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Assessing the Level of N-terminal Pro-peptide of Type III Collagen in Patients with Chronic Heart Failure and Metabolic Syndrome

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Abstract The development and progression of heart failure accelerate obesity, disorders of carbohydrate and lipid metabolism. These states are united by the term "metabolic syndrome". The hepatic manifestation of the metabolic syndrome is a non-alcoholic fatty liver disease (NAFLD). The combination of NAFLD and cardiovascular disease leads to increased risk of cardiovascular complications and has a significant impact on the prognosis and outcome of CHF. A key factor in the pathogenesis and progression of CHF is myocardial remodeling. The metabolic products of collagen (N-terminal pro-peptide of type III collagen) are considered as promising candidates for markers of myocardial remodeling and development of heart failure. In a number of papers increased level of PIIINP is a predictor of cardiac mortality or rehospitalization due to decompensation of heart failure associated with an increased risk of death. **Materials and Methods**: The study group included 39 patients with CHF and MS. The control group included 38 patients with chronic heart failure, without the metabolic syndrome. In all patients the diagnosis of heart failure was confirmed by quality measuring the NT-proBNP. The severity of the clinical manifestations of heart failure, functional status of the patient were assessed. All patients underwent biochemical blood tests. The size of the heart chambers, wall thickness of the myocardium and epicardial fat were estimated by echocardiography. All the patients underwent the calculation of Fatty Liver Index, NAFLD Fibrosis Score. **Results:** The level of the main group PIIINP is 3,3 ± 1,5 g / l; in the control group - 2,3 ± 1,3 g / l ($p = 0,00046$). Statistical analysis revealed significant correlation ($p<0.05$) between laboratory data and PIIINP: the level of uric acid, glucose level, GFR, value FLI, NFS; between the data of echocardiography and PIIINP: thickness of epicardial fat, IVS thickness, LV myocardial mass, RA dimensions, LA, ESD LV, ratio E / A, ratio E / e. **Conclusions:** The use of PIIINP in clinical practice will identify patients with CHF and MS with structural and functional changes in the myocardium in the early stages of the disease. Also the determination of the level of PIIINP in patients with CHF and MS will allow identifying patients with liver disease and selecting the ones for further assessment and selection of therapy taking into consideration attendant pathology.

Keywords: *chronic heart failure, metabolic syndrome, fibrosis, N-terminal pro-peptide of type III collagen, non-alcoholic fatty liver disease, Fatty Liver Index, NAFLD Fibrosis Score, non-invasive evaluation of hepatic steatosis, non-invasive assessment of liver fibrosis*

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1. Introduction

Chronic heart failure (CHF) is considered to be one of the major health problems in many countries of the world including Russia. Worldwide, heart failure affects more than 23 million people. In Russia, according to the trial " EPOCHA-O-CHF" - 7.9 million people [1,2,3].

Taking into account its popularity, CHF acquired epidemic characteristics and the economic damage of this disease is increasing every year. The Russian Federation spends from 55 to 295 billion roubles per year on the treatment of heart failure and the expenses on hospitalization for heart failure decompensation reach 184.7 billion. rub. [4].

The development and progression of heart failure accelerate obesity, disorders of carbohydrate and lipid metabolism. Today, these states are united by the term "metabolic syndrome" (MS). Metabolic changes that occur in MS, lead to structural and functional changes of the myocardium, blood vessels, the emergence and progression of hypertension and higher risk of developing coronary heart disease and heart failure [21,22,23].

The clinical manifestations of MS are varied and do not fit into the framework of one nosological diagnosis. There are several variants of the clinical course of MS (hypertension, coronary, diabetic, liver, gallstones, dyslipidemic and mixed version of MS). Thus, the basis of the clinical classification of MS variants is associated with MS diseases united by a common etiopathogenetic mechanism of MS - insulin resistance [22,23,24].

