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The Role of Tissue Inhibitor of Matrix Metalloproteinase-1 in Cardiac and Blood Vessels Remodeling and in Potential for Survival in Case of Chronic Heart Failure of Various Origins

RI Yatsyshyn and TI Salyzhyn

Abstract
One of the first manifestations of chronic heart failure (CHF) is cardiac remodeling. Such combination of alterations triggers abnormalities in the system of extracellular matrix (ECM). ECM homeostasis is maintained due to strict balance between matrix metalloproteinase (MMP) and their tissue inhibitors (TIMP).
The objective of the research was to study the prognostic value of TIMP-1 level and assess its impact on cardiac and blood vessels remodeling in patients with comorbidities.
Materials and methods. 86 patients participated in the research. They included 42 patients (Group I) with essential arterial hypertension (AH) with CHF IIA FC III (NYHA) and 44 patients (Group II) suffering from chronic kidney disease (CKD) of V stage improved by hemodialysis (HD) with concomitant CHF IIA FC III (NYHA). TIMP-1 was determined using immunoenzyme method with the use of a set of reagents "Bender MedSystems" GmbH (Austria). The level of endothelin-1 (ET-1) in blood serum was determined using "Biomedica" set (Austria) to study endothelial dysfunction (ED).
Results. Direct moderate reliable connection was established between TIMP-1 and end-diastolic volume (EDV) ($r=+0.36$; $p<0.05$), left ventricular mass index (LVMI) ($r=+0.46$; $p<0.05$), thickness of left ventricular posterior wall ($r=+0.33$; $p<0.05$), interventricular septum thickness ($r=+0.39$; $p<0.05$) in Group I ($p<0.05$), whereas the connection between TIMP-1 and end-systolic volume (ESV) ($r=+0.36$; $p<0.05$), EDV ($r=+0.38$; $p<0.05$), LVMI ($r=+0.42$; $p<0.05$), anteroposterior dimension of right ventricle ($r=+0.43$; $p<0.05$) was established in Group II. In order to assess the impact of TIMP-1 on ED we conducted correlation analysis between TIMP-1 and ET-1 between the studied parameters in both groups, in Group I ($r=+0.73$; $p<0.001$) and in Group II ($r=+0.70$; $p<0.001$). Increase in TIMP-1 level over 1040 ng/ml was associated with a greater risk of hospitalization for CHF decompensation and cardiovascular complications (CVC) development during 2 years in patients of both groups.
Conclusions. The results of this research indicate that increased TIMP-1 level is an independent predictor of increase in hospitalization and mortality of patients with CHF regardless of renal function. Increase in TIMP-1 level may promote cardiac and blood vessels remodeling in patients with comorbidities. Increase in TIMP-1 level is associated with the development of endothelial dysfunction in both groups.

Keywords: chronic heart failure; chronic kidney disease; tissue inhibitor of matrix metalloproteinase-1; endothelin-1; cardiac remodelling.

1. Introduction
Due to its high prevalence, chronic heart failure (CHF) deserves high-valuable status, since this disease leads to high hospitalization and mortality of patients [1]. Overlay of CHF in patients with end-stage chronic kidney disease (CKD) significantly impacts patients' survival. The presence of comorbidity 10-20 times increases the risk of mortality from cardiovascular complications (CVC) compared to the patients with preserved renal function [5]. All this leads to the search for new biomarkers helping to diagnose this pathology timely. One of the first manifestations of chronic heart failure (CHF) is cardiac remodeling. Such combination of alterations triggers abnormalities in the system of extracellular matrix (ECM) [3, 7, 8, 10]. ECM homeostasis is maintained due to strict balance between matrix metalloproteinase (MMP) and their tissue inhibitors. Increased matrix productivity towards increase in Types I and II collagen leads to fibrosis and increased myocardial stiffness, causing myocardial hypertrophy and diastolic dysfunction. When in the contrast collagen degradation increases over synthesis, myocardial elasticity decreases leading to cardiac cavities dilatation and systolic cardiac dysfunction [3, 7]. Increase in the level of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) as an integral marker of structural change of heart and vessels attracts attention of many

scientists. TIMP-1 is known to influence fibrosis development in the process of CKD progression. However, the impact of this biomarker on CHF development in terms of substitution therapy is poorly known [6].

