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GROWTH DIFFERENTIATION FACTOR 15 AS AN INTEGRAL MARKER OF CLINICAL AND FUNCTIONAL STATUS OF PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

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Aim. To study the relationship between growth differentiation factor 15 (GDF-15) level in blood serum and patient clinical and functional status parameters, and to determine predictors of GDF-15 level in pts with non-valvular atrial fibrillation (AF).

Material and methods. Eighty-seven pts (with the mean age of 56.9±9.2 years) with non-valvular AF were studied. A general clinical examination, as well as echocardiography and laboratory tests were performed. These included fasting serum glucose (mmol/l), highly sensitive C-reactive protein (h/s CRP) (mg/l), creatinine level (μmol/l) and subsequent calculation of glomerular filtration rate (ml/min/1.73m^2), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/ml). The level of GDF-15 (pg/ml) in blood serum was determined using an enzyme immunoassay with a human ELISA analytical kit.

Results. An increase in GDF-15 level was associated with age, ischemic heart disease, severity of hypertension, and heart failure, resulting in a higher risk of stroke, according to the CHA_2DS_2 -VASc score, carbohydrate metabolism disorders and obesity, increased h/s CRP and NT-proBNP levels, enlargement of the right and left atria, signs of diastolic left ventricular dysfunction and structural remodeling in the form of eccentric hypertrophy. Multiple linear regression analysis revealed 2 independent predictors of GDF-15 levels: age and fasting glucose.

Conclusion. GDF-15 is an integral biomarker of age-related metabolic disorders and structural and functional changes in the heart, which opens up prospects for further study of its prognostic significance in pts with non-valvular AF.

Key words: non-valvular atrial fibrillation; growth differentiation factor 15; structural remodeling of left ventricle; heart failure with preserved left ventricular ejection fraction

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Atrial fibrillation (AF) is the most common type of arrhythmia and is associated with a two-fold increased risk of death and a five-fold increased risk of stroke [1]. Since the number of AF in recent decades has increased significantly [2], the search for predictors of adverse outcomes in patients (pts) with AF is vital. Currently, the CHA_2DS_2-VASc clinical score is used for stroke risk stratification in non-valvular AF [3, 4]. There is plenty of evidence, however, that the assessment of clinical factors alone is not sufficient to determine risk in patients with AF.

Recently, much research has been done on risk stratification of adverse cardiovascular events in pts with AF various biomarkers circulating in their blood [5, 6]. Thus, in a subanalysis with RE-LY biomarkers, it has been shown that increased levels of certain biomarkers, namely N-terminal pro-B-type natriuretic peptide (NT-proBNP) and highly sensitive troponin I, is associated with higher rates of cardiovascular death and thromboembolic complications. Their addition to CHA_2DS_2-VASc therefore helps in improving its predictive value [7]. Subanalysis with ARISTOTLE biomarkers in pts with AF demonstrated the potential use of growth differentiation factor 15 (GDF-15) in risk stratifying - not only for cardiovascular and overall mortality, but also of major bleeding [8].

It is well-known that various cardiovascular risk factors, including age, arterial hypertension (HTN), obesity, and diabetes mellitus, are involved in the pathogenesis of AF through diastolic left ventricular (LV) dysfunction [9, 10] and eventual congestive heart failure (CHF) with preserved LV ejection fraction (LVEF). Since GDF-15 is expressed by many different types of cells in response to inflammation and myocardial stress [11, 12] and has great prognostic potential in pts with AF, it was interesting to study which clinical and functional parameters cause an increase in GDF-15 levels in pts with non-valvular AF and preserved LVEF.

This work aimed to study the relationship between GDF-15 level in blood serum and clinical and functional status parameters and to determine independent predictors of GDF-15 level in pts with non-valvular AF.

MATERIAL AND METHODS

A single-stage cohort study included 87 pts with non-valvular AF aged 27 to 72 years (mean age 56.9±9.2) consisted of 32 women and 55 men hospitalized at Tyu-

men Cardiology Research Center from April 2018 to October 2019 for primary radiofrequency pulmonary vein isolation. The exclusion criteria were thrombosis of left atrial appendage according to transesophageal echocardiography (EchoCG), acute or decompensated chronic comorbidities, chronic obstructive pulmonary disease, pregnancy, and patient refusal to participate in the study. The clinical characteristics of the patients are presented in Table 1.

