinal anamnesis (taking into account the acceptance of herbal remedies for the last 6 months) was conducted, past history of alcohol' intake (not more than 20 grams per day for men and 10 g/day for women) was investigated, as well as stigma and biochemical markers of alcohol consumption. The main criteria for the diagnosis of NAFLD, based on ultrasonography of abdomen, were: increase in liver size, increased echogenicity of liver, reduced sound transmission, the deterioration of the visualization of the branches of portal and hepatic veins, liver echogenicity greater than the echogenicity of kidneys, relatively reduced the density of the liver compared with the spleen (liver-to-spleen ratio<1).

Assessment of diastolic function and hemodynamics was performed via echocardiography, Doppler echocardiography and tissue Doppler studies (AcusonSequoia 512 using sector sensor 3V2Cs). Noninvasive assessment of fibrosis of the myocardium was performed during this work. Echocardiographic image in the jpeg format was recorded on Apparatus Acusón "Cardiac Difficult" (gray-scaled image, the transducer frequency of 3.5 MHz) with consequent transfer for subsequent evaluation in the computer, where they were analyzed using the software Image J 1.4 (NIH, 2009).

All the patients underwent the study of the level of galectin-3 in serum with use of enzyme-linked immunosorbent assay with help of sets "Platinum ELISA".

RESULTS

The analysis of the results anthropometric, clinical and laboratory methods of research was performed. Varying degrees of obesity, mainly abdominal (visceral) distribution of adipose tissue were significantly more frequently encountered in patients with MetS, p<0,05. The duration and degree of hypertension, and the prevalence of some cardiovascular diseases (hypertension, ischemic heart disease, heart failure, myocardial infarction in anamnesis) were more frequently met in patients with MetS in comparison with the control group (p<0,05). In addition, both groups (with MetS and control group) showed dyslipidemia (p>0,05). In the evaluation of lipid profile in patients with MetS, hypercholesterolemia and dyslipidemia caused more adverse quality changes in the composition of lipoproteins, namely hypertriglyceridemia, increased number of atherogenic low-density lipoprotein (LDL), the concentration of lipoproteins of very low density (VLDL), decreased level of high density lipoprotein (HDL) compared with the control group (p<0,05). These changes are considered as predictors of cardiovascular events.

Disorders of carbohydrate metabolism (namely diabetes mellitus type 2 (25,6%) and impaired glucose tolerance (27,9%)) were diagnosed only in the group with MetS in 53,5% of cases (p<0,001). Ultrasound criteria of steatosis was detected only in 72,1% of the main group and not detected in the control group at all, p<0,001 (Figure 1). The most frequent laboratory indication of nonalcoholic steatohepatitis (NASH) was increased activity of serum alanine and aspartate aminotransferase (ALT, AST> 40 U/l). Thus, NASH was detected in 20,9% of patients in the MetS group. In addition, steatosis of the pancreas by ultrasound of abdominal organs was diagnosed in 34,9% of patients in group with MetS and was not detected in the control group, p<0,001.

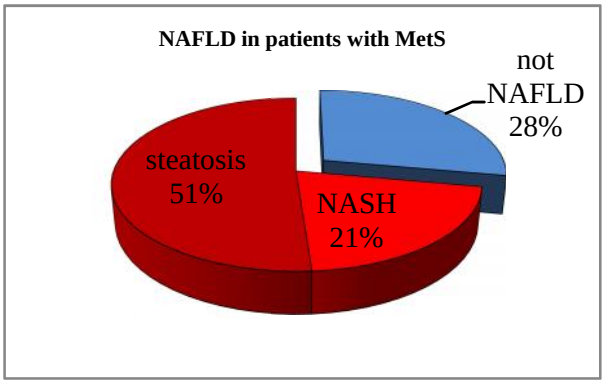

Figure 1 The frequency of NAFLD (steatosis and NASH) in patients with MetS.

While comparing two groups, according to the results of echocardiography, the following results were obtained: left ventricle hypertrophy of the myocardium (LVH), increased heart size, increased interventricular septum, narrowing of the diameter of the aortic root, as well as signs of atherosclerosis, increased thickness of epicardial adipose tissue and reduced ejection fraction of the left ventricle (LV),those factors were significantly more frequently encountered in the MetS group compared with the control group (p<0,05).

LVH was detected in 74,4% of cases in patients with MetS and in 30,4% in patients without MetS (p<0,001). As a result of echocardiographic index of diastolic function of LV (E/A) evaluation, there were significant differences identified in the frequency of diastolic dysfunction in patients with MetS - 88,4% compared to 45,5% in the group without MetS (p<0,001). Thus, impaired LV relaxation and obstruction of outflow of blood from the left atrium, were significantly more frequently met in patients in the MetS group. Chronic heart failure (CHF) was diagnosed in 81,4% of patients with MetS and in 51,5% of the control group (p=0,006).