2. Objective the Study

The objective of the research was to study the prognostic value of TIMP-1 level and assess its impact on cardiac and blood vessels remodeling in patients with CHF and preserved and lost renal function.

3. Materials and methods

86 patients participated in the research. They included 42 patients (Group I) with essential arterial hypertension (AH) with CHF IIA FC III (NYHA) and 44 patients (Group II) suffering from chronic kidney disease (CKD) of V stage improved by hemodialysis (HD) with concomitant CHF IIA FC III (NYHA). The average age of the patients constituted 50.8±5.85, median duration of HD treatment comprised (3.58±1.32) years. The examined patients included 49 (57%) men and 37 (43%) women. Control group consisted of 20 apparently healthy individuals. HD was performed to patients according to a standard program (3 times a week for 4-5 hours) using Innova device manufactured by "Gambro" company (Sweden) with the use of semisynthetic dialyzer and bicarbonate buffer. Provided dialysis dose (eKt / V coefficient) constituted at least 1.3.

Patients with severe heart rhythm disorders, decompensated diabetes mellitus as well as patients treated with outpatient HD not more than one year, with eKt/V less than 1.3, hemoglobin up to 90 GM/DL were excluded from the research.

Detailed characteristic of the patients depending on the presence of comorbidity is presented in Table 1.

Table 1: General structure of comorbidity of patients with CHF in both study groups

Comorbidities	Group I (AH with CHF) n=42	Group I (CKD V stage, treated with HD with CHF) n=44	Fisher's exact test, p
	n (%)	n (%)	
Diabetes mellitus	5 (11.9)	8 (15.9)	p=0.30
Anaemia	6(14.3)	38(86.7)	p=0.01
Coronary artery disease	13(30.9)	15(34.1)	p=0.46
Arterial hypertension	42(100)	37(84.1)	p=0.01

Note: n – number of patients in the group.

The cause of the end-stage CKD was assessed in Group II according to the type of kidney damage: patients with glomerular lesions numbered 15 people, group of patients with hypertensive nephropathy was distinguished and included 11 individuals, 10 patients suffered from non-glomerular lesions (pyelonephritis, cystic disease, renal abnormal development, urolithiasis), 8 patients suffered from diabetes mellitus. Specific gravity of patients by type of kidney damage is presented in Figure 1.

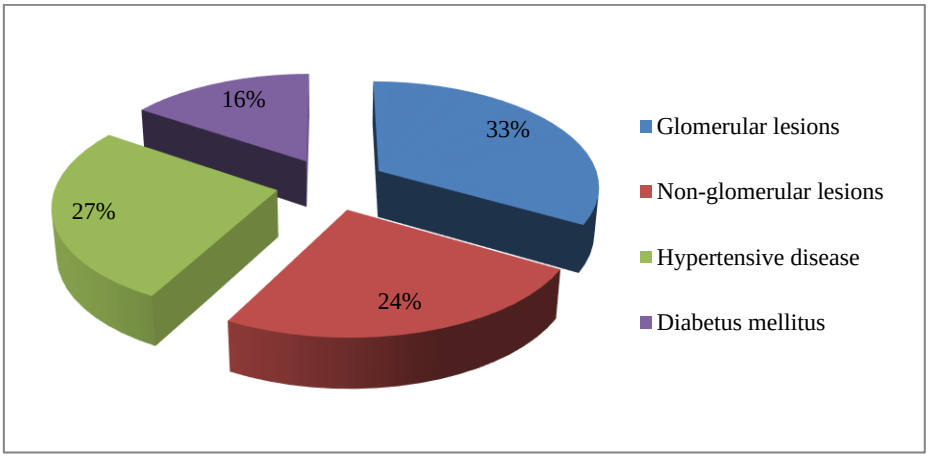

Fig 1: Characteristics of patients with CKD stage V by the type of kidney damage

In addition to full blood count and biochemical blood assay, daily variation of arterial blood pressure by daily monitoring of blood pressure and echocardiography were performed to all patients. The patient's clinical state was assessed by the sum of points according to the rating scale of clinical state (Yu.V. Marieiev 2000) and 6-minute walking test was conducted in order to clarify the functional class of CHF according to NYHA criteria (Table 2).