Table 1.

Clinical characteristics of patients

Characteristics	Indicators
Age (years)	56.9±9.2
Female, n (%)	32 (37%)
HTN, n (%):	74 (85%)
HTN 1 stage, n	10
HTN 2 stage, n	32
HTN 3 stage, n	32
IHD, n (%):	31 (35.6%)
IHD + HTN, n	29
Previous MI, n	4
CHF, n (%)	68 (78.2%)
CHF I FC, n	30
CHF II FC, n	34
CHF III FC, n	4
Paroxysmal AF, n (%)	62 (71.3%)
Persistent AF, n (%)	25 (28.7%)
Lone AF, n (%)	11 (12.6%)
HD AF<1 year, n	10
HD AF from 1 to 3 years, n	29
HD AF >3 years, n	48
No CM disorders, n (%)	74 (85.1%)
Impaired fasting glycemia, n (%)	3 (3.4%)
Impaired TT to glucose, n (%)	4 (4.6%)
Diabetes mellitus type 2, n (%)	6 (6.9%)
Obesity:	
No obesity, n (%)	42 (48.3%)
Obesity I degree, n (%)	27 (31.0%)
Obesity II degree, n (%)	17 (19.5%)
Obesity III degree, n (%)	1 (1.2%)
CHA_2DS_2-VASc (average score)	1.9
CHA_2DS_2-VASc 0 score, n	5
CHA_2DS_2-VASc 1 score, n	28
CHA_2DS_2-VASc 2 score, n	29
CHA_2DS_2-VASc 3 score, n	18
CHA_2DS_2-VASc 4 score, n	5
CHA_2DS_2-VASc 5 score, n	1
CHA_2DS_2-VASc ≥2 score, n	53
HAS-BLED 0 score, n	65
HAS-BLED 1 score, n	18
HAS-BLED 2 score, n	4

Notes: HTN - arterial hypertension, IHD - ischemic heart disease, MI - myocardial infarction, CHF - congestive heart failure, FC - functional class, AF - atrial fibrillation, HD - history of disease, CM - carbohydrate metabolism, TT - tolerance test.

All pts had symptomatic AF, including 71.3% with paroxysmal AF and 28.7% with persistent AF. The majority suffered from HTN - 74 (85%). Lone AF was observed in 11 pts (12.6%). Sixty-eight pts (78.2%) had signs of CHF, in which I and II functional class of CHF prevailed (73.5%).

Drug therapy included oral anticoagulants (OAC), antiarrhythmic drugs (AAD), and basic therapy for underlying diseases. OAC therapy was started in all pts before hospitalization and continued throughout their stay at the clinic. The distribution by type of OAC was as follows: dabigatran - 23 pts, rivaroxaban - 26, apixaban - 21, warfarin (with the maintenance of target INR level from 2 to 3) - 17 pts. Regarding AAD, 14 pts took amiodarone, 18 - propanorm (propafenon), 20 - sotalol, 6 - allapinin (lappaconitine hydrobromide), 21 - β-blockers and 8 pts did not take AAD. Angiotensin-converting enzyme inhibitors or sartans were taken as baseline therapy by 59 pts, diuretics by 24 pts, statins by 59 pts, and calcium antagonists by 11 pts.

All pts underwent detailed transthoracic EchoCG with assessment of chamber size and volume, structural and functional state of the heart, type of heart geometry [13], as well as LV diastolic function following the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) [14]. The studies were performed using a Vivid E9 ultrasound scanner (General Electric Medical Systems, USA) with subsequent recording on a hard disk and calculation of the mean values for 3 consecutive cardiac cycles. The type of LV geometry was determined based on calculations of LV myocardial mass index (MMI) and LV relative wall thickness (RWT) according to ASE and EACI Guidelines [13]. The following types of LV geometry were distinguished: type 1 (normal heart geometry): normal LVMMI (≤95 g/m^2 for women and ≤115 g/m^2 for men) and RWT ≤0.42; type 2 (concentric remodeling): normal LVMMI and RWT >0.42; type 3 (concentric hypertrophy): increased LVMMI (>95 g/m^2 for women and >115 g/m^2 for men) and RWT >0.42; type 4 (eccentric hypertrophy): increased LVMMI and RWT ≤0.42.