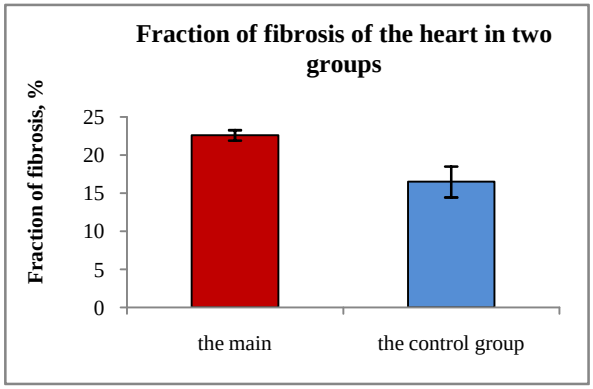

Figure 2 The average value of the fraction of fibrosis of the interventricular septum in the MetS and control groups with 95% confidence intervals (CI), p<0,001.

The results of the research showed that the average volume fraction of fibrosis in the interventricular septum was significantly different in the groups studied (22,6±4,45% in the group with MetS and 16,5±3,95% in the control group without MS, p<0.001). Figure 2. More pronounced fibrosis of LV myocardium in patients with MetS, possibly can be explained by long history of arterial hypertension (AH) of the patients, and aggravating role of metabolic disorders on metabolic syndrome. Thus, in patients with hypertension, average values of the fraction of fibrosis of the interventricular septum was amounted to 21,16±4,45%, in patients without hypertension – 12,84±3,14%. Figure 3.

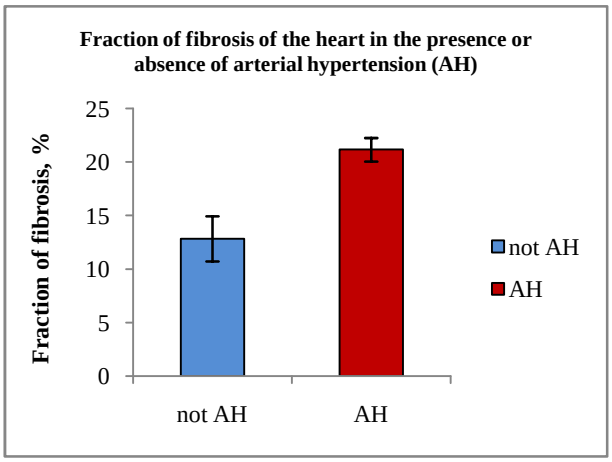

Figure 3 Fraction of fibrosis of the heart in the presence or absence of arterial hypertension (AH) with CI 95%, p<0,001.

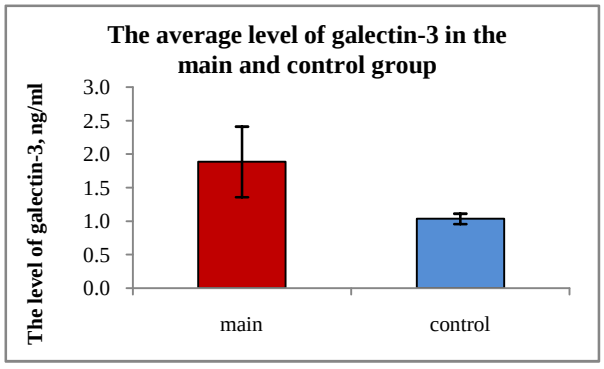

Figure 4 The average level of galectin-3 in the main and control groups with CI 95%, p=0,006.

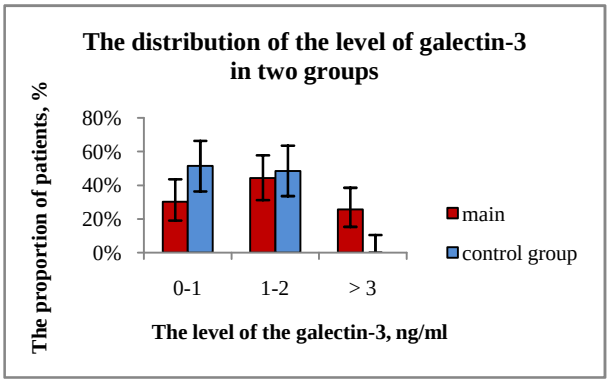

Figure 5 The distribution of the level of galectin-3 in two groups: with MetS (main) and without MetS (control).