Table 2: Clinical and laboratory characteristics of the patients

Parameters	Controln=20	Group I (AH with CHF) n=42	Group II (CKD stage V, treated with HD with CHF) n=44
Sex (M/F)	11/9	24/18	25/19
Age, years	37.8±4.37	54.6±5.47	49.1±6.12
AH duration, years	-	7.8±2.42	6.7±0.87
HD treatment, years	-	-	3.58±1.32
Hemoglobin, GM/DL	127.3±5.13	112.4±4.16*	96.4±3.07***^^
Red blood cells, 10^{12}/l	4.68±0.34	3.89±0.09	3.41±0.64*
White blood cells, 10^{9}/l	5.1±0.47	7.2±0.13	7.6±0.15
ESR, mm/h	6.88±2.13	7.23±1.43	14.4±1.25**^^^
Total protein, g/l	73.1±3.84	63.3±3.56*	58.4±2.47**

Albumins, g/l	52.2±3.21	44.2±1.57*	39.3±1.65**
Total cholesterol, mmol/L	4.17±1.11	5.7±0.97	6.3±1.12
Urea, mmol/L	6.3±0.19	7.1±0.24*	14.3±1.15***ˆˆˆ
Urea after dialysis	-	-	7.8±0.23*
Creatinine, mcmole/l	74.8±3.53	103.1±5.3	792.2±40.4***ˆˆˆ
Creatinine after dialysis	-	-	178.2±8.41***ˆˆˆ
ET-1, pg/ml	5.3±0.32	9.7±1.37**	12.01±1.36***ˆˆˆ
TIMP-1, ng/ml	486 [383; 522.8]	1113[1021;1174]***	1217[1156;1395]***ˆˆ
BMI, kg/m²	23.7±1.19	28.7±1.14***	27.1±1.07**
SBP, millimeter of mercury	124.2±4.68	154.3±7.41*	151.3±6.33*
DBP, millimeter of mercury	81.4±2.52	98.2±4.79*	96.4±5.13*
RSCS, points	0.32±0.01	7.73±0.07***	8.4± 0.06***
6-minute walking test, m	534±64.2	243.4±21.1**	234.2±23.2**

***Note*:** * - p<0.05; ** - p<0.01; *** - p<0.001; in comparison with the control group. ˆ - p<0.05; ˆˆ - p<0.01; ˆˆˆ - p<0.001; in comparison between Group I and Group II.

BMI – body mass index; SBP – systolic BP; DBP – diastolic BP; RSCS – rating scale of clinical state.

Echocardiography was performed using the Toshiba SSA-590A device (NEMIO MX) (Japan) according to the recommendations of the American Society of Echocardiography (2015) in M-mode and B-mode [9]. The following parameters were calculated: left ventricle end-diastolic diameter (LV EDD) and left ventricle end-systolic diameter (LV ESD), interventricular septum thickness (IVST) and thickness of left ventricular posterior wall (TLVPW). According to the formula the following parameters were calculated: end-diastolic volume (EDV), end-systolic volume (ESV), left ventricular ejection fraction (LVEF), left ventricular mass (LVM), LVM index (LVMI). According to the formula the following parameters were calculated: end-diastolic volume (EDV), end-systolic volume (ESV). Left ventricular ejection fraction (LVEF) was calculated according to the formula: LVEF = ((EDV–ESV)/EDV)*100%.