The hepatic manifestation of the metabolic syndrome is a non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease is pathological changes in the liver including steatosis, nonalcoholic steatohepatitis (NASG) with or without fibrosis and cirrhosis with its complications. The combination of NAFLD and cardiovascular diseases leads to increased risk of cardiovascular complications and has a significant impact on the prognosis and outcome of CHF [5].

Remodeling of the myocardium is a key part of the pathogenesis of heart failure. A key factor in the pathogenesis and progression of CHF is myocardial remodeling (RM). Prolonged exposure to a variety of physiological and pathogenic factors in the heart results in remodeling of the myocardium.

In CHF there are changes in the myocardium both in cardiomyocytes (CMC) and in the extracellular matrix (ECM). Basic proteins of ECM are presented by collagen type I (50%) and type III collagen (45%). Collagen types I and III are synthesized from procollagen precursors (PIP, TIMP-1) containing the C-terminal propeptide of procollagen type-I [PICP] and N-terminal propeptide of procollagen type III [PIIINP] [7,25].

The organization of collagen types I and III provides structural integrity of CMC, direction of myofibrils in cardiomyocyte. As a result of heart remodeling there is a change in the synthesis and degradation of collagen, the prevalence of type III collagen synthesis over type I, the loss of connections between cardiomyocytes, order of cross-linking of collagen, which causes damage to the structure and changes in myocardial function.

The process of the predominance of collagen synthesis over its disintegration is called fibrosis. [8] This process is influenced by numerous humoral factors, among which the leading role belongs to the renin-angiotensin-aldosterone system (RAAS).

To determine the fraction of fibrosis in the myocardium different diagnostic methods are used. Inter vivo myocardial biopsy with the determination of volume fractions of interstitial collagen is the "gold standard". High traumatism, cost and complexity of the procedure limits extensive use of the myocardium biopsy in clinical practice. In this connection, active work on the study of non-invasive diagnostic methods is being done.

One of the methods of diagnosis attracting much interest of scientists and clinicians, is the assessment of the level of serum markers of collagen metabolism. These include markers of synthesis (PICP, PIIINP) and collagen degradation (C-terminal telopeptide of type I collagen), activity of fibroblast markers (transforming growth factor β1) and markers of collagen degradation (tissue inhibitors of matrix metalloproteinases) [26].

To succeed in reducing mortality rate from heart failure early diagnosis and treatment of chronic heart failure are required. In this regard, there is active search for new biomarkers that can improve the diagnosis and therapy of the disease [1,2,9]. The products of collagen metabolism can be considered as promising candidates for markers of myocardial remodeling and development of heart failure.

N-terminal propeptide of collagen type III is a protein produced in the synthesis of type III collagen. In a number of papers increased level of PIIINP is a predictor of cardiac mortality or rehospitalization due to CHF decompensation associated with increased risk of death [13,14,27].

In this regard, in our work we have examined the N-terminal propeptide of collagen type III to assess the contribution of myocardial fibrosis to the development of heart failure in patients with the metabolic syndrome.

2. Materials and Methods

The study included 77 patients with CHF. In all patients the diagnosis of heart failure was confirmed by quality measuring NT-proBNP (> 125 pg / ml) by means of an express test (Getein Biotechnology, China).

The main group included 39 patients with CHF and MS. The control group included 38 patients with chronic heart failure, without the metabolic syndrome.

The severity of the clinical manifestations of heart failure by means of an evaluation scale of clinical condition in CHF, functional status of the patient were assessed using a six-minute walk test.

All patients underwent clinical and biochemical blood tests, an electrocardiogram. The size of the heart chambers, wall thickness of the myocardium and epicardial fat by echocardiography were estimated on the apparatus Siemens Sequoia 512 with a sector probe 3V2Cs.

According to the practical recommendations of the American College of Gastroenterology, the American Association for the Study of Liver Diseases, the American Gastroenterological Association for the diagnosis of non-alcoholic fatty liver disease for liver fibrosis diagnosis it is encouraged to use NAFLD fibrosis score (NFS). The value of the use of NFS is shown in a meta-analysis of 13 studies involving 3064 patients. So the value of <1.455 (90% sensitivity and 60% specificity) indicates the absence of significant fibrosis, with the value of> 0.676 (67% sensitivity and 97% specificity), the likelihood of liver fibrosis is very high [10].

