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Level of the growth differentiation factor-15 in patients with acute myocardial infarction

Aim	To reveal relationships between growth differentiation factor-15 (GDF-15) and laboratory and instrumental indexes in patients with myocardial infarction in acute phase.
Material and methods	The study included 118 patients younger than 70 years with ST-segment elevation or non-ST segment elevation myocardial infarction (MI). For these patients, GDF-15 was measured by enzyme immunoassay within 48 h of MI clinical onset along with a routine examination. Statistical significance of differences in qualitative variables was assessed by the Student's t-test for normal distribution and by the nonparametric Mann-Whitney U-test; significance of differences in quantitative variables was assessed by the Pearson's chi-squared test. The presence of a relationship between quantitative variables was assessed with the Pearson's correlation coefficient and the Spearman's rank correlation coefficient.
Results	For patients with MI, mean GDF-15 concentration was 2.25±1.0 ng/ml. Moderate correlations were found for GDF-15 and levels of natriuretic peptide (r=0.36, p<0.01), white blood cells (r=0.32, p<0.01), and ejection fraction (Simpson rule) (r=-0.32, p<0.01); weak correlations were found with levels of troponin I (r=0.21, p=0.02) and urea (r=0.20, p=0.04), and interventricular septal thickness by echocardiography (r= -0.26, p<0.01). GDF-15 was higher in patients with ST-segment elevation MI (2.36±1.02 vs 1.99±0.96, p<0.05) and in the presence of hypo- or akinetic areas (2.35±1.05 vs 1.85±0.70, p<0.05). No dependence of GDF-15 on the presence of traditional cardiovascular risk factors was observed.
Conclusion	GDF-15 correlates with major markers of myocardial injury; its level is higher in patients with ST-segment elevation MI regardless of the infarct location.

Keywords	Growth differentiation factor-15; GDF-15; acute myocardial infarction
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Introduction

Growth differentiation factor-15 (GDF-15) is a protein of the transforming growth factor-beta (TGF-β) superfamily and is a marker of oxidative stress and inflammation. GDF-15 is typically expressed in the placenta, prostate gland, and other organs and tissues, but not in the heart [1].

GDF-15 expression is induced in different tissues by such stressors as hypoxia, inflammation, or acute lesion. In the experimental model of cardiovascular disease in mice, e.g., myocardial infarction (MI), increased GDF-15 expression was detected in cardiac tissues [2, 3].

GDF-15 is a new biomarker used to assess the risk of cardiovascular events in various clinical situations. However, data on the real clinical value of this marker in acute MI is insufficient.

Several studies of patients with acute coronary syndrome (ACS) showed plasma levels of GDF-15 correlating with a history of diabetes mellitus (DM), hypertensive heart disease (HHD), history of MI [4, 5]. Decreased creatinine clearance and higher levels of natriuretic peptide, C-reactive protein, and troponin T were associated with higher levels of GDF-15 in this category of patients [4–6]. Increased levels of GDF-15 were determined to be associated with mortality in ACS patients [4–7].

GDF-15 was studied in patients with chronic heart failure (CHF), and several studies determined that this marker correlated with structural and functional parameters of diastolic function of the heart [8]. Its inclusion in multi-marker scores increased the prognostic value of such scores for the risk of developing and course of heart failure [9].

GDF-15 is acknowledged as a biomarker which improves the stratification of hemorrhage and death risk in patients with atrial fibrillation receiving anticoagulant therapy [10]. Thus, it was included in the ABC bleeding risk score for this category of patients [11].

Before putting a new biomarker into real-life practice, it needs to be studied in greater detail in different patient categories. Thus, the aim of our study was to identify the correlations of GDF-15 with laboratory and clinical indicators in patients with acute MI.

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All currently available studies of GDF-15 in patients with ACS have been conducted abroad, thus making our study relevant.

Materials and methods

The study included 118 patients with acute MI who had signed informed consent. The following exclusion criteria were applied: age over 70 years; any acute inflammation and/or exacerbation of chronic inflammatory disease within six months before hospitalization; connective tissue diseases; chronic obstructive pulmonary disease; diabetes mellitus type 1 or 2; cerebrovascular accident or transient ischemic attack in less than six months before the inclusion; acute heart failure functional class II and higher (T. Killip); heart failure with ejection fraction <40% (Simpson) on echocardiogram; any heart rate disorders requiring drug treatment, including atrial fibrillation; blood creatinine >160 μmol/L; transaminases increased 3-fold from normal levels; pregnancy and lactation; alcohol or substance use disorders; and a history of cancer.