Left ventricular mass (LVM) was calculated in our research according to Penn Convention formula: LVM (r) = 1.04*([EDD+TLVPW+ IVST]3–[EDD]3)–13.6. LVM index (LVMI) = LVM/S, where S (м²) = (100+W+(H–160))/100 (Jssakson formula)), where S – body area measured in m², H – body height measured in cm, W – body weight measured in kg. Left ventricular hypertrophy (LVH) was stated in case of LVMI>134 g/m² in men and LVMI >110 g/m² in women. Left ventricular relative wall thickness (RWT) = 2* TLVPW / EDD. Types of cardiac remodeling were determined according to the following parameters:

- Normal geometry – RWT<0.42, LVMI – norm (N);
- Concentric remodeling – RWT>0.42, LVMI – N;
- Concentric hypertrophy – RWT>0.42, LVMI – ↑N;
- Eccentric hypertrophy – RWT<0.42, LVMI – ↑N.

TIMP-1 was determined using immunoenzyme method with the use of a set of reagents "Bender MedSystems" GmbH (Austria) and Stat-Fax 303+ analyzer. The level of endothelin-1 (ET-1) in blood serum was determined using immunoenzyme method with the use of "Biomedica" set (Austria) and Stat-Fax 303+ analyzer to study endothelial dysfunction (ED).

All patients participating in the research signed informed consent.

Statistical processing of the data was performed with the use of "Statistica 8.0 for Windows" taking into account the test for normal distribution using Kolmogorov-Smirnov's test. In case of normal distribution, mean values (M) and mean error of arithmetical average (m) as well as standard deviation (SD) were calculated. Student's t-test was used to compare average values in two independent samples. In case of non-conformity of normal distribution law to describe the signs, median and interquartile range (25% and 75%) was applied. Nonparametric Mann–Whitney U test was used for comparative analysis. Correlation relationship was investigated using Pearson's test (in case of normal distribution) and according to Spearman (in case of the absence of normal distribution). The difference was considered significant at p<0.05. Fisher's exact test was applied to assess the possible impact of certain factors on the development of the disease. Survival was determined according to Kaplan-Meier method; the date of blood sampling for TIMP-1 determination was considered to be the initial point of monitoring.

Results and discussion

The results of performed investigations indicated that EDD and ESD indices in patients with AH and CHF were significantly increased by 1.19 (p<0.001) and 1.17 times respectively (p<0.01). EDV and ESV increased by 1.32 (p<0.001) and 1.28 (p<0.01) times indicating LV dilatation. However, these indices were significantly higher in dialysis patients being greater than normal EDD and ESD indices by 1.24 and 1.20 times (p<0.001) and EDV and ESV indices by 1.52 and 1.53 times respectively (p<0.001). According to the results of our research EDV in Group II was significantly higher in comparison with Group I (p<0.05). Thus, according to the provided data LV dilatation in dialysis patients was more significant than in patients with AH. Similar changes were detected in the process of IVST and TLVPW measurement. Thus, these indices increased by 1.37 and 1.32 times (p<0.001) in the group of patients with AH and by 1.43 and 1.41 times (p<0.001) respectively in dialysis patients in comparison with similar indices in apparently healthy individuals. Significant increase in IVST in Group II in comparison with Group I (p<0.05) attracts attention. EF and stroke volume (SV) in both groups slightly differed from normal findings.

LVM and LVMI indices significantly increased, especially in dialysis patients. Thus, above mentioned indices exceeded normal values by 2.12 and 2.07 times (p<0.001) in Group I and by 2.33 and 2.21 times (p<0.001) in Group II. RWT indices were significantly higher in Group I exceeding normal values by 1.21 (p<0.01), while in Group II they exceeded the norm by 1.16 times (p<0.05).

