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Predictive value of growth differentiation factor-15 in patients with myocardial infarction

Sabirzyanova A. A., Galyavich A. S., Baleeva L. V., Galeeva Z. M.

Aim. To evaluate the prognostic value of growth differentiation factor-15 (GDF-15) in patients with acute myocardial infarction (MI).

Material and methods. The study included 118 patients under the age of 70 with ST- and non-ST segment elevation myocardial infarction, who, in addition to routine examination, were tested for GDF-15 by enzyme-linked immunosorbent assay in the first 48 hours from the onset. The statistical significance of the differences in quantitative indicators was assessed by the Student's t-test for a normal distribution and by the nonparametric U Mann-Whitney test for a non-normal distribution, while in qualitative indicators — by Pearson's chi-squared test. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used as an indicator of strength of relationship between quantitative indicators.

Results. The average GDF-15 level in patients with MI was 2,25±1,0 ng/ml. For 6 months of follow-up, 15,25% of patients were rehospitalized for unstable angina or recurrent myocardial infarction. The GDF-15 level in 82,6% of cases was in the third and fourth quartiles (≥2,07 ng/ml). All patients with recurrent MI had GDF-15 levels in the upper quartile (≥2,73 ng/ml). Patients with GDF-15 levels in the upper quartile had a significantly higher risk of rehospitalization (hazard ratio, 3,3 (95% CI, 1,65-6,76), p<0,05) compared with patients with GDF-15 levels in other quartiles. The potential for the combined use of GDF-15 and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels to assess the risk of readmission has been evaluated. Patients who had both GDF-15 and NT-proBNP levels in the upper quartiles (GDF-15 >2,73 ng/ml, NT-proBNP >1418 pg/ml) had 4,8 times higher risk of rehospitalizations for unstable angina or recurrent myocardial infarction.

Conclusion. In patients with MI, the determination of the GDF-15 level has prognostic value and may serve as an additional marker of the risk of recurrent cardiovascular events.

Keywords: growth differentiation factor-15, GDF-15, myocardial infarction; cardiovascular events.

Relationships and Activities: none.

Kazan State Medical University, Kazan, Russia.

Sabirzyanova A. A.* ORCID: 0000-0002-2130-0593, Galyavich A. S. ORCID: 0000-0002-4510-6197, Baleeva L. V. ORCID: 0000-0002-7974-5894, Galeeva Z. M. ORCID: 0000-0002-9580-3695.

*Corresponding author:
S2101-Sash@yandex.ru

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Myocardial infarction (MI) holds one of the leading positions in the hospital mortality structure in patients with a therapeutic profile. In this regard, the search for new markers for a more accurate assessment of patient prognosis continues. Growth differentiation factor-15 (GDF-15) may be a candidate for this role. GDF-15 — one of the proteins of the transforming growth factor-β superfamily. Proteins of this family are involved in the processes of development, differentiation and repair of tissues of various organs. GDF-15 expression is normally found in the placenta and prostate. It was found that GDF-15 can be expressed under the influence of various stress factors, including hypoxia, inflammation, or acute tissue damage, including cardiac muscle [1].

There are not many studies on GDF-15 in patients with MI today. According to the available data, GDF-15 levels are elevated and are independently associated with mortality in patients with MI with both ST-segment elevation (STEMI) and non-ST-segment elevation (NSTEMI) on an electrocardiogram (ECG) [2-4].

Material and methods

The study included 118 patients with STEMI or NSTEMI on ECG. The enrollment criteria were: acute stage of MI, age of patients up to 70 years, signed patient's voluntary informed consent to participate in the study. The exclusion criteria were: age over 70 years; refusal to sign an informed consent to participate in the study; acute inflammatory disease and/or exacerbation of chronic inflammatory disease of any etiology and localization within 6 months before hospitalization; chronic obstructive pulmonary disease; connective tissue diseases; type 1 or type 2 diabetes mellitus; acute cerebrovascular accident or transient ischemic attack in less than 6 months prior to enrollment; any cardiac arrhythmias and conduction disorders requiring medication, including atrial fibrillation, grade II or III atrioventricular blockades, bradycardia ⩽50 beats/min, sinoatrial nodal block; heart failure of class II and higher according to Killip; heart failure with Simpson ejection fraction of <40% according to echocardiography (EchoCG); increased blood creatinine levels >160 mmol/l; increased levels of blood transaminases 3 times or more from upper limit of norm; pregnancy and lactation; alcoholism; drug addiction; cancer in anamnesis of any localization.