Another surrogate marker for NAFLD is the Fatty Liver Index. The value of this test has been shown in the RISC Study. The study included 1307 patients and 60 people without diabetes with a high cardiovascular risk. The results of the study claimed that FLI was connected with IR, ТИМ, with an increased risk of coronary heart disease [11].

The calculations of FLI and NFS were done for all patients to assess the presence of steatosis and fibrosis of the liver.

Fatty Liver Index (FLI) is calculated by the formula [10]:

$e^{0,953 \times \log e (TG) + 0,139 \times BMI + 0,718 \times \log e (GGT) + 0,053 \times WC - 15,745} / 1+(e^{0,953 \times \log e (TG) + 0,139 \times BMI + 0,718 \times \log e (GGT) + 0,053 \times WC - 15,745})x100$

NAFLD Fibrosis Score (NFS) is calculated by the formula [11]:

1,675 + 0,037 x A + 0,094 x BMI + AST/ALT – 0,013 x PL – 0,66 x Al

TG- triglycerides, g/l; BMI - body mass index kg/m$^{2;}$ GGT- gamma-glutamyl-transferase, IU/L;
WC - waist circumference, sm; A – age, years; AST – Aspartate aminotransferase, IU/L; PL – Platelets, 10^9/l; ALT – Alanine aminotransferase, IU/L; Al – Albumin, g/l

In this group of patients we measured markers of collagen synthesis - N- terminal propeptide of collagen type III (PIIINP) to assess the process of fibrosis and the contribution of this process to the development of heart failure by means of immunoassay («USCN Life Science», China).

3. Results

All the patients had clinical signs and symptoms of CHF. Of the 77 patients - 25 (32%) males. The average age is 63,9 ± 10,3 years. In the first group there are 17 men (43%), in the second one there are 18 men (47%). The average age in the group of patients with MS 63,0 ± 11,0 years in the control group - 64,8 ± 9,5 years.

The duration of heart failure anamnesis in all patients ranged from 2 to 19 years (average duration of heart failure anamnesis is 8,3 ± 6,3 years). The patients of the main group had the average duration of heart failure anamnesis 9,6 ± 7 years, in the control group it was 7 ± 5,2 (p = 0,07). The differences in the duration of heart failure anamnesis in the two groups are not revealed. The average score for Scale of clinical state, among all the patients was 5 (50% OR 4-7). In the main group the average score for Scale of clinical state was 6 (50% OR 4-7). In the control group the average score for Scale of clinical state was 5 (50% OR 4-7).

3.1. Laboratory Research

In the evaluation of the laboratory data statistically significant differences in ALT and GGT levels are revealed in the two groups. Indicators do not exceed the normal range, but in the group of patients with chronic heart failure and the metabolic syndrome the present rates are higher, reflecting hepatic involvement in the pathological process. Also this group of patients was characterized by a higher level of uric acid (p = 0,00003) and this figure was increasing with the increase of the stage of AH.

The level of glycosylated hemoglobin was definitely higher (p = 0,0014) in the main group (5,8 ± 1,8%) and correlated with the level of GGT (r = 0,69; p = 0,04), which likely reflects the process of liver damage with the increase of the level of glycosylated hemoglobin in patients with CHF and MS.

3.2. N- terminal Propeptide of Collagen Type III (PIIINP)

The value of PIIINP level in the main group made up 3,3 ± 1,5 µg/l in the control group - 2,3 ± 1,3 µg/l (p = 0,00046). These differences are statistically significant. To evaluate the clinical information content of PIIINP level the correlations between clinical, laboratory and instrumental characteristics of all patients in the study were analyzed.
The main group:

1) in the main group PIIINP level was significantly higher in patients with stage III of AH (p = 0,007 Kruskal-Wallis test);

2) patients with abdominal obesity had significantly higher PIIINP levels (p = 0,0009 U-Mann-Whitney test), and is 3,3 ± 1,5 µg/l;

3) the presence of hepatic steatosis, disorders of carbohydrate and lipid metabolism in the main group significantly affect the level of PIIINP. Table 1.

