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The role of markers galectin-3 and H-FABR in current forecast chronic heart failure in patients undergoing stenting and coronary artery bypass grafting, with and without type 2 diabetes

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ABSTRACT

Cardiovascular diseases remain the main cause of death and disability in patients with type 2 diabetes mellitus (DM2) DM2 aggravates the underlying mechanisms of atherosclerosis and heart failure.

To study the role of galelectin-3 and H-Fabr markers in the forecast of CHF in patients with type 2 diabetes mellitus and stenting

80 patients (prospectively) with type 2 diabetes were examined at the Acad. VV Vakhidov.

Of these, there were 29 women and 51 men. The average age of men was 67 ± 4.2 years, and the average age of women was 64 ± 5.6 years. 10 patients with DM 2 without coronary artery disease of the corresponding age made up the control group.

The study used clinical and biochemical research methods (glycemia, glycated hemoglobin, ALT, AST, bilirubin, urea, creatinine, PTI, studies of CHF biomarkers (galectin-3, H-FABR), as well as instrumental methods of examination-ultrasound of internal organs, ECG, Echo-ECG, as well as statistical techniques.

The mean values of galectin 3 and H-FABR in the preoperative period were normal in patients of groups 2 and 4, but were significantly high in patients of groups 1 and 3, that is, with a combination of DM 2 and CHF, approaching critical threshold values. Thus, the average values of galectin-3 in the 1st group of patients were within 8.68±0.04 ng/ml, and in the group 7.62±0.08 ng/ml. The average H-FABR data in group 1 reached 17.1±0.4 ng/ml, and in the group 13.5±0.7ng/ml.

The increase in the concentration of Galectin-3 and H-FABR in all patients with type 2 DM with concomitant CHF, as well as the high sensitivity and specificity of the test, prove the value of this marker for diagnosing CHF in patients with type 2 DM.

KEYWORDS: galectin-3, H-FABR, type 2 diabetes mellitus, chronic heart failure

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an epidemic metabolic disease with increasing prevalence, affecting more than 463 million people today. It has been estimated that approximately 700 million people will have type 2 diabetes in 2045.[1].The main reasons for this marked increase are altered living conditions with a sedentary lifestyle and less physical activity leading to an increase in obesity among a growing world population with longevity.[2].Since type 2 diabetes increases the risk of developing various diseases, such as cancer and cardiovascular disease (CVD), the duration and quality of life of patients are significantly reduced.[3-5].Due to microvascular and macrovascular changes, the risk of cardiovascular disease in patients with type 2 diabetes is twice as high as in those with euglycemia. Approximately 80% of T2DM-related deaths are associated with the progression of CVD and the occurrence of its acute manifestations, including heart failure, myocardial infarction and stroke[6-8].An increased risk of cardiovascular disease is present not only in T2DM, but also in early pre-diabetic form.[9].

In the diagnosis of heart failure (HF), NT-proBNP represents the gold standard laboratory parameter, but also galectin-3 has shown promising results in relation to the presence of cardiac dysfunction.[10,11].Since galectin-3 has been shown to be involved in inflammatory and fibrotic processes, as well as in cardiac

remodeling[12, 13],the authors showed that galectin-3 may be a specific and additional biomarker, especially for heart failure caused by hyperglycemia[14].The authors concluded that, in a large population cohort, galectin-3 was superior to NT-proBNP in predicting heart function over a five-year period in patients with T2DM. Although galectin-3 is inferior to NT-proBNP in predicting survival, it may represent a valuable tool to provide additional information in monitoring and predicting cardiac function in high-risk patients with T2DM. The standard deviation of galectin-3 was 5 ng/ml. The first tertile (Galectin-3 ≤ 12.2 ng/mL) included 4925 subjects, the second tertile (Galectin-3 > 12.2 to ≤ 15.3 ng/mL) included 4934 subjects, and the third tertile (Galectin-3 > 15.3 ng/ml) included 4934 people. 4924 people participated. Lower levels of galectin-3 have been associated with a euglycemic state, while higher levels of galectin-3 were associated with a higher prevalence of prediabetes (an increase of about 50% from the first to the third tertile) and T2DM (almost a tripling of the prevalence from the first to the third). With increasing levels of galectin-3, individuals were older and more often female, and there was also a higher prevalence of arterial hypertension, dyslipidemia, obesity, and all assessed comorbidities. As expected, higher galectin-3 levels were associated with a higher prevalence of HF. and there was also a higher prevalence of hypertension, dyslipidemia, obesity, and all comorbidities assessed. As expected, higher galectin-3 levels were associated with a higher prevalence of HF. and there was also a higher prevalence of hypertension, dyslipidemia, obesity, and all comorbidities assessed. As expected, higher galectin-3 levels were associated with a higher prevalence of HF.[14].In T2DM, the risk of all-cause mortality was comparable at low and intermediate levels, but nearly doubled in subjects with high galectin-3 levels (first and second tertile versus third tertile). In contrast, CV mortality was approximately tripled at intermediate levels (first vs. second tertile) and increased to a six-fold risk at high levels of galectin-3 (first vs. third tertile). In general, the level of galectin-3 significantly correlated with the risk of cardiovascular and overall mortality. In addition, galectin-3 has shown prospective value for cardiovascular and all-cause mortality in individuals with T2DM.[14].