After conducting a comprehensive survey of all patients, the level of galectin-3 was investigated.

The average level of galectin-3 in the group with MetS was significantly higher and amounted to 1,89±1,71 ng/ml, compared to the group without MetS – 1,03±0,22 ng/ml, p=0,006 (Figure 4).

Figure 5 presents the distribution of the level of galectin-3 in two groups.

In the control group the maximum value of the level of galectin-3 was 1,5 ng/ml, while in the group of patients with MetS, 27 % of patients had the value of galectin-3 greater than 3 ng/ml (maximum value was 8.5 ng/ml).

Positive correlations have been revealed between the level of galectin-3 and:

1. Chronic heart failure (r=0,35, p=0,040) (Figure 6);
2. Left ventricle hypertrophy (LVH) of the myocardium (r=0,3, p=0,004) (Figure 7);
3. Functional class (FC) coronary heart disease (CHD) (r=0,35, p=0,012), when with increasing functional class CHD, the level of galectin-3tends to increase (Figure 8);

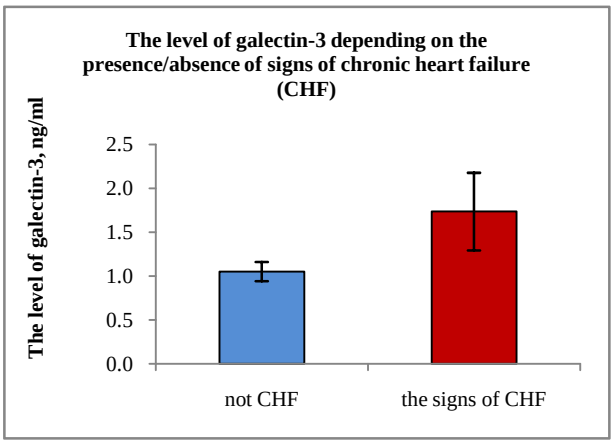

Figure 6 The level of galectin-3, depending on the presence/absence of signs of chronic heart failure (CHF) with CI 95%, p=0,04.

4. Fraction of fibrosis of the heart (r=0,24, p=0,011). Due to the strong non-compact distribution of the level of galectin-3 in the study of correlations, we have moved from initial values of galectin-3 to their decimal logarithms (log10). Figure 9 demonstrates a direct correlation between the fraction of fibrosis of the heart and the level of galectin-3, leading to the conclusion that increasing of the concentration of galectin-3 tends to increase the fraction of fibrosis of the heart.
5. Hepatic (r=0,43, p=0,002) and pancreatic (r=0,24, p=0,037) steatosis. As shown in Figure 10, increase of concentrations of galectin-3 lead to growth of the proportion of patients with steatosis of the liver. At the level of galectin-3 over 3 ng/ml, more than 80% of patients with MetS showed hepatic steatosis.
6. The level of leptin (r=0,31, p=0,018) (Figure 11).

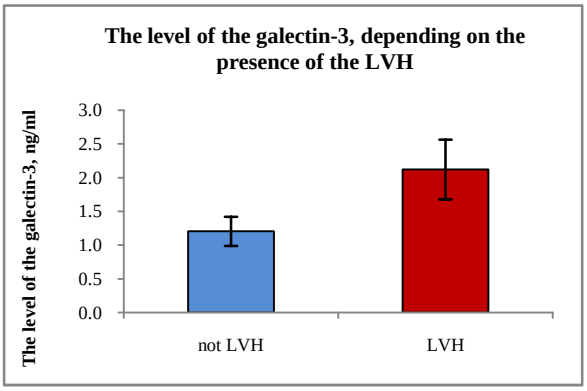

Figure 7 The level of galectin-3, depending on the presence of the LVH with CI 95% (p=0,004).

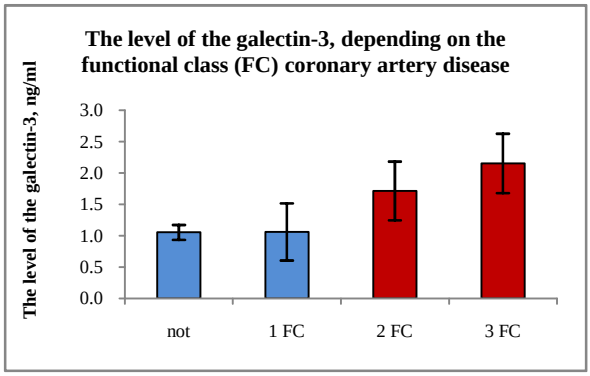

Figure 8 The distribution of the level of galectin-3, depending on functional class (FC) coronary heart disease (NYHA), CI 95%, p=0,040. Between not (1 FC) coronary artery disease and 3 (4) FC significant differences (p<0,05).