Table 1. Factors affecting the level of PIIINP in patients with CHF and MS.

	Patients with CHF and MS n=39			**p**
Hepatic steatosis	no	yes		0,025
	2,07±0,8 µg/l	3,3±1,5 µg/l		
Disorders of lipid metabolism	2,2±1,0 µg/l	3,1±1,5 µg/l		0,015
Disorders of carbohydrate	**normal**	**hyperglycemia**	**DM 2**	**P**
	2,8±0,8 µg/l	3,3±1,6 µg/l	3,6±1,6 µg/l	0,01

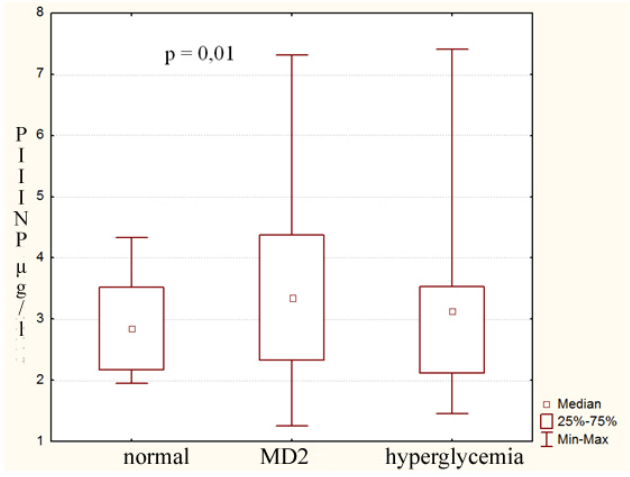

Figure 1. Factors significantly affecting the level of PIIINP in patients with CHF and MS. Violation of carbohydrate metabolism

As shown in Table 1 in patients with chronic heart failure and MS with the presence of hepatic steatosis PIIINP level was 3,3 ± 1,5 µg/l, with type 2 diabetes - 3,6 ± 1,6 µg/l, with atherogenic dyslipidemia - 3,1 ± 1,5 µg/l. Figure 1, Figure 2.

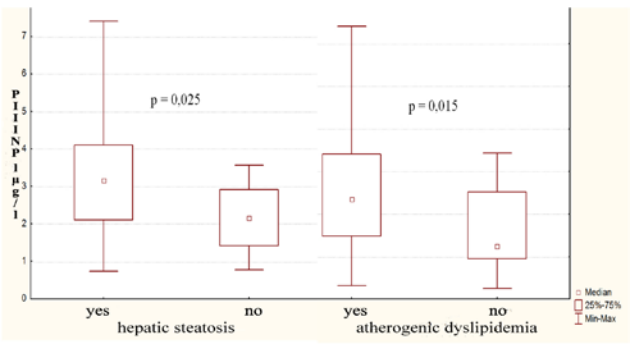

Figure 2. Factors significantly affecting the level of PIIINP in patients with CHF and MS. Hepatic steatosis and atherogenic dyslipidemia

The statistical analysis revealed significant correlations between laboratory data and PIIINP: the level of uric acid (r = 0,37; p = 0,001); glucose level (r = 0,29; p = 0,011) .GFR (r = -0,37; p = 0,002); value FLI (r = 0,47; p = 0,001); Figure 3; NFS (r = 0,31; p = 0,007); Figure 4.

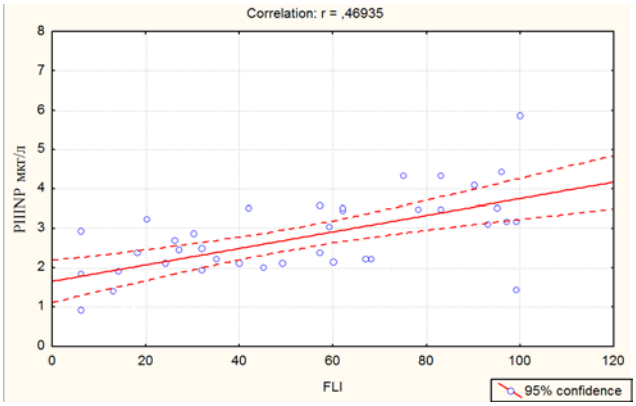

Figure 3. Direct correlation between the level of PIIINP and value of FLI in patients with MS and heart failure, n = 39.