Laboratory methods of investigation included complete blood count and biochemical blood test including fasting glucose levels (mmol/L), creatinine (μmol/L), followed by calculation of glomerular filtration rate (GFR) using CKD-EPI formula (ml/min/1.73 m^2), NT-proBNP (pg/mL), high-sensitivity C-reactive protein (h/s CRP) (mg/L).

Determination of GDF-15 level venous blood was taken on an empty stomach; after centrifugation for 15 minutes at 2500 rpm, blood serum was aliquoted for further freezing (at -70 °C). GDF-15 level (pg/ml) in blood serum was determined by a quantitative method using a direct enzyme immunoassay. We used a Stat Fax 4200 microplate photometer (USA), an analytical kit «Human

GDF-15/MIC-1 ELISA» (BioVender, Czech Republic), intended for research purposes, with determination range from 35 to 2240 pg/ml. Median values in different age groups were taken as indicative reference values (according to the instructions): 378-648 pg/ml for men, 444-653 pg/ml for women.

Statistical data analysis

The data were statistically processed using Statistica 12.0 software package. The distribution of continuous variables was investigated using the Kolmogorov-Smirnov test. Data were presented as median (Me) and interquartile range [25%; 75%]. The Mann-Whitney U-test was used when comparing indicators in 2 independent groups concerning abnormal distribution; when comparing 3 or more independent groups, the Kruskal-Wallis test with Bonferroni correction was used. Qualitative indicators were compared using the χ^2 test and Fisher's exact test. Evaluation of correlations between pairs of quantitative characteristics was carried out with normal distribution using Pearson's correlation coefficient, and, in the absence of normal distribution, using Spearman's rank correlation coefficient. Multiple linear regression with stepwise inclusion of variables was used to determine independent predictors of GDF-15 level. The results were assessed as statistically significant at $p < 0.05$; at $p \leq 0.1$ - as a statistical trend.

The study complies with the provisions of the Declaration of Helsinki and the study protocol has been approved by the local ethics committee. Informed consent was obtained from all subjects.

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RESULTS

GDF-15 levels in pts in the study ranged from 204 to 1752 pg/mL, with a median of 767.5 [590.0; 951.0] pg/mL. Correlation analysis of GDF-15 levels with clinical and demographic parameters showed a positive moderate relationship between GDF-15 and age: r=0.5262 (p=0.00002) (Fig. 1a). Comparative analysis showed no significant differences in the level of GDF-15 between men and women: 750.0 [546.0; 924.5] and 788.0 [665.0; 988.0] pg/mL, respectively (p=0.2471). Higher levels of GDF-15 were observed in pts with cardiovascular diseases (CVD) compared to pts with isolated AF: 810.7 [630.0; 965.0] and 590.0 [381.0; 759.0] pg/mL, respectively (p=0.023112). There was a tendency towards higher levels of GDF-15 in pts with ischemic heart disease compared to those who did not have it: 838.3 [692.0; 951.0] and 720.0 [504.0; 961.5] pg/mL, respectively (p=0.0729). No association of GDF-15 level with such clinical characteristics as history and form of AF was found. There was also no correlation between GDF-15 level and such factors as smoking and history of anemia.