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The protocol of this study was approved by the Local Ethics Committee. All participants received written, voluntary, informed consent to participate in the study prior to the enrollment.

All enrolled patients underwent routine examination: general blood analysis; biochemical blood assay, including determination of creatinine, urea, potassium, sodium, lipid profile; blood levels of highly sensitive troponin and NT-pro-brain natriuretic peptide (NT-pro-BNP), glomerular filtration rate by MDRD formula; ECG; daily monitoring of ECG; EchoCG.

In each patient, the GDF-15 level was determined by enzyme immunoassay. Venous blood was collected in the first 48 hours from the beginning of MI clinical picture. After collection, the blood samples were centrifuged and frozen at a temperature of -70° C. The enzyme immunoassay was performed using ELISA Kit for Growth Differentiation factor 15 reagents (Cloud-Clone Corp., USA). The detection range was 0,156-10,0 ng/ml, the sensitivity was 0,065 ng/ml.

The obtained data analysis was carried out according to 110 parameters, including clinical, laboratory and instrumental indicators.

The patients' clinical state was assessed by a survey after 1, 3 and 6 months after their discharge from hospital.

Statistical processing of the obtained data was carried out with the help of computational program STATISTICA v10.0. Quantitative indicators were assessed for compliance with the normal distribution using the Kolmogorov-Smirnov test. The description of quantitative indicators that had a normal distribution was presented in the form of arithmetic averages (M) and standard deviations (σ) in the form of M±σ. Quantitative indicators whose distribution was different from the normal one were described using the values of median (Me) and lower and upper quartiles (Q1-Q3). The statistical significance of differences in quantitative values were assessed by Student's t-test for normal distribution and by non-parametric U Mann-Whitney test for a distribution other than normal. For qualitative indicators, the Pearson criterion χ^2 was applied. The Pearson and Spearman correlation coefficients were applied as an indicator of relationship tightness between quantitative indicators. The results were considered statistically significant at the value of $p<0,05$.

Results

Of the 118 enrolled patients, 82,2% were men. The average age of the enrolled patients was 57,3±8,7 years. In the anamnesis, 65,3% of patients had hypertension disease, and 12,7% of patients had post-infarction cardiosclerosis.

The average GDF-15 level in the acute stage of MI was 2,25±1,0 ng/ml. The patients' division into

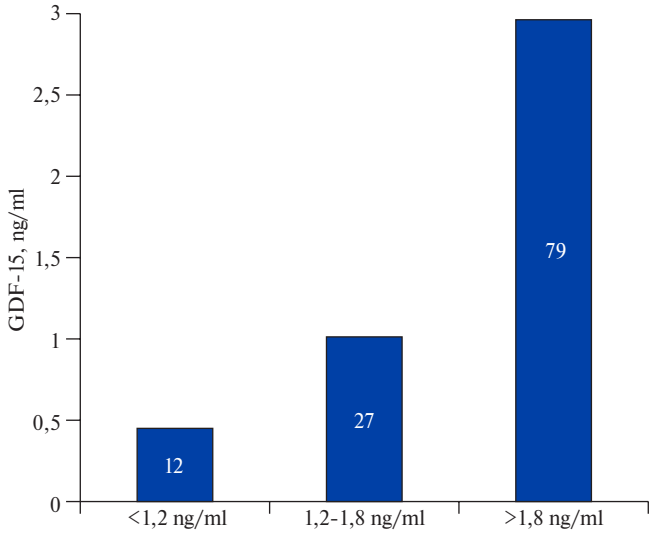

Figure 1. GDF-15 levels in acute stage of MI.
Abbreviation: GDF-15 — growth differentiation factor-15.