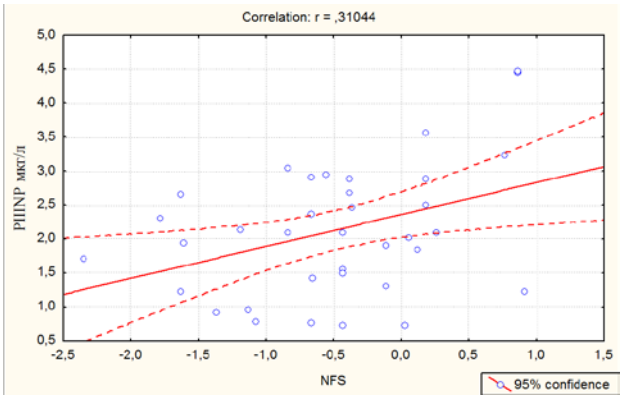

Figure 4. Direct correlation between PIIINP level and the value of NFS in patients with MS and heart failure, n = 39.

Statistical analysis revealed significant correlations between the data of echocardiogram and PIIINP: epicardial fat thickness (r = 0,33; p = 0,004) Figure 5; IVS thickness (r = 0,33; p = 0,003); LV myocardial mass (r = 0,36; p = 0,002); RA dimensions (r = 0,34; p = 0,043); LA (r = 0,35; p = 0,034); ESD LV (r = 0,31; p = 0,006); ratio E / A (r = 0,28; p = 0,013); ratio E / e (r = 0,24; p = 0,038).

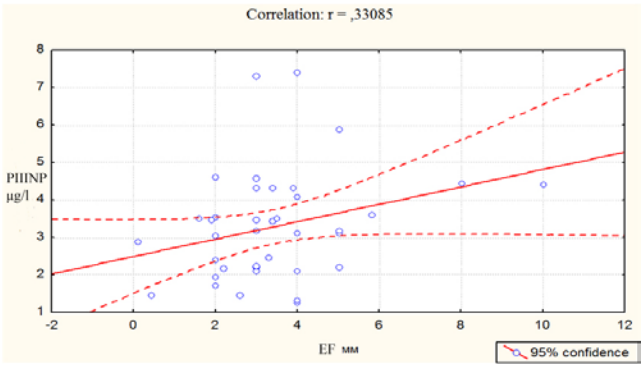

Figure 5. Direct correlation between the level of PIIINP and thickness of EF in patients with MS and chronic heart failure, n = 39.

The control group:

1) in this group the level of PIIINP is also significantly higher in patients with stage III of AH (p = 0,044 Kruskal-Wallis test);

2) the presence of coronary artery disease affects the differences in the level of PIIINP (p = 0,032 U-Mann-Whitney test);

3) patients without AO the level of PIIINP is 2,2 ± 0,9 µg/l (p = 0,0009 U-Mann-Whitney test).

In all patients the presence of IM, CODL does not affect the level of PIIINP. In the presence of arrhythmias the PIIINP level is higher in the group of patients with AF, but these differences are not reliable (p = 0,052 U-Mann-Whitney test).

4) statistical analysis revealed significant correlation between laboratory data and PIIINP: uric acid (r = 0,34; p = 0,048); NFS (r = 0,38; p = 0,017); GFR (r = -0,49; p = 0,001).