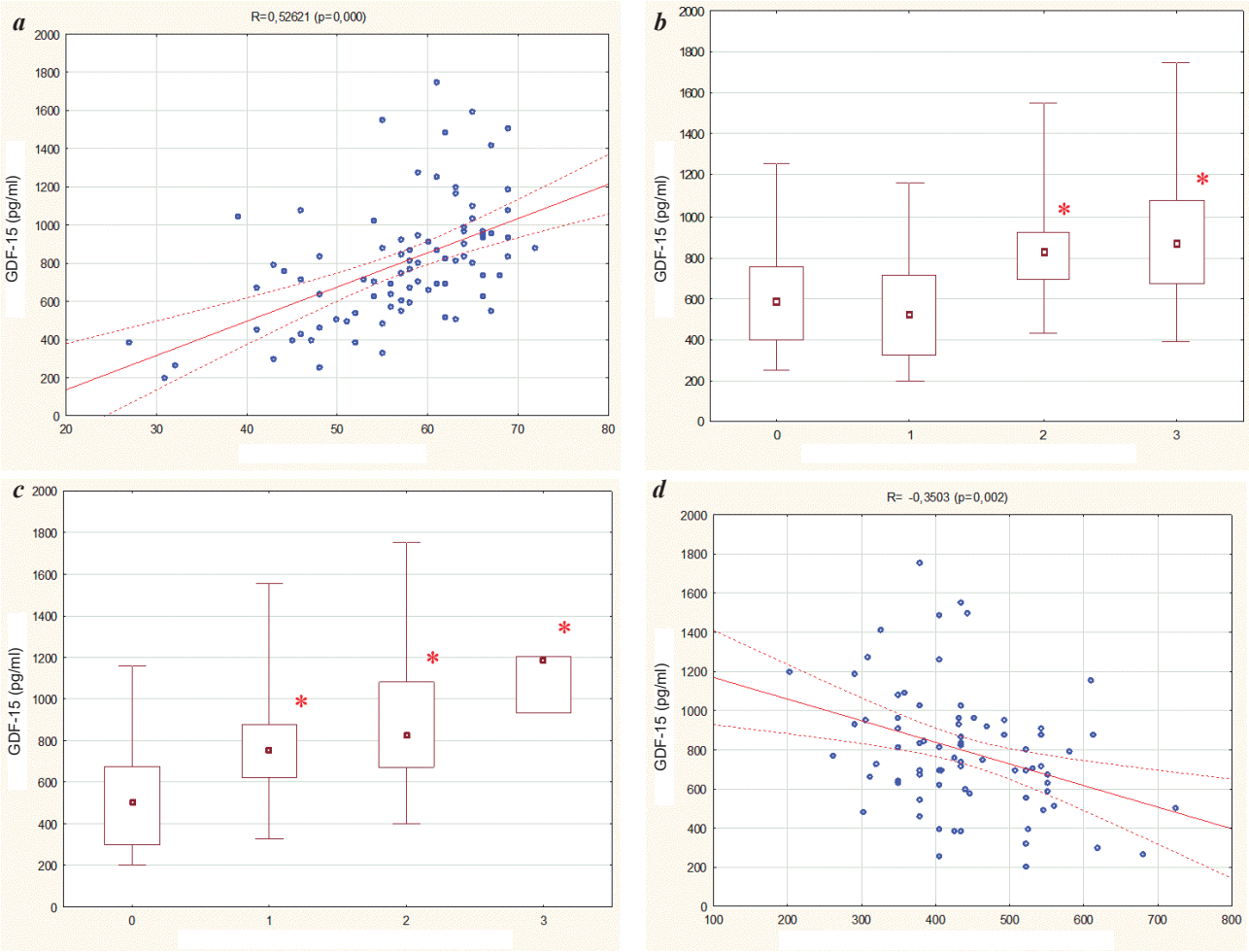

Fig. 1. Data of correlation and comparative analysis characterizing the relationship between the level of GDF-15 with: a - age, b - presence and stage of arterial hypertension (HTN), c - functional class (FC) of congestive heart failure (CHF), d - distance in 6-minute walk test; * - p<0.05 compared to the absence of HTN or CHF.

An increase in GDF-15 level was found in the presence of HTN, gradually rising with the progression of the disease (p=0.0126) and the grade of HTN (p=0.0024) (Fig. 1b). Also, GDF-15 level increased in the presence and severity of CHF (Fig. 1c), a weak negative relationship between the level of GDF-15 and the distance in 6-minute walk test was found: r=-0.35 (p=0.002) (Fig. 1d). Following the above correlations, GDF-15 levels statistically significantly increased with rising risk of thromboembolic complications (TEC) according to the CHA_2DS_2-VASc scale (p=0.0041) (Fig. 2). However, there was no correlation between GDF-15 level and HAS-BLED score. This may be because there were no pts with a high risk of bleeding in the study group.