Table 3: Indices of echocardiography in patients

Indices	Control n=20	Group I (AH with CHF) n=60	II група (CKD stage V, treated with HD with CHF) n=60
EDD, mm	42.9±0.77	51.1±0.56*	55.2±1.41*ˆ
ESD, mm	30.9±0.91	36.6±0.55*	42.1±0.93**
EDV, ml	97.4±3.57	129.4±34.41***	149.3±6.24***ˆ
ESV, ml	43.2±4.75	57.3±21.91	59.8±8.32*
SV, ml	78.5±5.16	71.5±17.79	95.2±8.47
EF, %	62.4±0.60	55.4±6.17	56.4±1.12
IVST, mm	8.2±0.23	11.7±0.12**	12.2±0.41**
TLVPW, mm	8.4±0.24	11.5±0.29**	12.9±0.34**ˆ
LVM, g	126.1±7.83	275.4±76.4***	294.1±11.7***
ILVM, g/m²	69.4±3.21	146.8±42.1***	168.6±4.7***
RWT, %	0.38±0.01	0.46±0.02*	0.44±0.04*
RV, mm	22.3±0.23	27.5±0.32*	28.6±0.37*

***Note*:** * - p<0.05; ** - p<0.01; *** - p<0.001 in comparison with the control group. ˆ - p<0.05; ˆˆ - p<0.01; ˆˆˆ - p<0.001; in comparison between Group I and Group II.

RV – anteroposterior dimension of right ventricle; other abbreviations are in the text.

Having analyzed the correlation matrix, direct moderate reliable connection was established between TIMP-1 and EDV, LVMI, TLVPW, IVST in Group I (p<0.05), whereas the connection between TIMP-1 and ESV, EDV, LVMI, anteroposterior dimension of right ventricle (p<0.05) was established in Group II, there was no reliable relation with TLVPW and IVST (Table 4).

Table 4: Correlation between TIMP-1 and heart size in Group I and Group II (Spearman rank correlation)

	ESV	EDV	LVMI	SV	RV	TLVPW	IVST
Group I TIMP-1, ng/ml;	0.20	0.36*	0.46*	0.46*	0.11	0.33*	0.39*
Group II TIMP-1, ng/ml;	0.36*	0.38*	0.42*	0.34*	0.43*	0.15	0.21

***Note*:** * - value at p<0.05.

The established relation indicated that TIMP-1 level had more distinct connection with the indices of the heart wall thickness in Group I, whereas this marker was more associated with the indices of cardiac cavity dilatation (volume indices) in Group II.

The detected differences in the study groups led to the need for detailed analysis of the heart remodeling types. Analysis of the structural and geometric parameters characterizing the size and volume of the left ventricle demonstrated that concentric LVH developed the most often in two groups: in 52.2% of patients in Group I and in 42.85% of patients in Group II. However, the prevalence of eccentric LVH (30.95%) was also high in Group II, this variant of remodeling was observed in patients with AH less often, namely in 12.0% of patients only (Table 5). Having compared TIMP-1 level and remodeling types, we noted that increase in TIMP-1 level over 1200 ng/ml was characteristic of eccentric remodeling, while for concentric alteration this biomarker level did not exceed the specified level.

Table 5: TIMP-1 concentration in case of different variants of cardiac remodeling

	Remodeling type	Group I (AH with CHF) n=42 (100%)	II група (CKD stage V, treated with HD with CHF) n=44 (100%)	Fisher's exact test, p
Norm:	n (%) TIMP, ng/ml;	2 (5.0%) 643 [425;799]	- -	p=0.23
Concentric remodeling:	n (%) TIMP, ng/ml	12 (30.0%) 1001 [928; 1078]	11 (26.2%) 1076 [1044; 1133]	p=0.44
Concentric LVH:	n (%) TIMP, ng/ml;	21 (52.5%) 1030 [943; 1070]	18 (42.85%) 1150 [1071; 1202]	p=0.26
Eccentric LVH:	n(%) TIMP, ng/ml;	5 (12.5%) 1207 [1189; 1225]	13 (30.95%) 1348 [1226; 1440]	p=0.03

According to the obtained results, increase in TIMP-1 level over 1200 ng/ml promoted the development of eccentric remodeling in both study groups, whereas other remodeling types were characterized by lower indices of investigated marker. Many articles describe the relationship of this biomarker and CHF functional class, however, the relationship of the marker with the type of cardiac remodeling has not been studied in these works [3, 7, 10]. We may assume that increase in TIMP-1 level over 1200 ng/ml was accompanied by a more significant imbalance in the MMP system towards preponderance of collagen degradation over synthesis. Certainly, concentrations of TIMP-1 and different MMP in blood serum should be compared for a more detailed study of this assumption [3, 10]. Comparing cardiac remodeling indices and TIMP-1 value we detected similar dependence between TIMP-1 level and cardiac remodeling type in both study groups making it possible to use TIMP-1 as sensitive and specific marker of cardiac remodeling.