In all included patients GDF-15 levels were measured by immunoenzymatic assay. Venous blood was collected within the first 48 hours after the onset of clinical symptoms of myocardial infarction, then centrifuged and frozen at –70°C. Immunoenzymatic assay was performed using Growth Difference Factor 15 ELISA Kit (Cloud-Clone Corp., USA). The detection range was 0.156–10.0 ng/mL, sensitivity was 0.065 ng/mL. Based on available literature, the following reference values of GDF-15 are used for patients with acute MI to group patients: <1.2 ng/mL, 1.2–1.8 ng/mL, and >1.8 ng/mL [5, 6].

All patients underwent a comprehensive examination including complete blood count, biochemical profile (creatinine, urea, potassium, sodium, lipid profile, high-sensitivity troponin, natriuretic peptide, glomerular filtration rate (MDRD)), electrocardiography (ECG), echocardiography, 24-hour ECG monitoring.

The study was carried out following Good Clinical Practice and the Declaration of Helsinki. The local ethics committee approved the study protocol.

The collected data was statistically processed using STATISTICA v10.0. Quantitative indicators with normal distribution are presented as mean values and standard deviations (M±σ). Quantitative indicators with non-normal distribution are described using the median values (Me) and the lower and upper quartiles [Me (Q1 – Q3)]. Quantitative indicators were estimated for compliance with the normal distribution using the Kolmogorov-Smirnov test. Student's T-test and non-parametric Mann–Whitney U-test were used to evaluate the statistical significance of differences in quantitative indicators normal distribution. Pearson's χ^2 test was used to compare qualitative indicators. Pearson's correlation coefficient r and Spearman's rank correlation coefficient were calculated to show a close correlation between quantitative indicators. The results were statistically significant at $p<0.05$.

Results

The study included 118 patients with acute ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). The mean age of patients was 57.3±8.7 years, 82.2% of patients were male; 65.3% of patients had hypertension, 12.7% post-infarction cardiosclerosis, and 2.5% history of coronary artery bypass grafting (CABG). The main characteristics of the included patients are presented in Table 1.

The mean level of GDF-15 was 2.25±1.0 ng/mL, with a minimum value of 0.64 ng/mL and maximum of 7.79 ng/mL. All patients were divided into 3 groups:
1)patients with significantly elevated GDF-15 levels (>1.8 ng/mL) – 79 (66.9%);
2) patients with moderately elevated GDF-15 (1.2–1.8 ng/mL) – 27 (22.9%); and
3) patients who had insignificantly elevated GDF-15 (<1.2 ng/mL) – 12 (10.2%). GDF-15 levels are shown in Figure 1.

The mean level of GDF-15 was 2.26±1.02 ng/mL in male patients and 2.22±0.99 ng/mL in female patients (p=0.84). GDF-15 was also correlated with the patient's age.

The correlations between various quantitative demographic, clinical, and laboratory indicators with GDF-15 are presented in Table 2.

The study found moderate to weak statistically significant correlations between GDF-15 and the following laboratory and clinical parameters: levels of N-terminal pro-brain natriuretic peptide (NTproBNP) (r=0.36, p<0.01), troponin I (r=0.21, p=0.02), WBCs (r=0.32, p<0.01), urea (r=0.20, p=0.04), and echocardiogram findings of EF (Simpson) (r= –0.32, p<0.01), and interventricular septal (IVS) thickness (r= –0.26, p<0.01).

In this study, 29.7% of patients had acute MI of the inferior left ventricular (LV) wall, 28.8% – anterolateral MI, 16.1% – anterior MI, 4.2% – anteroseptal MI, 9.3% inferolateral MI, 5.1% lateral MI, 2.5% acute circular MI, and 4.2% of patients had acute MI of unspecified localization. There was no correlation between elevated levels of GDF-15 and the localization of acute MI.

The following differences in GDF-15 levels were found in different patient groups: GDF-15 levels were