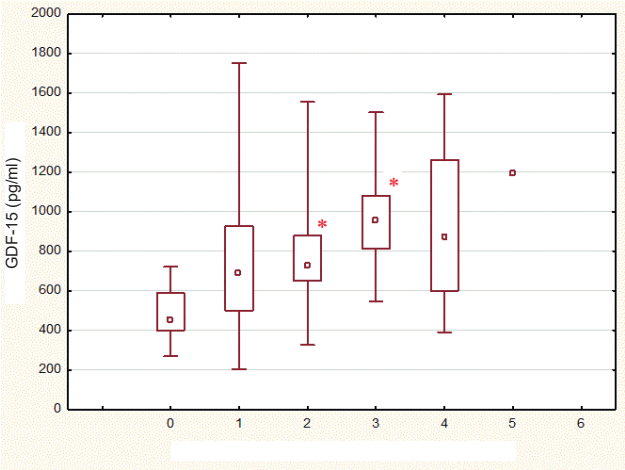

Fig. 2. GDF-15 level depending on the risk on CHA_2DS_2-VASc score, where * - p<0.05 compared to 0 score.

There was a tendency towards a higher level of GDF-15 in pts with diabetes mellitus compared to those without it: 1074.0 [910.0; 1487.0] and 754.7 [582.3; 941.5] pg/mL, respectively (p=0.0760), as well as a moderate positive correlation with fasting blood glucose: r=0.4048 (p=0.0001). As for the association of GDF-15 level with disorders of fat metabolism, a weak positive association of GDF-15 level with body mass index (BMI) was found r=0.21 (p<0.05). When studying the relationships between GDF-15 level and other biomarkers, weak positive relationships were found with the level of h/s CRP (r=0.2924, p=0.01) and NT-proBNP (r=0.2407, p=0.03), as well as a weak negative relationship with GFR (r=-0.2832, p=0.009). No significant relationship with blood creatinine level was noted.

The study of the relationship between GDF-15 level and echocardiographic parameters did not reveal any correlations with LV systolic function sizes and indices, mean LVEF was 64.6±7.8%. At the same time, there was a weak positive correlation between GDF-15 and right atrial volume (Fig. 3a) and left atrial size (Fig. 3b), as well as a moderate negative correlation with such indices of LV diastolic function as the velocity of septal (Fig.3c) and lateral parts of the fibrous ring of the mitral valve in diastole (Fig. 3d).