Thus, diabetic patients with known cardiovascular diseases, including atherosclerosis, stable coronary artery disease (CHD), acute coronary syndrome/myocardial infarction (MI), heart failure (HF), arrhythmias (atrial fibrillation and flutter), and cardiomyopathies, have higher risk of mortality than non-diabetics with cardiovascular disease [15-17].

In 2019, the European Society of Cardiology (ESC) announced a new clinical guideline for diabetes, prediabetes and cardiovascular disease [18]. This recommendation contains a section on circulating cardiac biomarkers that are promising predictors of CAD, HF, and major adverse cardiovascular events (MACEs) in patients with DM. Notably, DM2 and diabetes-induced target organ damage are considered factors hindering the clinical interpretation of peak levels of circulating biomarkers [19].

Evidence shows that traditional CVD risk factors negatively affect mortality and quality of life in T2DM patients, and it is suggested that cardiac biomarkers reflecting various pathophysiological stages of cardiac remodeling such as biomechanical stress, inflammation, necrosis/apoptosis, fibrosis, ECM hypertrophy and remodeling will be of additional value in predicting clinical outcomes (death, MACEs, hospitalization, onset of HF) in a patient population. In addition, measurement of circulating levels of cardiac biomarkers may demonstrate new individual prognostic information that may be of greater predictive power than conventional cardiovascular risk factors. However, each biomarker has strengths and weaknesses, which affect cost, specificity, sensitivity, predictive value, and head-to-head superiority. Since there are many circulating biomarkers with unproven ability to predict clinical outcomes in individuals before and with DM[20].

Galectin-3 (Gal-3) is a versatile protein that belongs to the lectin family and is predominantly involved in fibrosis and inflammation of the heart, liver, and kidneys [21,22]. Overexpression of Gal-3 is associated with the accumulation of advanced glycation end products (AGEs), products of oxidative stress. Gal-3 predicts cardiac remodeling and cardiovascular events that are independently associated with it, such as HF and atrial fibrillation [23.24]. Serum Gal-3 levels in T2DM patients showed a modest increase from baseline with the SGLT2 inhibitor canagliflozin compared with placebo, while both NT-proBNP and hs-cTnI concentrations showed a downward trend for >2 years [25].

All of the above emphasizes the relevance of this study.

In this regard, we formulated the following goal of the research work.

Purpose of the study -to study the role of galectin-3 and H-FABR markers in the prognosis of CHF in patients with type 2 diabetes mellitus undergoing CABG and stenting.

MATERIALS AND METHODS

80 patients (prospectively) with type 2 diabetes were examined at the Acad. V.V. Vakhidov on the basis of a scientific agreement together with the RSNPMTSE of the Ministry of Health of the Republic of Uzbekistan named after acad. Y.H. Turakulova. At the same time, 300 case histories of patients with type 2 diabetes who underwent CABG in this center were retrospectively analyzed.

All observed 80 patients were divided into 4 groups:

1 gr. – 25 patients with CHF and type 2 diabetes, stent
2 gr. – 25 patients with CHF without type 2 diabetes, stent
3 gr. – 10 patients with CHF and DM2, CABG
4 gr. – 20 patients with CHF without DM 2, CABG
The control group consisted of 10 patients with type 2 diabetes without CHF.

Of these, there were 29 women, 51 men. The average age of men was 67 ± 4.2 years, and the average age of women was 64 ± 5.6 years.