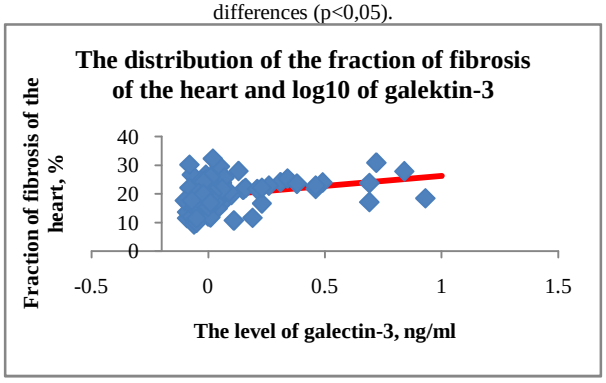

Figure 9 The distribution of the fraction of fibrosis of the heart and log10 of galectin-3 (r=0,24, p=0,011).

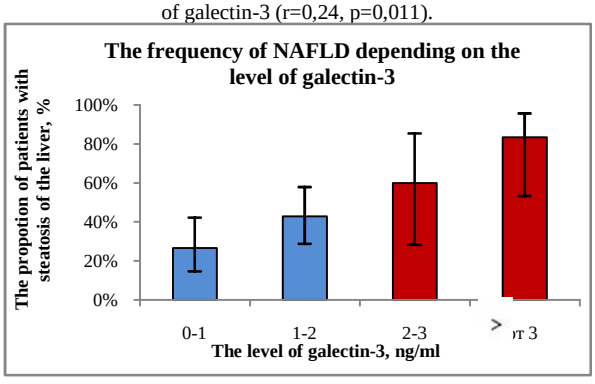

Figure 10 The frequency of hepatic steatosis depending on the level of galectin-3 with CI 95%. Between the level of the leptin 0-1 (1-2) and 2-3 (>3) significant differences (p<0,05).

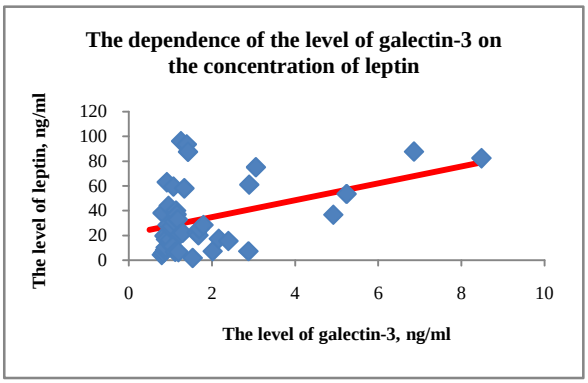

Figure 11 The distribution of the level of galectin-3, depending on the concentration of leptin (r=0,31, p=0,018).

Also, a link between the level of galectin-3 and NAFLD fibrosis score (r=0,23, p=0,05) was identified. The rating scale of the degree of liver fibrosis in NAFLD (NAFLD fibrosis score) was calculated based on the published formula (http: //nafld - core.com).

Thus, the correlation between the level of galectin-3 in serum and clinical markers of fibrosis of the heart (LVH, CHF, ischemic heart disease, the fraction of fibrosis of the heart) and liver (hepatic steatosis on ultrasound criteria NAFLD, and NAFLD fibrosis score) was detected.

CONCLUSIONS

Metabolic syndrome – systemic disease in which inflammation and fibrosisplaythe main role, and these pathological processes affect many organs and tissues. At the moment, there are a number of works devoted to the influence of galectin-3 on the development and progression of fibrosis of various organs.

1. In this research, we identified the relationship between the level of galectin-3 on the one hand, and pathology of the cardiovascular system (LVH, CHF, ischemic heart disease), liver disease (hepatic steatosis, a scale for assessing the degree of fibrosis in NAFLD (NAFLD fibrosis score) and steatosis of the pancreas) in patients with MetS, on the other hand.
2. All patients from the MetS group had significantly higher levels of galectin-3, which can be seen as evidence of more pronounced fibrosis of the heart and liver in this group of patients.
3. Serum marker of fibrosis (galectin-3) may be a valuable molecule for assessing the prognosis and the effectiveness of therapy in patients with MetS.

Abbreviations

AH - arterial hypertension
LVH - left ventricle hypertrophy of the myocardium
CHD – coronary heart disease
MetS - metabolic syndrome
NAFLD - nonalcoholic fatty liver disease
NASH – nonalcoholic steatohepatitis
FC - functional class
CHF - chronic heart failure

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