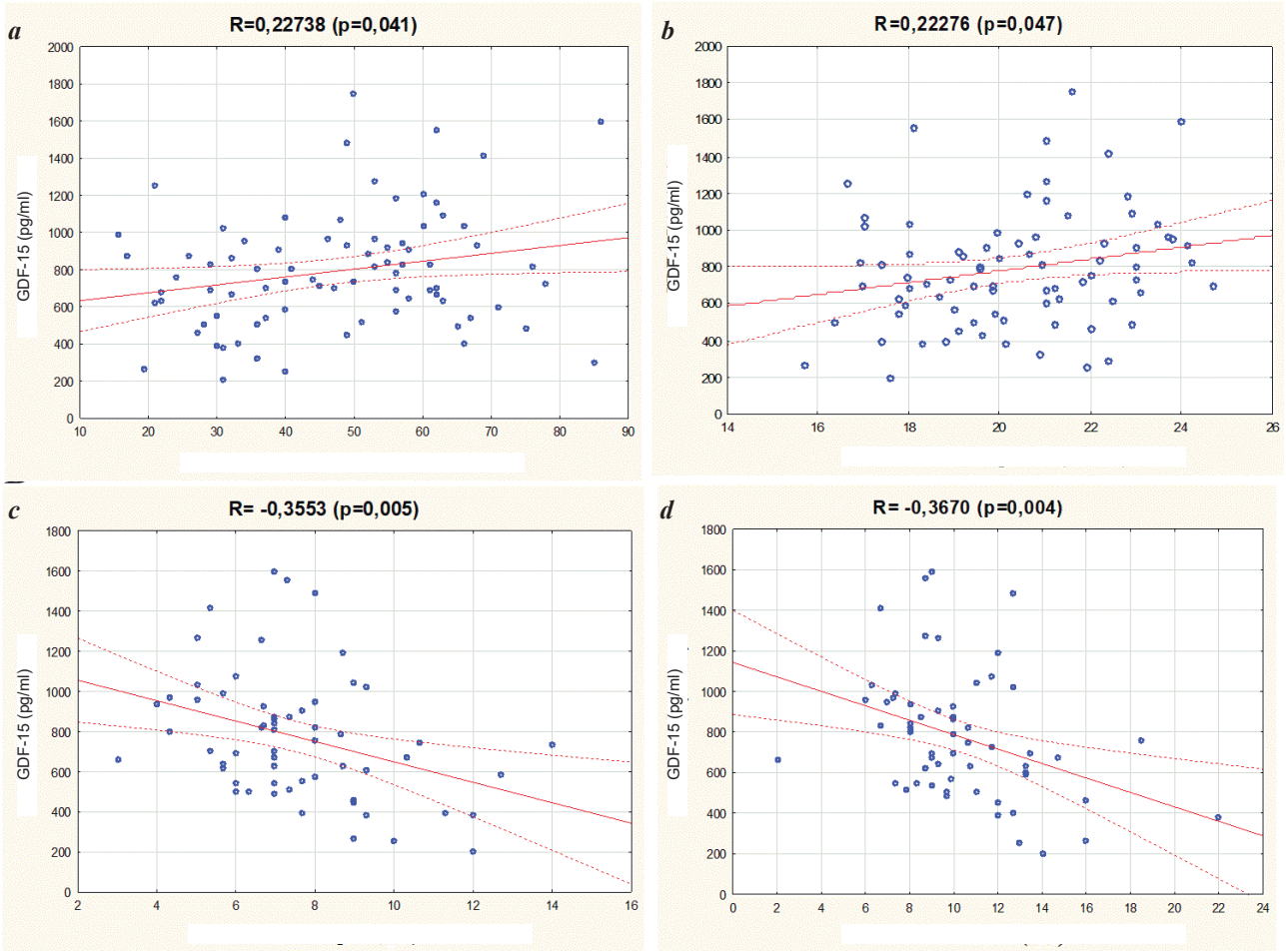

Fig. 3. Correlations between GDF-15 level and echocardiographic parameters: a - right atrial (RA) volume, b - left atrial (LA) size, velocity of septal (c) and lateral (d) parts of mitral valve fibrous ring in diastole.

It was of interest to study the relationship between the level of GDF-15 in the blood and structural LV remodeling since we previously demonstrated that the severity of LA fibrosis depended on the type of heart geometry [15]. According to the above criteria, pts were grouped according to the type of heart geometry: normal geometry - 46 people, concentric remodeling - 20, concentric hypertrophy - 7, eccentric hypertrophy - 14. GDF-15 level in pts with normal heart geometry was conventionally taken as the reference GDF-15 level. Comparative analysis showed higher GDF-15 levels only in pts with eccentric hypertrophy compared to patients without structural heart remodeling (Fig. 4), which agrees with our previously published data: it was eccentric LV hypertrophy that was an independent predictor of severe fibrosis, ≥35% of LA area [15].

To compare the contribution of all the above factors that have significant associations with GDF-15 level in its variance as well as identify independent predictors of GDF-15 level, we applied multiple linear regression analysis with the method of stepwise inclusion of variables. GDF-15 level was taken as a dependent variable, while all variables (clinical and demographic, biomarkers, EchoCG data) which showed a significant correlation with GDF-15 level, were taken as independent factors. The results are presented in Table 2.

As shown in the table, the independent predictors of GDF-15 level were two variables that had the greatest effect on the dispersion of GDF-15 value: age and fasting blood glucose level. The predictors were ranked in descending order by the significance of their influence on GDF-15 level and are as follows: age (regression coefficient β=0.5017, p=0.0001), fasting blood glucose level (β=0.2757, p=0.0254). A positive regression coefficient for both predictors means that blood GDF-15 levels increase with age and fasting blood glucose.

DISCUSSION

GDF-15 (MIC-1) is a member of the cytokine superfamily of transforming growth factor β (TGF-β) [16, 17]. It is expressed by many different types of cells, including adipocytes and myocytes, in response to inflammation and stress: e.g., cell ischemia, mechanical and oxidative stress [6, 11, 12]. Although GDF-15 is widely expressed in various tissues under physiological conditions, its expression level increases in response to pathological stress associated with inflammation or tissue damage [18, 19].