The study used clinical and biochemical research methods (glycemia, glycated hemoglobin, ALT, AST, bilirubin, urea, creatinine, PTI, studies of CHF biomarkers (galectin-3, H-FABR), as well as instrumental methods of examination - ultrasound of internal organs, ECG, Echo-ECG, as well as statistical methods.

used for echocardiographyVivid e9 or Vivid I (General Electric, Fairfield, CT)with M4S-RS transducer (1.5-3.6 MHz). All measurements in M-mode were performed in accordance with the recommendations of the American Society of Echocardiography.

RESULTS AND DISCUSSION

Table 1 shows the distribution of patients by sex and age. As can be seen from Table 1, patients in the age group from 45 to 59 years old both among men and women predominated - 44 out of 80 patients (55.0%).

Table 1.
Distribution of prospectively studied 80 patients by sex and age (WHO, 2017)

Indicators		**Number of patients (n=80)**									
		1 group (n=25)		**2 group (n=25)**		**3 group (n=10)**		**4 group (n=20)**		**Control (n=10)**	
		abs	%	abs	%	abs	%	abs	%	abs	%
Age periods, years	18-44	-	-	-	-	-	-	-	-	-	-
	45-59	15	60.0	14	56.0	6	60.0	9	45.0	4	40
	60-74	10	40.0	eleven	44.0	4	40.0	eleven	55.0	6	60
	75 and >	-	-	-	-	-	-	-	-	-	-
Total		25	31.25	25	31.25	10	12.5	20	25.0	10	12.5
Average age		62.7±5.6		61.6±7.8		63.8±6.9		64.7±3.6		62.5±7.8	
sex	Male	19	76.0	18	72.0	6	60	13	65	5	50.0
	Female	6	24.0	7	28.0	4	40	7	35	5	50.0
Total		25	31.25	15	31.25	15	12.5	20	25.0	10	12.5

Next, we studied the clinical and anamnestic characteristics of patients by groups (Table 2).

Table 2. Clinical and anamnestic characteristics of patients included in the study (abs. number)

Feature/indicator	**1 group (n=25)**	**2 group (n=25)**	**3 group (n=10)**	**4 group (n=20)**	**control (n=10)**
Women/men	19/6	18/7	6/4	13/7	5/5
Main disease: __SD 2, n= 35	19/6	-/-	6/4	-/-	5/5
Concomitant disease: __obesity 1 st : n =14 __obesity 2 st: n =5 — CHF, n=80	4/3 1/- 19/6	1/- 2/- 18/7	4/2 -/1 6/4	-/- -/1 13/7	-/- -/- -/-
Complication of DM 2: DNR: n=11 (13.75%) DNP: n = 20 (25%)	6/3 8/4	-/- -/-	3/2 5/3	-/- -/-	-/- 2/2
Hereditary burden for DM2 n=8 (22.8%) Hereditary burden for CVD: n=20 (25%)	3/1 4/2	-/- 2/3	2/2 3/1	- /- 1/4	1/1 -/-
PICS, n=17 (21.3%)	6/2	3/3	7/4	7/5	-/-
stroke, n =0	-/-	-/-	-/-	-/-	-/-
Prescription of DM 2, years Up to 5 years, n = 11 (13.75%) From 5 to 10 years old, n=17 (21.3%) Over 10 years, n=12 (15%)	2/3 2/3 3/2	-/-	1/1 3/3 7/-	-/-	1/3 4/2 -/-
SBP, mm Hg	136.3±7.3*	141.7±8.2*	138.6±6.5 *	139.8±8.7 *	118.4±6.7
DBP, mm Hg	89.1±7.4*	90.1±3.8*	87.1±9.8*	86.1±6.8*	73.1±3.9*
Heart rate, beats/min	86.6±8.3	78.6±6.3	78.6±5.7	78.6±5.4	70.6±1.3
BMI, kg/m2	32.5±2.1*	29.9±7.5*	28.7±4.8*	31.6±5.6*	24.9±6.1*

Note:AH - arterial hypertension,DBP = diastolic blood pressure, SBP = systolic blood pressure, DNR = diabetic non-proliferative retinopathy– * – significance criterion, where $p < 0.005$, DNP – diabetic neuropathy

As can be seen from table 2,the significance of differences in comparison with the control relative to SBP, DBP, BMI in the studied patients was established ($p<0.05$). It should be noted that out of 35 patients of the main group with type 2 DM, 8 (22.8%) had a hereditary burden for DM2, while in general, among 80 examined patients, hereditary burden for CVD was only 20 cases (25.0%). 19 (23.8%) patients out of 80 had grade 1-2 obesity. Diabetic non-proliferative retinopathy was detected in 11 out of 35 patients with DM 2 (31.4%), that is, in a third of cases, and diabetic nephropathy -. in 20 (25%) - in one fourth of patients.