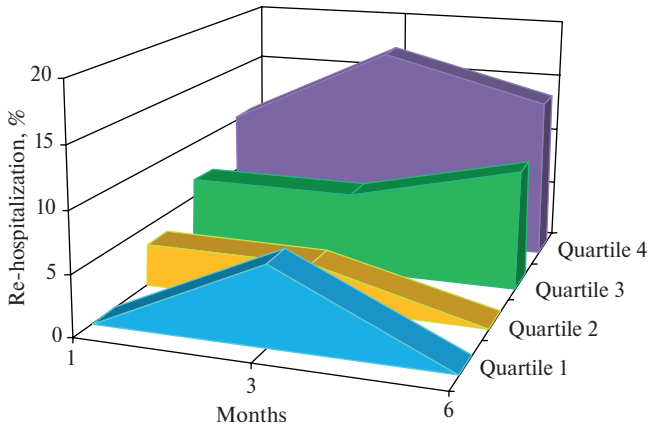

Figure 2. Re-hospitalizations due to unstable angina or recurrent MI in the time section, depending on GDF-15 levels (quartile division).

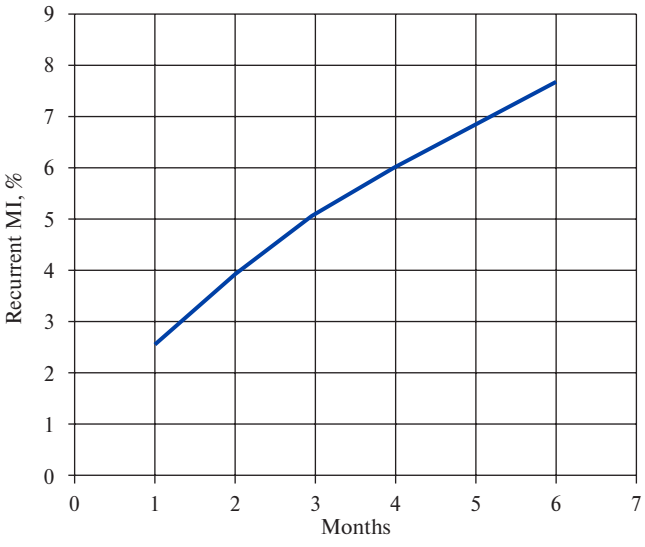

Figure 3. Dependence curve of recurrent MI on time in patients with GDF-15 in the upper quartile (>2,73 ng/ml).

