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Specific Features of Changes in the Serum Biomarker Profile in Cardiac Comorbidity: Arterial Hypertension and Coronary Heart Disease

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ABSTRACT

Introduction. Cardiovascular diseases have remained one of the leading causes of mortality for decades. The investigation of biomarkers such as N-acetyl-β-D-glucosaminidase (NAG), tissue inhibitor of metalloproteinases-1 (TIMP-1), and proMMP1 in patients with arterial hypertension (AH) and coronary heart disease (CHD), including cases of postinfarction cardiosclerosis (PIC), may offer new diagnostic approaches for assessing the severity of these pathological conditions and facilitating their early detection.

Objective. To examine the serum levels of N-acetyl-β-D-glucosaminidase (NAG), tissue inhibitor of metalloproteinases-1 (TIMP-1), and proMMP1 in patients diagnosed with arterial hypertension, coronary heart disease, and postinfarction cardiosclerosis.

Materials and Methods. The study involved 120 patients (60 males and 60 females, average age 53±10 years), who were assigned to three clinical groups: AH, CHD, and CHD with PIC. The control group included 20 clinically healthy volunteers (10 males and 10 females, average age 55±10 years). Serum levels of NAG and TIMP-1 were measured by enzyme-linked immunosorbent assay (ELISA) using test systems from Vector-Best (Russia). Statistical analysis was performed using the Statistica 10.0 software package.

Results. Elevated TIMP-1 levels were observed in patients with AH, CHD, and CHD with PIC, with varying degrees of statistical significance compared to the control group. Additionally, a significant increase in NAG levels was detected in patients with CHD and PIC.

Conclusions. The findings suggest a potential role of inflammatory and cytolytic biomarkers in the pathogenesis of arterial hypertension. Their concentrations were shown to progressively increase with the advancement of cardiovascular complications, such as heart failure and coronary heart disease, including the development of cardiosclerotic changes.

Keywords: coronary heart disease, arterial hypertension, heart failure, cardiosclerosis, NAG, TIMP-1, proMMP1

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1. INTRODUCTION

Numerous large-scale studies have demonstrated a strong association between elevated levels of proinflammatory cytokines and the onset, progression, and clinical outcomes of heart failure. Existing evidence suggests that inflammatory markers may play a significant role in the pathogenesis and prognostication of heart failure outcomes [1, 2]. It is assumed that inflammatory mechanisms are crucial in the development of heart failure associated with coronary heart disease (CHD) and arterial hypertension (AH). Various inflammatory processes are likely to contribute to both the development and progression of ischemic and hypertensive forms of heart failure [3]. In this context, the investigation of serum regulatory mediators in patients with cardiovascular pathology, particularly those with AH and CHD accompanied by cardiosclerotic changes, appears especially relevant.

One of the representative hydrolases—lysosomal hydrolytic enzymes—is N-acetyl-β-D-glucosaminidase (NAG) [4]. Previous studies have shown that NAG activity in rats varies under different pathological conditions. Increased NAG activity has been observed in the serum of patients with varicose veins, insulin-dependent diabetes mellitus, and thyroid disorders. In contrast, patients with hypertension combined with CHD, vascular atherosclerosis, and rheumatologic diseases exhibited a significant decrease in enzyme activity [5].

Earlier research focused on alterations in NAG activity in rats, which were found to change under various pathological states. Increased NAG activity was detected in the serum of patients with varicose veins, insulin-dependent diabetes mellitus, and thyroid pathology, whereas markedly reduced enzyme activity was observed in individuals with hypertension in combination with CHD, vascular atherosclerosis, and rheumatic diseases [6].