Next, we studied the biochemical characteristics of patients (table3).

Table 3

Average biochemical parameters of blood of patients in the studied groups in the preoperative period

Index	**1 group**	**2 group (n=25),**	**3 group (n=10),**	**4 group**	**control**

	(n=25), M ± m	M ± m	M ± m	(n=20), M ± m	(n=10), M ± m
Fasting glucose, mmol/l	9.4±2.6	4.3±0.8	8.2±0.7	5.2±0.1	6.2±0.7
Postprandial glycemia	12.4±2.3	7.5±1.2	13.9±1.6	7.7±1.2	11.5±1.2
HbA1C, %	7.2±1.7	5.5±0.9	8.5±0.9	5.5±0.9	7.3±0.4
Bilirubin total, μmol/l	12.8±1.4	13.5±2.1	13.5±3.1	14.3±2.4	14.5±2.1
Urea, μmol/l	1.8±0.3	2.6±0.4	3.8±0.7	2.6±0.6	2.1±0.4
Creatinine, μmol/l	100±8.9	87.6±6.2	98.6±11.2	79.6±9.2	89.6±9.2
Total cholesterol, mmol/l	7.6±1.6	5.2±1.3	5.2±1.2	4.8±1.0	4.6±1.7
LDL, mmol/l	0.78±0.08*	0.14±0.02*	1.12±0.9*	1.09±0.08*	3.14±1.2
HDL, mmol/l	1.1±0.04	1.4±0.3	1.2±0.7	1.3±0.3	1.5±0.31
TG, mmol/l	2.82±0.8*	2.87±0.1*	2.94±0.8*	2.88±0.5*	1.35±0.4
Galectin 3 ng/ml	8.68±0.04**	0.59±0.03	7.62±0.08**	0.73±0.09	0.64±0.09
H-FABR ng/ml	17.1±0.4*	2.8±0.3	13.5±0.7*	4.3±0.9	3.3±0.31

Note: HbA1C — glycated hemoglobin, LDL — low density lipoprotein, TG — triglycerides, GFR — glomerular filtration rate.

As can be seen from Table 3, in patients of groups 1 and 3, a significant increase in fasting glycemia, postprandial glycemia, and glycated hemoglobin was found..($p < 0.05$). Mean values of total bilirubin, urea,blood creatinine levels were normal ($p<0.05$) against the background of dyslipidemia (decrease in LDL, normal levels of HDL, increased TG in all groups and TC in group 1).

Mean values of galectin 3 andH-FABR in the preoperative period were normal in patients of groups 2 and 4, but were significantly high in patients of groups 1 and 3, that is, with a combination of DM 2 and CHF, approaching critical threshold values. So, the average values of galectin -3 in the 1st group of patients were within8.68±0.04ng/ml, and in the group7.62±0.08 ng/ml. Average dataH-FABR in group 1 reached values17.1±0.4ng/ml, and in the group13.5±0.7ng/ml.The next stage of our work was the analysis of Echo-ECG data from our patients (Table 4).

Table 4
Echo-ECG parameters by groups (M ± m)

Indicators	1 group (n=25), M ± m	2 group (n=25), M ± m	3 group (n=10), M ± m	4 group (n=20), M ± m	Norm
KDR LV, cm	2.8±0.3 *	3.7±0.6	2.6±0.5*	3.8±0.3	4.6-5.7
CSR, ml	26.9±4.5*	32.3±7.6	27.5±4.6*	31.6±6.8	33-68
KDO, ml	73.8±7.6*	82.4±6.4*	76.5±8.2*	87.6±6.5*	96-157
LV CVD, cm	0.6±0.04*	0.7±0.06*	0.5±0.09*	0.5±0.05*	0.95 -2.05
LP, cm	4.8±0.8	4.7±0.2	4.9±0.7	3.9±0.2	2.3–4.5
TMZhP, cm	1.3±0.02	1.2±0.07	1.4±0.09	1.3±0.06	0.75 -1.1
SDLA mmHg.	20.8±2.5*	19.8±2.3	22.7±2.8*	16.8±2.4	12-15
DT, ms	114.8±10.2*	101.2±8.6*	120.2±8.9*	99.7±6.8*	60-70
TZSLZH, cm	1.9±0.3*	1.7±0.6	1.9±0.7*	1.6±0.9	0.6-1.1
PrZh, mm	22.6 ± 2.1	21.2±3.4	23.6±3.2	23.3±4.9	9.5 -20
EF, %	36.6±6.4*	39.2±3.3*	33.6±5.8*	41.4±3.1*	59 ± 65
E/A	0.67±0.07*	0.99±0.05*	0.64±0.06*	0.71±0.09*	1.5-1.7.
IVRT, ms	105.9±7.9*	98.6±8.3*	108.8±7.9*	95.6±5.9*	70-75
MMLV, g	149.9±8.9*	142.8±8.8*	148.9± 11.5*	141.9± 6.5*	95-135