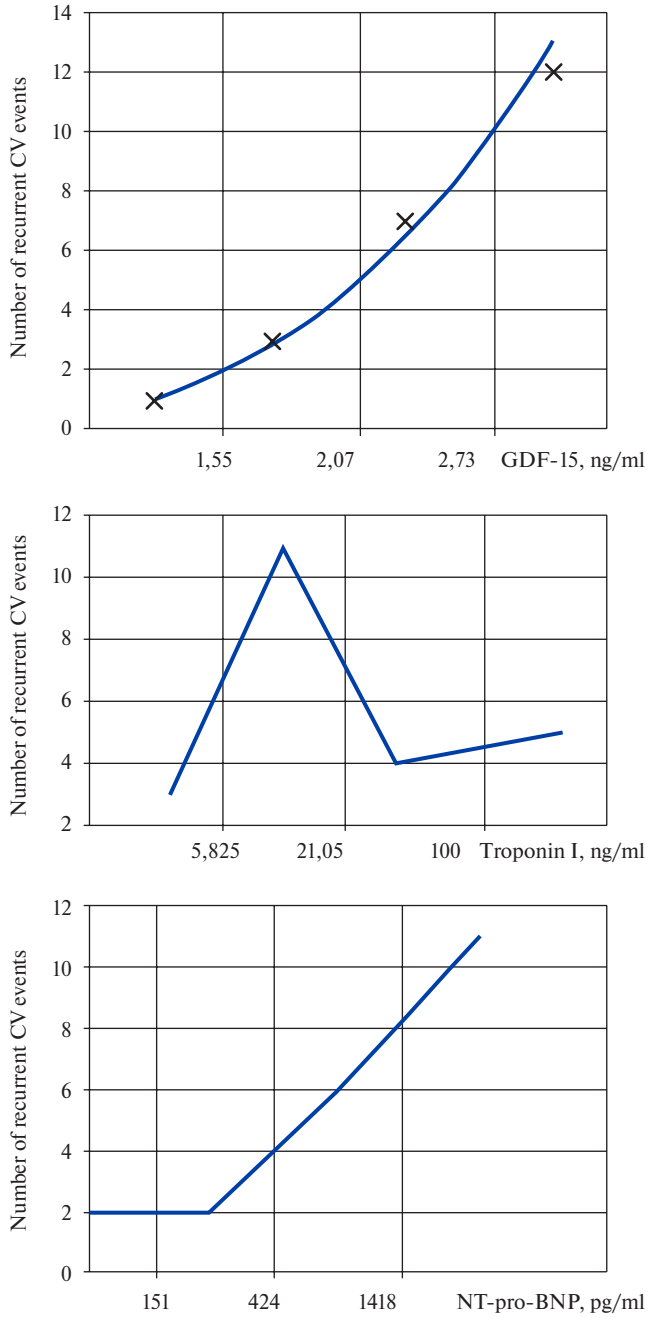

Figure 4. Simultaneous graphs of the dependence of repeated cardiovascular events (hospitalization due to unstable angina and recurrent MI) on the biomarker levels in blood plasma.
Abbreviations: CV — cardiovascular, GDF-15 — growth differentiation factor-15, NT-pro-BNP — NT-pro-brain natriuretic peptide.

groups according to the reference values of GDF-15 <1,2 ng/ml, 1,2-1,8 ng/ml and >1,8 ng/ml was carried out in accordance with the literature data [4]. In 79 patients (66.9%), GDF-15 levels were significantly increased (>1,8 ng/ml), in 27 patients (22,9%) — moderately increased (1,2-1,8 ng/ml), and in 12 (10,2%) — slightly increased (<1,2 ng/ml). The GDF-15 levels by group are shown in Figure 1.

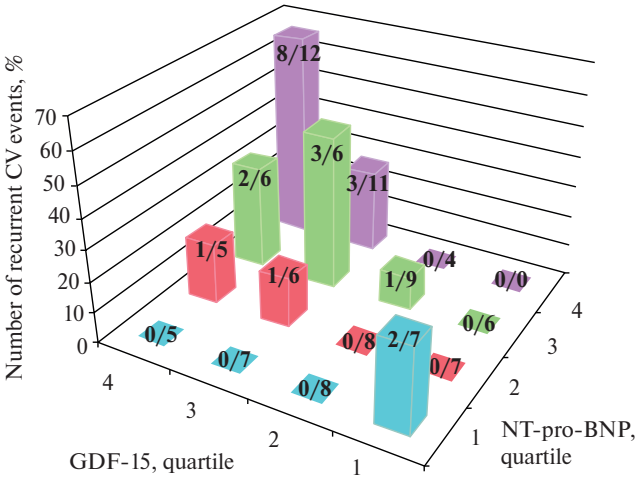

Figure 5. Hospitalization due to unstable angina and recurrent MI in 6 months, depending on the baseline levels of GDF-15 and NT-pro-BNP (quartile division).
Abbreviations: CV — cardiovascular, GDF-15 — growth differentiation factor-15, NT-pro-BNP — NT-pro-brain natriuretic peptide.

As a result of subgroups analysis, differences in the GDF-15 level between men and women (2,26±1,02 ng/ml vs 2,22±0,99 ng/ml, p=0,84), as well as depending on the patients' age were not detected. Association of GDF-15 levels with the presence of hypertension, post-infarction cardiosclerosis, body mass index, smoking history, as well as with the levels of total cholesterol and low-density lipoprotein cholesterol in patients was not detected.

The GDF-15 level was higher in patients with STEMI on ECG compared to patients with NSTEMI (2,36±1,02 ng/ml vs 1,99±0,96 ng/ml, p<0,05), and it was also higher in patients with hypo- or akinesis zones according to EchoCG data (2,35±1,05 ng/ml vs 1,85±0,70 ng/ml, p<0,05) and in patients without left ventricular hypertrophy according to EchoCG data (2,51±1,09 ng/ml vs 2,10±0,94 ng/ml, p<0,05).