There is a lack of data in the scientific literature regarding the variability of this biomarker in the serum of comorbid patients, particularly those with AH, CHD, and postinfarction cardiosclerosis (PIC). For this reason, a study was conducted to assess the activity of N-acetyl-β-D-glucosaminidase in patients with cardiovascular diseases, as this enzyme may serve as an indicator of the intensity of cytolytic processes within the cardio-endothelial continuum. The tissue inhibitor of metalloproteinases-1 (TIMP-1) is a 28-kDa glycoprotein with multiple disulfide bonds and acts as a specific inhibitor of collagenases and other matrix metalloproteinases (MMPs) [7].

Under normal physiological conditions, TIMP-1 is predominantly synthesized in the ovaries, bone tissue, and trophoblast cells. Low-level expression of TIMP-1 has been observed in most cell types. Its expression can be induced, among other factors, in response to stimulation by basic fibroblast growth factor. TIMP-1 is a soluble protein that is localized in the extracellular space [8]. This protein exhibits anti-apoptotic activity. TIMP-1 functions as a modulator of endothelial cell growth and serves as both a marker of extracellular matrix degradation and an indicator of cardiovascular mortality risk [7, 8].

In light of this, the present study was conducted to investigate the variability of this biomarker in more detail and to identify potential correlations with the aforementioned indicators. It is known that matrix metalloproteinases (MMPs) are secreted by cells in an inactive form—as proenzymes (proMMPs)—which are subsequently activated by human MMPs and bacterial proteinases [9, 10]. Proteolytic processes are suppressed by proteinase inhibitors, particularly the tissue inhibitor of MMP-1 (TIMP-1). According to the available literature, the dynamics of the ratio between proteolytic enzymes and their inhibitors in various cardiovascular diseases have not been thoroughly studied. Therefore, a comparative analysis of proMMP-1 levels and proteinase inhibitors in the plasma of patients with coronary heart disease and arterial hypertension is of particular

scientific interest [11–13].

Objective: To investigate the serum levels of N-acetyl-β-D-glucosaminidase (NAG), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1), and proMMP-1 in patients diagnosed with arterial hypertension (AH), coronary heart disease (CHD), including cases with postinfarction cardiosclerosis (PIC).

Materials and Methods: The study included 120 patients (60 males and 60 females, with a mean age of 53 ± 10 years), who were assigned to three clinical groups: AH, CHD, and CHD with PIC. The control group consisted of 20 clinically healthy volunteers (10 males and 10 females, with a mean age of 55 ± 10 years). Serum levels of N-acetyl-β-D-glucosaminidase (NAG) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) were measured using enzyme-linked immunosorbent assay (ELISA) with commercial test kits manufactured by Vector-Best (Russia). Statistical analysis was performed using the Statistica 10.0 software package.

All participants provided written informed consent prior to inclusion in the study. Patients were excluded if they presented with glycated hemoglobin levels above 10%, anemia, renal failure, recent (within 10 days) episodes of acute heart failure, acute coronary syndrome within the previous three months, active inflammatory diseases, paroxysmal tachycardias, or occlusive peripheral artery disease of the lower extremities. The diagnostic workup included chest radiography (to verify signs of pulmonary venous congestion), echocardiography, the 6-minute walk test, and electrocardiography.

The concentrations of NAG and TIMP-1 in serum were determined using ELISA kits (Vector-Best, Russia). Statistical analysis included calculation of arithmetic means, standard deviations, and standard errors of the mean. Data with normal distribution were presented as M±m, where M represents the arithmetic mean and m the standard error of the mean. Group differences were assessed using Student's *t*-test. A *p*-value of ≤0.05 was considered statistically significant.

2. RESULTS AND DISCUSSION

Analysis of the cytokine profiles demonstrated that all patient groups exhibited a statistically significant increase in TIMP-1 and proMMP-1 levels compared to those in the control group. Statistical testing confirmed that the differences in biomarker concentrations between patients and healthy controls were highly significant ($p < 0.001$) (Table 1).