The development of vascular endothelial dysfunction (ED) attracts the attention of many scientists as it plays an important role in LV remodeling and CHF progression. Endothelin-1 impact on ED development was proved in many studies [2, 4]. In order to assess the impact of TIMP-1 on ED we conducted correlation analysis between TIMP-1 and ET-1 and established direct moderate reliable connection between the studied parameters in both groups: r=+0.73(p<0.001) in Group I and r=+0.70 (p<0.001) in Group II. Such a strong relationship indicated that TIMP-1 influences ECM restructuring not only in the heart but also the vessels leading to vascular ED (Fig. 2-3).

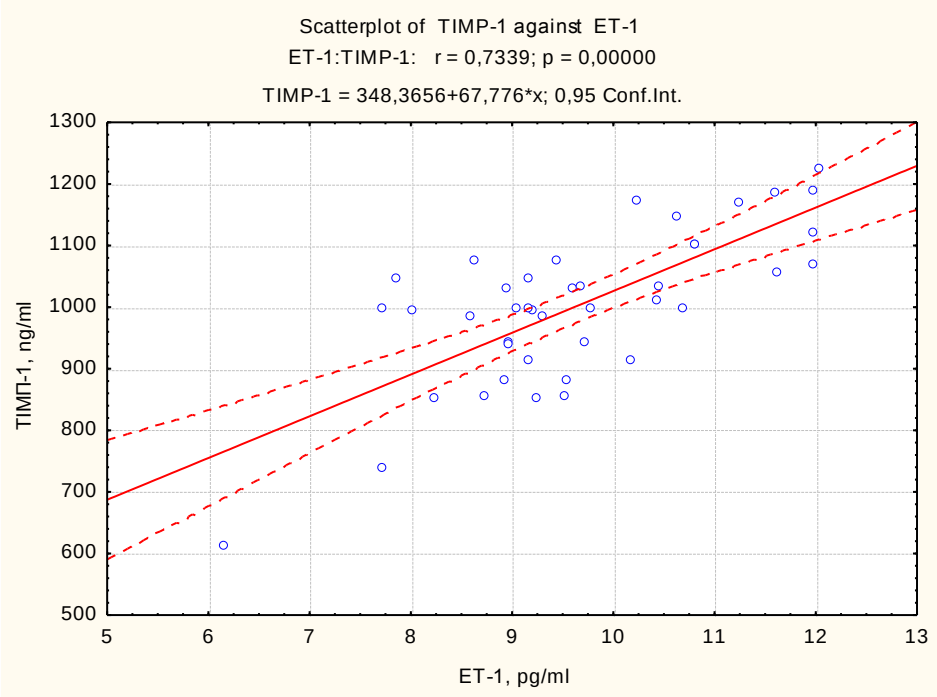

Fig 2: Correlation between TIMP-1 and ET-1 in patients of Group I (AH with CHF)