All revealed correlations of GDF-15 levels with laboratory and tool parameters were of moderate or weak order: with NT-pro-BNP level (r=0,36, p=0,0001), with the number of white blood cells (r=0,32, p=0,0003), with troponin I levels (r=0,21, p=0,02) and urea (r=0,20, p=0,04), with the Simpson left ventricular ejection fraction (r=-0,32, p=0,0003) and thickness of interventricular septum according to EchoCG data (r=-0,26, p=0,004).

For further analysis of the obtained results, the GDF-15 levels were divided into quartiles: quartile 1 — <1,55 ng/ml, quartile 2 — 1,55-2,07 ng/ml, quartile 3 — 2,07-2,73 ng/ml, quartile 4 — >2,73 ng/ml.

During 6 months of follow-up, 15,25% of patients had repeated hospitalizations for unstable angina or recurrent MI (23 cases). During the first month of follow-up, there were 6 hospitalizations (1 of them due to recurrent MI); for 3 months — 10 re-hospitalizations (2 of them due to recurrent MI); for 6 months of follow-up — 7 hospitalizations (3 of them due to recurrent MI).

The GDF-15 level in 82,6% of cases of repeated hospitalizations was in the upper (third and fourth) quartiles. Figure 2 demonstrates a graph of repeated hospitalizations due to unstable angina or recurrent MI, depending on the GDF-15 levels.

In all patients with recurrent MI, the GDF-15 level was in the upper quartile (>2,73 ng/ml). This relationship with MI in patients with GDF-15 levels in the upper quartile was close to linear (Figure 3).

We compared the effects of baseline levels of cardiac troponin I, NT-pro-BNP and GDF-15 on re-hospitalizations. For this purpose, the levels of troponin I and NT-pro-BNP were divided into the quartiles. For troponin I: quartile 1 — <5,82 ng/ml, quartile 2 — 5,82-21,05 ng/ml, quartile 3 — 21,05-100 ng/ml, quartile 4 — >100 ng/ml, For NT-pro-BNP: quartile 1 — <151,0 pg/ml, quartile 2 — 151,0-424,0 pg/ml, quartile 3 — 424,0-1418,0 pg/ml, quartile 4 — >1418,0 pg/ml.

Patients with GDF-15 levels in the upper quartile had a higher risk of re-hospitalization for unstable angina and recurrent MI (risk ratio (HR) 3,3 (95% confidence interval (CI) 1,65-6,76), p<0,05) compared to patients with GDF-15 levels in other quartiles. In 20,6% of patients whose GDF-15 level was in the upper quartile, recurrent MI was recorded during 6 months of follow-up. The high NT-pro-BNP levels were also associated with a significant increase in the hospitalization risk due to unstable angina and recurrent MI (RR 6,2 (95% CI 1,21-32,08), p<0,05). The significant association of cardiac troponin I levels with recurrent cardiovascular events was not detected. Figure 4 demonstrates the graphs of repeated cardiovascular event dependence (hospitalization due to unstable angina and recurrent MI) on levels of biomarkers in blood plasma over the follow-up period of 6 months.

We assessed the possibility of combining GDF-15 and NT-pro-BNP levels to assess the risk of repeated hospitalizations for unstable angina and recurrent MI. Patients with GDF-15 and NT-pro-BNP levels in the upper quartiles (GDF-15 2,73 ng/ml, NT-pro-BNP 1418 pg/ml) had 4,8 times higher risk of re-hospitalization compared to patients with both of these biomarkers in the lower quartiles (RR 4,8 (95% CI 2,55-9,27), p<0,05). 66,6% of patients with GDF-15 and NT-pro-BNP levels in the upper quartiles within 6 months were re-hospitalized. Figure 5 demonstrates a graph of hospitalizations due to unstable angina and recurrent MI over the follow-up period of 6 months, depending on baseline levels of GDF-15 and NT-pro-BNP.