Table 1. Serum Levels of NAG, TIMP-1, and proMMP-1 in Study Groups

Indicator	*1st group AH n=33*	*2nd group CHD n=45*	*3rd group CHD+PIC n=42*	*Control group (healthy) n=20*
N-acetyl-beta-D-glucosaminidase (pg/ml)	2,2±0,3	5,8±0,3*#	5,9±1,0*##	2,5±0,5
Tissue inhibitor of matrix proteinases-1 (pg/ml)	220±7,8*ss	172±8,2	380±8,0*ss	165±9,5
Pro-matrix Metalloproteinase 1 (Pro-MMP-1) (pg/ml)	3100±88,1**	3300±103,0**	5800±110,0*# s	2100±40,1
Molar ratio TIMP1/ proMMP1	0,070	0,055	0,067	0,082

*Note: *- the differences are significant in relation to the indicators of the comparison group – healthy (p0,001).*

***- the differences are significant in relation to the indicators of the comparison group – healthy (p0,01).*

#- the differences are significant in relation to the indicators of group 1 – patients with hypertension (p0.05).

##- the differences are significant in relation to the indicators of group 1 – patients with hypertension (p0,001).

s- differences are significant in relation to the indicators of group 2 – patients with coronary heart disease (p0,01)

ss– differences are significant in relation to the indicators of group 2 – patients with coronary heart disease (p0,001)

Analysis of NAG levels across the study groups revealed that patients with CHD and CHD with PIC (Groups 2 and 3, respectively) exhibited significantly elevated NAG concentrations (5.8 ± 0.3 pg/ml in Group 2 and 5.9 ± 1.0 pg/ml in Group 3) compared to the control group (2.5 ± 0.5 pg/ml) ($p < 0.001$) and to patients with arterial hypertension in Group 1 (2.2 ± 0.3 pg/ml) ($p < 0.05$; $p < 0.001$) (Table 1, Figure 1).

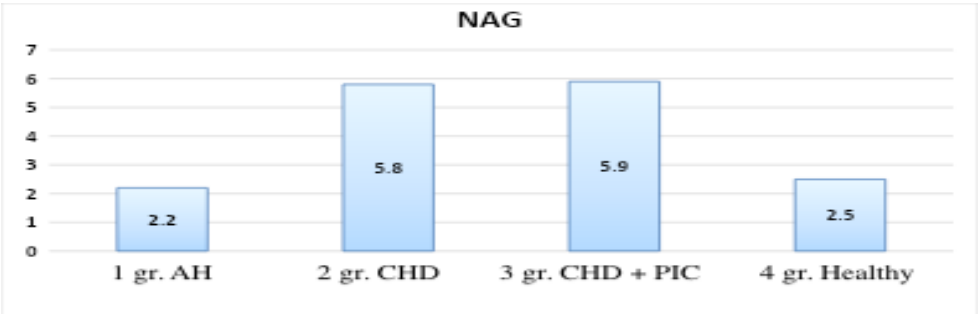

Figure 1. Analysis of NAG levels in patient groups

The analysis of TIMP-1 levels in the study groups showed that patients with arterial hypertension and those with CHD and PIC (Groups 1 and 3, respectively) had significantly higher TIMP-1 concentrations (225 ± 7.4 pg/ml in Group 1 and 378 ± 8.4 pg/ml in Group 3) compared to the control group (167 ± 9.8 pg/ml) ($p < 0.001$) and to patients with CHD without PIC in Group 2 (173 ± 7.9 pg/ml) ($p < 0.001$) (Table 1, Figure 2).