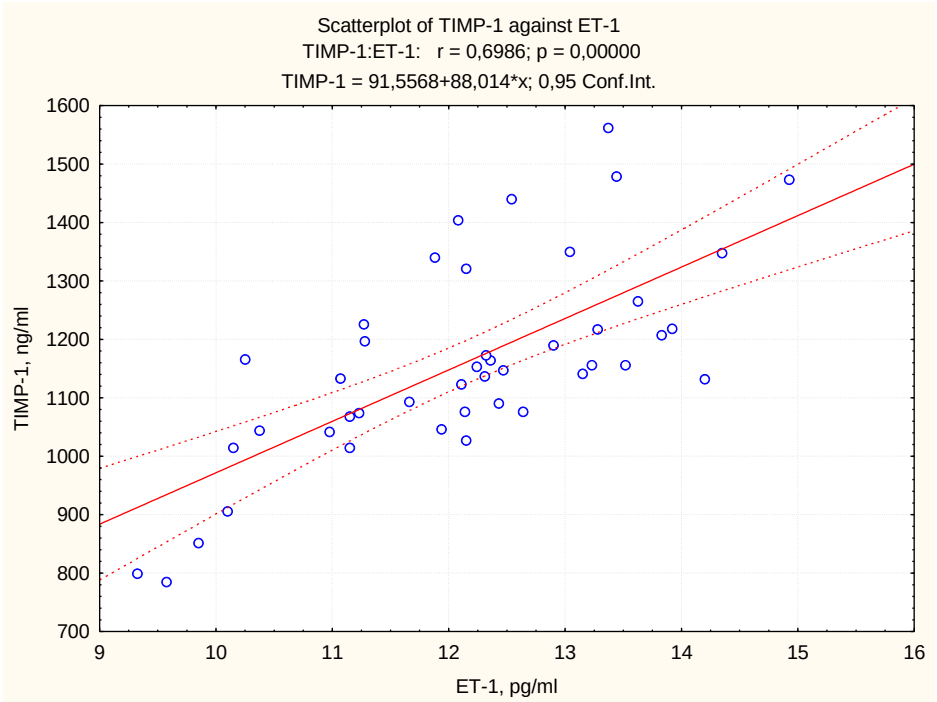

Fig 3: Correlation relationship between TIMP-1 and ET-1 indices in the patients of Group II (CKD stage V, treated with HD with CHF)

Our patients were monitored for 2 years. During this period 12 patients of Group I and 18 patients of Group II were admitted to hospital repeatedly concerning CHF decompensation taking into account 4 dialysis patients who died (CVC were the cause of lethality). During the monitoring, we recorded the incidence of the primary endpoint including all kinds of mortality from CVC. Cases of hospitalization for CHF decompensation, and development of non-fatal myocardial infarction or stroke, events of coronary revascularization or bypass surgery were considered to be the combined secondary endpoint.

It should be mentioned that increase in TIMP-1 level over 1040 ng/ml was associated with a greater risk of hospitalization for CHF decompensation and cardiovascular complications (CVC) development during 2 years in patients of both groups (Fig. 4-5).

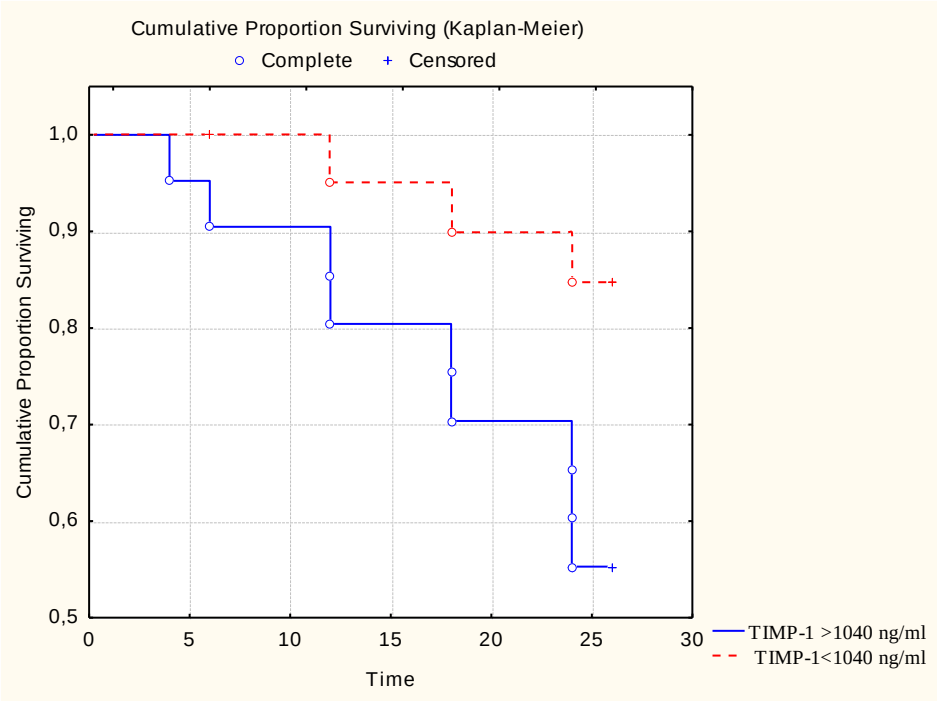

Fig 4: Influence of TIMP-1 on the prognosis of cardiovascular complications in patients of Group I