According to our data, the GDF-15 level correlates both with risk factors and severity of CVD, which, in turn, are closely associated with the development of AF. Thus, statistically significant correlations of GDF-15 with such factors as age, BMI, the severity of HTN, CHF, GFR, and NT-proBNP confirm this. Our results correspond with the data of other researchers who proved that the level of GDF-15 was associated with almost all risk factors for CVD (age, carbohydrate metabolism disorders, GFR, obesity) [8, 19]. The difference in our data was that we did not obtain an association of GDF-15 level with male gender, smoking, and persistence of AF [8]. This may be due to the small size of the study group.

Similar to ARISTOTLE biomarker subanalysis [8], we obtained a significant correlation of GDF-15 level with CHA_2DS_2-VASc score; moreover, GDF-15 level increased progressively with increasing risk of TEC. In contrast to our data, Tong Liu et al. in their study on the association of GDF-15 with the CHA_2DS_2-VASc scale found no difference in GDF-15 level in low-risk and high-risk patients, explaining this by the peculiarities of the Chinese population and the small size of the study group [20]; at the same time, the predictive value of GDF-15 levels did not depend on the CHA_2DS_2-VASc score.

Our data on the relationship between the level of GDF-15 and impaired carbohydrate and fat metabolism, as well as with h/s CRP, are consistent with the results of other researchers. Thus, according to I. Dostalova et al., an increase in the concentration of GDF-15 in blood serum was associated with an increase in BMI, adipose tissue mass, and levels of triglycerides, glucose, glycated hemoglobin, and CRP in blood serum [19]. The co-authors believe that MIC-1 (GDF-15) can be considered as "a possible etiopathogenetic candidate and/or metabolic marker of obesity and such associated diseases as insulin resistance or type 2 diabetes mellitus" [19]. M. Carstensen et al. published the results of a prospective cohort study showing that base-

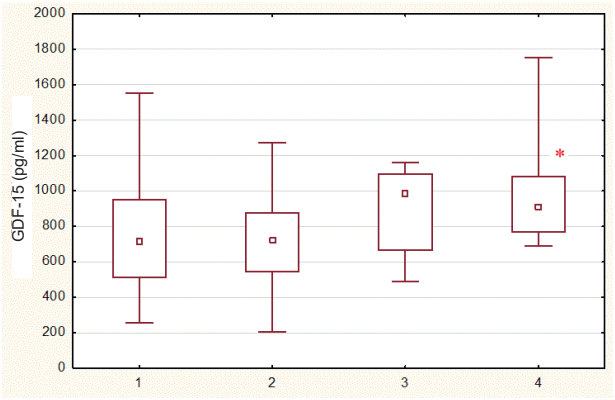

Fig. 4. Comparison of GDF-15 level between patients with different types of heart geometry, where 1 - normal geometry, 2 - concentric remodeling, 3 and 4 - concentric and eccentric hypertrophy, * - p=0.0161 between geometry types 1 and 4.

Table 2.

Results of multiple linear regression analysis

Predictors	R=0.6045, R2=0.3854 F(3.45)=8.4340 p<0.00015					
	β	Standard error β	B	Standard error B	t (45)	p
Free term			-994.07	389.56	-2.55	0.0142
Age (years)	0.5017	0.1193	17.83	4.24	4.21	0.0001
FBG (mmol/l)	0.2757	0.1193	126.01	54.51	2.31	0.0254

Note: FBG - fasting blood glucose.

line GDF-15 levels were significantly higher in individuals who subsequently developed type 2 diabetes mellitus compared to those who did not [21]. The relationship between GDF-15 and h/s CRP revealed in our study can also confirm the concept of the role of immune inflammation in the development and progression of CHF with preserved LVEF [22], including pts with AF.