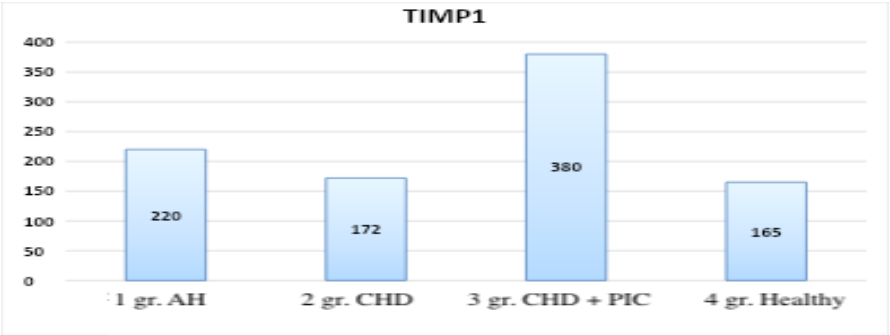

Figure 2. Analysis of TIMP-1 levels in patient groups

According to the literature, tissue inhibitors of metalloproteinases (TIMPs) bind to the active enzyme molecule in a 1:1 molar ratio [14]. Based on this information, and taking into account the molecular weights of TIMP-1 and proMMP-1, the molar ratio of these proteins was calculated in serum to estimate their potential inhibitory capacity.

In patients with coronary heart disease combined with postinfarction cardiosclerosis, a significantly lower TIMP-1/proMMP-1 ratio was observed (see Table 1).

Our study showed a statistically significant increase in proMMP-1 levels in all patient groups compared to the control group ($p < 0.01$) (Table 1). Among patients with arterial hypertension and coronary heart disease, including those with cardiosclerosis, proMMP-1 concentrations reached their highest values ($p < 0.001$), which may indicate the presence of persistent chronic inflammation that worsens with the progression of heart failure.

In patients with arterial hypertension, a decrease in proMMP-1 concentration was observed, likely reflecting reduced gene expression of this metalloproteinase. At the same time, TIMP-1 levels increased. In contrast, patients with coronary heart disease exhibited the lowest TIMP-1/proMMP-1 molar ratios.

Conclusions: 1. The serum level of N-acetyl-β-D-glucosaminidase was significantly elevated in patients with coronary heart disease compared to the control group, with the highest values observed in patients with myocardial cardiosclerotic changes. 2. The concentration of tissue inhibitor of metalloproteinases-1 was markedly higher in individuals with arterial hypertension and coronary heart disease associated with cardiosclerotic myocardial lesions, compared to healthy volunteers. 3. Analysis of serum proMMP-1 levels in the patient groups revealed a significant increase in this marker compared to the control. The most pronounced elevation was recorded in patients with AH and CHD, possibly indicating persistent chronic inflammation that intensifies with the progression of heart failure.

3. CONCLUSION

Dynamic monitoring of N-acetyl-β-D-glucosaminidase activity enables the assessment of the intensity and extent of fibrotic changes. The results obtained suggest that elevated activity of this biomarker in the presence of cardio-endothelial dysfunction reflects the presence and severity of cytolytic processes, the progression of which contributes to connective tissue proliferation (in patients with CHD, this manifests as the aggravation and spread of cardiosclerotic lesions). These

findings support existing literature indicating that alterations in the coordinated function of lysosomal hydrolases—whose levels reflect the presence, severity, and dynamics of extracellular matrix metabolism—play a significant role in connective tissue remodeling.

The assessment of N-acetyl-β-D-glucosaminidase activity may be recommended as an objective biochemical marker in clinical practice, particularly for evaluating the severity of myocardial injury.

The statistically significant elevation of tissue inhibitor of metalloproteinases-1 in patients with arterial hypertension and coronary heart disease accompanied by cardiosclerotic myocardial changes, compared to the control group, is likely due to intensified destructive processes in the extracellular matrix associated with postinfarction cardiosclerosis. This phenomenon warrants further investigation through additional studies and prospective analysis.

Thus, the varying intensity of collagenolytic processes observed across patient groups supports the involvement of extracellular matrix remodeling in the pathogenesis of the studied cardiovascular conditions.

The investigation of matrix metalloproteinase systems and their inhibitors remains a timely and clinically relevant task, given their potential application not only in oncology and inflammatory diseases but also as early diagnostic and prognostic markers for atherosclerotic vascular lesions and myocarditis of various etiologies.

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