Figure 1. GDF-15 levels in patients with acute myocardial infarction

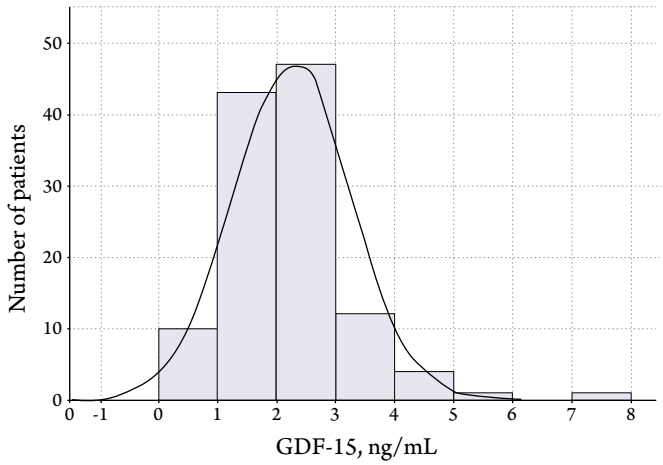

Table 1. Main characteristics of the patients included

Characteristics	Patients (n=118), M±σ
Age, years	57.3±8.7
Male, %	82.2
Systolic blood pressure at admission, mm Hg	129.6±19.2
Diastolic blood pressure at admission, mm Hg	78.2±11.2
History of hypertensive heart disease, %	65.3
Smoking, %	35.6
History of post-infarction cardiosclerosis, %	12.7
History of stenting, %	5.9
History of coronary artery bypass grafting, %	2.5
History of cerebrovascular accident, %	6.8
Body mass index, kg/m^2	28.0±4.6
Total cholesterol, mmol/L	5.0±1.3
Low-density lipoprotein cholesterol, mmol/L	3.3±1.2
Creatinine, μmol/L	93.1±15.6
GDF-15, ng/mL	2.25±1.0
Left ventricular ejection fraction (Simpson), %	50.8±7.4

Table 2. Correlations of main quantitative demographic, clinical, and laboratory indicators with GDF-15

Indicator	GDF-15	
	r	p
Age	0.143	0.12
Body mass index	–0.02	0.83
EF (Simpson)	–0.32	0.01
IVS thickness	–0.26	0.01
EDV	0.16	0.07
LV mass	0.01	0.85
Myoglobine	0.05	0.55
Troponin	0.21	0.02
Natriuretic peptide	0.36	<0.01
AST	0.17	0.05
ALT	0.03	0.89
Creatinine	0.16	0.07
Urea	0.2	0.04
Total cholesterol	–0.06	0.49
LDL	0.01	0.88
HDL	–0.08	0.36
Triglycerides	–0.17	0.05
RBC	–0.2	0.02
White blood cells	0.32	<0.01
Platelets	–0.05	0.55
aPPT	0.13	0.14
Prothrombin time	0.19	0.03

EF, ejection fraction; IVS, interventricular septum; LV, left ventricle; AST, aspartate transaminase; ALT, alanine transaminase, LDL, low-density lipoprotein; HDL, high-density lipoprotein; aPPT, activated partial thromboplastin time.

significantly higher in patients with acute STEMI (2.36±1.02 ng/mL) than those with acute NSTEMI (1.99±0.96 ng/mL; p<0.05).

The two groups were comparable in sex, age, body mass index and generally met all of the inclusion and exclusion criteria. The ejection fraction (measured by Simpson's method) was significantly lower in the STEMI group. However, in the acute NSTEMI group, the number of patients with a history of HHD prevailed. There was also a higher percentage of patients with a history of post-infarction cardiosclerosis, coronary stenting, and CABG, albeit without statistically significant differences in the latter three parameters. Thus, in our study, patients with acute NSTEMI had a more compromised history with higher EF according to echocardiogram findings, but significantly lower GDF-15 levels. The comparison of the two groups of patients with acute STEMI and NSTEMI is shown in Table 3.

A further subgroup analysis of GDF-15 levels did not show a statistically significant dependence on the presence of cardiovascular risk factors, such as smoking,

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body mass index, post-infarction cardiosclerosis, and history of HHD.

At the same time, GDF-15 levels were significantly higher in patients with hypo- or akinesis areas (2.35±1.05 ng/mL; p<0.05) according to echocardiography, than in patients without regional local contraction abnormalities (1.85±0.70 ng/mL; p<0.05). Another echocardiographic parameter which was used to group patients, was IVS thickness. This allowed us to determine that GDF-15 levels were higher in patients without IVS hypertrophy (2.51±1.09 ng/mL vs 2.10±0.94 ng/mL; p<0.05). At the same time, no correlations with such echocardiographic parameters as LV mass and LV mass index were found.

Discussion

The determination of GDF-15 in patients with acute MI is of interest and practical significance, since in patients with acute STEMI and NSTEMI [6, 7], elevated GDF-15 levels have been shown to be associated with higher risks of death and recurrent MI within 12 months after the event. It is therefore essential to study the new biomarker and its correlations with other clinical and laboratory indicators before putting it into real-life practice.

In our study, the median GDF-15 level (2.07 (1.55–2.73) ng/mL) was higher than in previous foreign studies of patients with MI. For example, in one of the studies, the median GDF-15 was 1.47 (0.24–31.86) ng/mL, and the same study found no difference in the biomarker levels in patients with STEMI and NSTEMI [12]. In the other study including only patients with acute NSTEMI, the median GDF-15 level was 1.43 (1.03–2.08) ng/mL [6]. The higher mean GDF-15 level in our study may be associated with a predominance of patients with acute STEMI (71.2% of all included patients). Their blood biomarker levels were significantly higher than in patients with acute NSTEMI. Statistically significant higher GDF-15 levels in patients with acute STEMI and hypo- or akinesis regions, in turn, may indicate that the biomarker is able to reflect the extent and depth of myocardial lesions.