As it has been already noted above, many risk factors of AF realize their role in the pathogenesis of AF through the development of diastolic LV dysfunction [9], leading, to progressive heart failure with preserved LVEF. This was reflected in the results we obtained. GDF-15 level correlated positively with indicators characterizing the volume and size of the right and left atria but negatively with the velocity of septal and lateral parts of the fibrous ring of the mitral valve in diastole. At the same time, an increase in GDF-15 level was associated with a rise in the functional class of CHF, a decrease in the distance in the 6-min walk test, and an increase in NT-proBNP level. This data corresponds with the results of other researchers. Thus, according to R. Stahrenberg et al. increased GDF-15 levels correlated with certain markers, namely LV diastolic dysfunction as E/e' and LA volume index and LVMMI and was independently associated with decreased distance in 6-min walk test [23]. A study by O.M.Drapkina et al. showed a negative association of GDF-15 level with the ratio of peak E to peak A of trasmitral blood flow in diastole (r=-0.26) [22]. These studies, as well as our data, show that GDF-15 may be a potential indicator of a grade of diastolic dysfunction and may also serve as an additional biomarker for the diagnosis of CHF with preserved LVEF.

When studying the relationship between the level of GDF-15 and LV structural remodeling, an increase in GDF-15 levels was found in pts with eccentric LV hypertrophy. As mentioned above, this type of geometry combines 2 features: the presence of LV myocardial hypertrophy and RWT ≤0.42.

LV hypertrophy is known to be a strict marker of adverse outcomes in various populations: from the general population to the population of persons affected by CVD [24], but it is not included in the risk assessment score for TEC in non-valvular AF [4]. According to RE-LY analysis, it was found that LV hypertrophy detected by electro-, or echocardiography is a marker of increased risk of adverse outcomes in pts with AF [25]. Subanalysis RE-LY with biomarkers investigated the association of cardiac biomarkers and LV hypertrophy with adverse outcomes in patients with non-valvular AF [24]. It was found that the GDF-15 level in pts with LV hypertrophy was higher than in pts without it, although LV hypertrophy yielded biomarkers including GDF-15 in predicting the risk of death and stroke; when considered together as predictors, it lost its independent predictive value. We did not find statistically significant correlations between GDF-15 level and the thickness of the interventricular septum, LV posterior wall, and LVMMI, but we found a relationship between GDF-15 level and the presence of eccentric LV hypertrophy which, along with hypertrophy, is characterized by the initial signs of LV dilatation. Moreover, we did not find any data in literature indicating the association of GDF-15 level with the presence of a certain type of heart geometry and, in particular, eccentric LV hypertrophy.

Age was the most significant and independent predictor of GDF-15 level. This corresponds with a large amount of evidence that GDF-15 is a marker of body aging and is associated with the deterioration of biological functions [18, 19, 26]. There is evidence that mitochondrial dysfunction is one of the signs of aging associated with the pathogenesis of many age-related disorders [26]. Another independent predictor of GDF-15 in our study was fasting blood glucose level. It should be noted that the presence of signs of mitochondrial dysfunction was also found in insulin resistance and diabetes mellitus [27]. It has been shown that GDF-15 can be used as a diagnostic marker of mitochondrial diseases - congenital disorders caused by mitochondrial and nuclear genomic mutations that lead to defective mitochondrial oxidative phosphorylation and impaired energy production [27]. It can be assumed that the predictors of increased GDF-15 level that we identified may, in turn, be united by the presence of mitochondrial dysfunction, which is one of the manifestations of an organism aging.

Thus, our data confirm that GDF-15 is an integral marker of cellular stress, organ dysfunction and biological aging of the cardiovascular, endocrine, and renal systems [6, 28]. Further studies are needed to determine the reference levels of GDF-15 in different age groups with and without CVD [28], to study the prospects for using GDF-15 in the search for new targets and the choice of a treatment strategy for CVD, including AF [29].

STUDY LIMITATIONS

The single-stage study included a small number of pts. There was no control group of pts without AF, which made it impossible to study the contribution of AF to the variance of GDF-15 level in blood. When determining the level of GDF-15, an analytical assay for research purposes was used, which dictates the need to expand the scope of the study and determine its reference values.

CONCLUSION

The results of our study confirm that GDF-15 manifests itself as an integral biomarker of age-associated metabolic disorders and structural and functional changes of the heart, which opens prospects for further study of its prognostic significance in pts with non-valvular AF.

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