5) the statistical analysis revealed significant correlation between the echocardiogram and PIIINP: peak E (r = 0,4; p = 0,015); LV dimensions (r = 0,4; p = 0,012); RA (r = 0,44; p = 0,009); ESD LV (r = 0,44; p = 0,005); EDV LV (r = 0,35; p = 0,029); ESV ЛЖ (r = 0,49; p = 0,002); EF (r = -0,69; p = 0,001); ratio E / A (r = 0,54; p = 0,001).

Thus, the level of PIIINP in the both groups correlates with an indicator of kidney function disorder, indicators of liver fibrosis and steatosis. The level of PIIINP in the both groups also correlates with many indicators of echocardiography.

3.3. Discussion of Results

The pathogenesis of heart failure is closely connected with the processes of myocardial fibrosis and blood vessels. Until recently, to estimate the amount of collagen in the myocardium and the vessels biopsy was used. The emergence of the possibility of assessing biomarkers of synthesis and degradation of collagen allowed scientists to significantly advance the understanding of the pathogenesis of heart failure. Recently, much attention has been paid to such a biomarker of the clinical course of CHF as the N-terminal pro-peptide of type III collagen.

PIIINP is a protein that is formed during the synthesis of type III collagen. In several studies the patients with HF-PEF - and metabolic disorders were marked by a higher level of this marker. When evaluating the N-terminal propeptide of collagen type III in our work it was revealed that its level is significantly higher in the group of patients with MS and CHF (3,3 ± 1,5 mg / l, p = 0,00046). The presence of these components of the syndrome such as the violation of carbohydrate and lipid metabolism, hepatic steatosis is significantly associated with higher levels of PIIINP in patients with CHF and MS.

In the work of the English scientist Tanwar S, 2013, the higher level of PIIINP was associated with the presence of steatosis and fibrosis of the liver, and correlated with the histological picture of NAFLD [12]. In our study similar results were obtained, namely PIIINP level correlated with the value of FLI (r = 0,47; p = 0,001) and NFS (r = 0,31; p = 0,007) in patients with CHF and MS.

In the works of Cicoira M., 2004 and Zannad F., 2010, it has been shown that the higher level of PIIINP is associated with more severe heart failure and increased risk of death in patients with heart failure [13,14]. Thus, a higher level of this marker in patients with heart failure and MSC indicates a more severe course of chronic heart failure.

In our study, in the main group the PIIINP level was significantly correlated with the size of the heart chambers

(LA, RA, ESD LV), the thickness of the IVS and LV myocardial mass. As it is known, PIIINP reflects collagen synthesis, fibrosis and remodeling processes of the heart. In patients with MS these processes are more active than in those without MS [20]. Our results also confirm this theory.

We examined patients with CHF and MS and revealed the correlation between the level of PIIINP and the thickness of EF (r = 0,33; p = 0,004). The increase of TEF is associated with an increase in LV myocardial mass, the thickness and size of the heart chambers in patients with MS [15,16]. Also, the increase of TEF results in increased arrhythmogenic of the myocardium [17]. According to the authors of the above mentioned works, the basis of these processes is strengthening the processes of myocardial fibrogenesis. We obtained a correlation between the level of PIIINP and EF thickness, which confirms this theory.

Also in our study, in the both groups there is a statistically significant correlation between the level of PIIINP and the ratio E / A, which allows using PIIINP as an early marker of diastolic dysfunction in patients with chronic heart failure, regardless of the presence of MS.

Our work revealed correlations between GFR, the level of uric acid and PIIINP in the both groups. As discussed above, an increased level of PIIINP is associated with more severe heart failure and increased risk of death in patients with CHF. Thus, it can be concluded that the deterioration of renal function is a risk factor for severe heart failure and an increased risk of death in patients with heart failure, regardless of the MS. Similar results were obtained in the domestic and foreign scientists [18,19].

4. Conclusion

The above results confirm the importance of determining the level of PIIINP in the assessment of severity of heart failure. The use of this marker in clinical practice will identify patients with CHF and MS with structural and functional changes in the myocardium in the early stages of the disease. Also the determination of the PIIINP level in patients with CHF and MS will allow identifying patients with liver disease and choosing patients for further examination and selection of therapy, taking into account ongoing pathology.

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