Data for GDF-15 levels differs depending on sex. In the Rancho Bernardo study, male patients had higher levels of GDF-15 [13], and in the PROVE IT-TIMI 22 study, higher levels of biomarker were by contrast observed in female patients [4]. The Dallas Heart Study did not find a difference between male (0.67 (0.5–0.92) ng/mL) and female patients (0.66 (0.48–0.9) ng/mL) [14], which is consistent with our findings, i.e., no significant sex-associated differences in the GDF-15 levels.

Table 3. Comparative characteristics of patients with acute STEMI and NSTEMI

Characteristics	Acute STEMI (n=84), M±σ	Acute NSTEMI (n=34), M±σ	p
Male, %	85.7	73.5	0.11
Age, years	56.88±9.57	58.38±6.16	0.78
Body mass index, kg/m^2	28.01±4.74	28.06±4.52	0.92
Ejection fraction (Simpson), %	49.69±7.23	53.73±7.13	<0.01
Smoking, %	36.9	32.4	0.64
History of hypertensive heart disease, %	58.3	82.4	<0.01
History of post-infarction cardiosclerosis, %	9.5	20.6	0.10
History of stenting, %	4.8	8.8	0.39
History of coronary artery bypass grafting, %	1.2	5.9	0.14
GDF-15, ng/mL	2.36±1.02	1.99±0.96	<0.05

Data shows correlations between GDF-15 and the patient's age. It was observed that GDF-15 levels increased on average by 11% over time, e.g., from 1.10 (0.94–1.35) ng/mL at baseline to 1.24 (0.99–1.69) ng/mL 5 years later in the PIVUS study [15]. Our study did not show a correlation between the GDF-15 levels and the patient's age. However, we should not forget that the study did not include patients over 70 years of age, and the PIVUS study assessed the GDF-15 levels in the 70 and 75-year-old subjects. This may suggest that GDF-15 is indicative of the aging process, which is known to be associated with cumulative oxidative stress, protein glycosylation, and inflammation, i.e., the processes that also cause the GDF-15 expression. The design of our study specifically excluded such effects on the GDF-15 levels.

The available findings of the prospective studies suggest that the GDF-15 levels are positively correlated with smoking, HHD, and diabetes mellitus, history of MI, renal dysfunction [4, 5], and negatively correlated with total and high-density lipoprotein cholesterol levels [13, 16]. There are also correlations between GDF-15 and the levels of NTproBNP and C-reactive protein. These were moderate but statistically significant (r=0.24, p<0.001 for each) [4]. There was also a positive correlation between the levels of GDF-15 and troponin T [4–6].

However, we did not identify a statistically significant difference or any significant correlation between the GDF-15 levels and the presence of traditional cardiovascular risk factors such as smoking, body mass index, post-infarction cardiosclerosis, and history of HHD, as well as the levels of total and low-density lipoprotein cholesterol.

Nevertheless, our findings concerning correlations with several laboratory parameters are consistent with the available data. Thus, GDF-15 correlates with the significant markers of myocardial dysfunction and damage, specifically, NTproBNP and troponin I, as well as WBCs and urea levels.This meets the definition of GDF-15 as a marker of inflammation in general and is consistent with its ability to indicate renal dysfunction.

The PIVUS study concluded that the higher the GDF-15 level, the more pronounced the myocardial remodeling and LV hypertrophy [15]. Foreign authors showed antihypertrophic and anti-remodeling effects of GDF-15 in mice [2, 17]. This contradictory data is still a matter of discussion. If GDF-15 has antihypertrophic and anti-remodeling effects, the elevated levels of the biomarker should logically indicate improved LV function and normal geometry. In our study, GDF-15 levels were higher in patients without IVS hypertrophy according to echocardiography. However, it is impossible to definitiveely judge the correlations between GDF-15 and LV hypertrophy, since we did not find any relationship between this biomarker and LV mass index. This question requires further investigation. It should be borne in mind that the small patient samples limited the interpretation of the results of the analyzed studies concerning GDF-15 and echocardiographic parameters.

Conclusion

1. GDF-15 levels are significantly higher in patients with ST-segment elevation acute MI and patients with hypo- or akinesis areas as shown by echocardiography, irrespective of the MI location.
2. No significant correlations of the GDF-15 levels with the patient's age and sex were identified.
3. GDF-15 is positively correlated with the main laboratory markers of myocardial damage and dysfunction, i.e., NTproBNP and troponin I.
4. GDF-15 is negatively correlated with echocardiographic parameters, specifically EF and IVS thickness. GDF-15 levels are significantly higher in patients without IVS hypertrophy.

Abbreviations

MI, myocardial infarction; ACS, acute coronary syndrome; CHN, chronic heart failure; ECG, electrocardiogram; GDF-15, growth differential factor 15.

No conflict of interest is reported.

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