Discussion

A number of studies have identified relationships between GDF-15 levels and other cardiac markers. In the PROVE IT TIMI-22 study, patients with MI showed a moderate correlation of GDF-15 levels with NT-pro-BNP and C-reactive protein r=0,24, (p<0,001 for each indicator) [5]. In our study, a moderate correlation was detected between the levels of GDF-15 and NT-pro-BNP (r=0,36, p=0,0001), and a weaker relationship between the levels of GDF-15 and troponin I (r=0,21, p=0,02). The absence of a correlation between the levels of GDF-15 and cardiac troponin in the study [5] can be explained by the fact that blood sampling followed by determination of GDF-15 concentration was carried out during 3-5 days from the development of MI clinical picture, while the enrollment of patients with subsequent blood sampling was carried out earlier — within 48 hours from MI onset. It is understood that GDF-15 levels do not change significantly over 4 months after MI [5]. The GDF-15 levels of do not show the typical dynamics in the form of an increase followed by a drop in blood concentration, unlike cardiac troponins. Such changes in laboratory parameters over time can explain the presence or absence of relationships between the GDF-15 and troponin levels in different studies.

In the GUSTO-IV study, two-thirds of patients with NSTEMI had GDF-15 levels >1,2 ng/ml [4]. In our study, 89,8% of patients had GDF-15 level >1,2 ng/ml, It should be noted that our study included patients with both STEMI on ECG and NSTEMI, and GDF-15 levels were higher in patients with STEMI (2,36±1,02 vs 1,99±0,96, p<0,05).

The results of studying the GDF-15 levels as a prognostic marker in patients with MI were presented in several studies. In the GUSTO-IV study, it was noted that in patients with GDF-15 levels >1,8 ng/ml, the mortality rate for 1 year was 14,1%. It was concluded that the GDF-15 levels are associated with mortality rate in patients with NSTEMI [4].

In our study, it was not possible to assess the relationship of GDF-15 with the mortality rate of patients with MI, because during the follow-up period of 6 months, no deaths were reported. At the same time, patients with GDF-15 levels in the upper quartile had a higher risk of re-hospitalization for unstable angina and recurrent MI (RR 3,3 (95% CI 1,65-6,76), p<0,05) compared to patients with GDF-15 levels in the lower three quartiles.

In the PROVE IT TIMI-22 study, the elevated GDF-15 levels were also associated with a significantly higher risk of death or recurrent MI (5,5% vs 12,6%; RR 2,40 (95% CI 1,88-3,06); p<0,001) [5].

In our study, the high NT-pro-BNP level was associated with an increased risk of hospitalization due to unstable angina and recurrent MI, and also showed a significant association with the occurrence of recurrent MI (RR 6,2 (95% CI 1,21-32,08), p<0,05). The combined use of the two biomarkers in our study was more pronounced: patients whose GDF-15 and NT-pro-BNP levels were in the upper quartiles had a 4.8 times higher risk of re-hospitalization due to unstable angina and recurrent MI.

It is acknowledged that the GDF-15 level reflects integral information on cell oxygenation, inflammatory response, and cardiac dysfunction [6]. In addition, there is evidence that the GDF-15 and NT-pro-BNP levels are associated with the level of soluble angiotensin converting enzyme of type 2 and cause a high risk of mortality [7]. There are also facts confirming the direct effect of GDF-15 on the processes of inflammation, hypertrophy and fibrosis leading to heart failure [1].

Based on the above-described pathological processes in the heart and the results obtained by us, it can be assumed that the GDF-15 level determination can be included in the multi-marker risk stratification scales for patients with MI along with the NT-pro-BNP level. One of the previous studies showed the possibility of GDF-15 integration into risk scales for patients with MI, namely, the inclusion of GDF-15 in the GRACE scale increased the prognostic value of the scale in patients with NSTEMI [8].

Study limitations: small sample of patients, small number of repeated cardiovascular events, including the absence of fatal outcomes for 6 months of follow-up.

Conclusion

1. In patients with MI, the elevated GDF-15 level reflects a high risk of re-hospitalizations due to unstable angina and recurrent MI within 6 months.
2. The GDF-15 level has a prognostic value and can serve as an additional marker of the risk of repeated cardiovascular events.

Relationships and Activities: none.

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