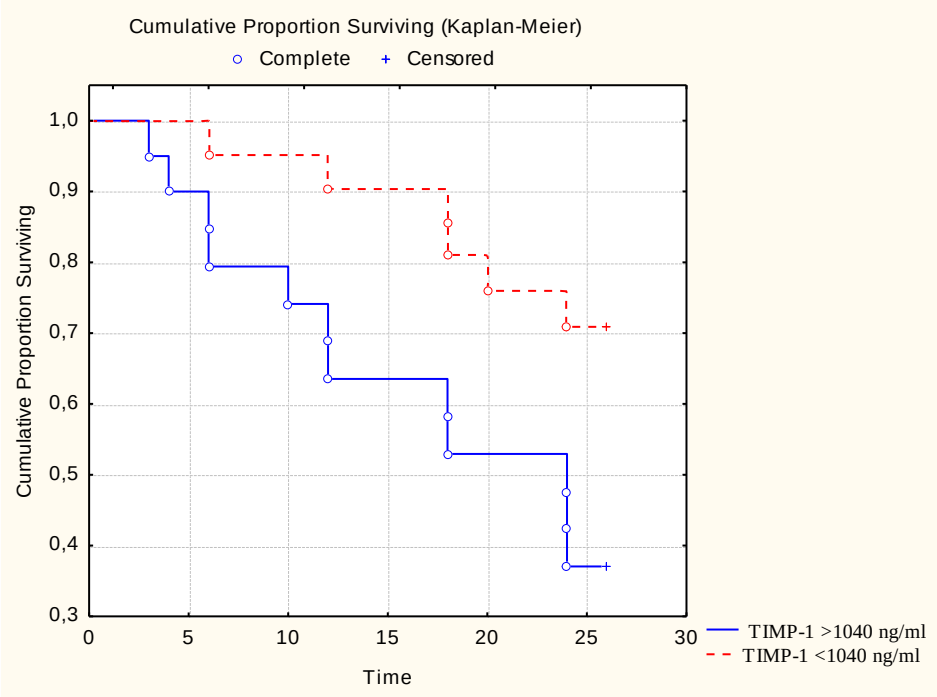

Fig 5: Influence of TIMP-1 on the prognosis of cardiovascular complications in patients of Group II

Analyzing the prognosis of deterioration in patients' condition depending on TIMP-1 level, the patients with TIMP-1 less than 1040 ng/ml were found to have almost the same survival rates in both study groups while the patients with high TIMP-1 level had significantly worse indices. Thus, 2 years after the primary determination of TIMP-1 level cumulative fraction of patients without CVC and individuals with this index not exceeding 1040 ng/ml constituted 84% in Group I and 71% in Group II. Two-year cumulative survival in study groups constituted 56% and 38% respectively at initially high level of TIMP-1 (over 1040 ng/ml). Two-year survival analysis provided an opportunity to establish significant dependence between TIMP-1 level and prognosis for deterioration (Log-Rank test p=0.03 for Group I and p=0.02 for Group II). The differences between the study groups were noted. The number of patients without CVC in the group of dialysis patients was by 1.2 and 1.5 times lower in comparison with patients with AH.

Conclusions

The results of this research indicate that increased TIMP-1 level is an independent predictor of increase in hospitalization and mortality of patients with CHF regardless of renal function. Increase in TIMP-1 level may promote cardiac and blood vessels remodeling in patients with preserved and lost renal function. Increase in TIMP-1 level is associated with the development of endothelial dysfunction in both groups.

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