LVMI, g/m2	143.5±11.5*	128.9±11.4	138.9±10.7*	136.3±12.3*	109-124

Note: *Differences are significant, p < 0.05.:EDD — end diastolic size, ESR — end systolic size, LA — pulmonary artery, LV — left ventricle, LA — left atrium, n/a — unsignificant difference between the compared parameters, RV — right ventricle, SBP — systolic blood pressure, TZSLV — thickness posterior wall of the left ventricle, VTRV — thickness of the interventricular septum, EF — ejection fraction, CHF — chronic heart failure, HR — heart rate, DT — early diastolic filling blood flow deceleration time, IVRT — LV isovolumic relaxation time, E/A — peak ratio E and A wave velocities, EDV – end diastolic volume, ESV – end systolic volume, LVMI – LV myocardial mass, LVMI – LVMI index, SPPA – mean pulmonary artery pressure

As can be seen from Table 4, there is a significant difference in the parameters of central hemodynamics in the studied groups compared with the normal values. Indicators such as BWW, DT, EF, E/A,IVRT, LVMI, LVMI significantly differed from the norm in all 4 observation groups($p<0.05$).At the same time, the average values end diastolic size of the left ventricle (LV EDD), end systolic volume (ESV), mean pressure in the pulmonary artery of SPPA, slowing down time of early diastolic filling blood flow (TZSLV), were significantly changed in groups 1 and 3 ($p <0.05$), and not significantly changed in groups 2 and 4 ($p>0.05$). The average values of the volume of the left atrium (LA) and the right ventricle (RV), the thickness of the interventricular septum (VAT) were insignificantly increased in all the studied groups ($p>0.05$).

Next, we evaluated the correlation between the biomarkers Galectin-3 and H-FABR with various laboratory instrumental data (Tables 5 and 6).

Table 5. Correlation (R) of Galectin-3 values with laboratory and instrumental indicators in the studied groups

eGFRml/min/1.73 m2	**Glycemia on an empty stomach mmol/l**	**HbA1C %**	**EF of the left ventricle**	**Mean pressure in the pulmonary artery**	**ratio of peak velocities of waves E and A(E/A).**	**GFR, ml/min**
1 gr	0.65	0.68	0.67	0.58	0.57	0.44
2 gr	0.67	0.66	0.69	0.56	0.71	0.75

Note: EF - ejection fraction

Table 6. Correlation (R) valuesH-FABRfrom laboratory and instrumental indicators in the studied groups

eGFRml/min/1.73 m2	**Glycemia on an empty stomach mmol/l**	**HbA1C %**	**EF of the left ventricle**	**Mean pressure in the pulmonary artery**	**ratio of peak velocities of waves E and A**	**GFR, ml/min**
1 gr	0.62	0.71	0.69	0.58	0.68	0.74
2 gr	0.55	0.59	0.58	0.74	0.71	0.76

We see that the correlation between these indicators was significant. All this highlights the possibilities of using biomarkers.Galectin-3 and H-FABRas factors predicting the outcomes of the course of CHF in type 2 diabetes and without type 2 diabetes, as indicated in the literature.

Further, the relationship between the level of galectin-3,H-FABRand systolic, diastolic function in CHF and DM2 were assessed using the study of the correlation and Student's test of significance(table 7).. Diastolic or systolic dysfunction has not been associated with galectin-3 in individuals without type 2 diabetes. In T2DM, systolic function decreased with increasing levels of galectin-3, regardless of age,

gender, comorbidities, and HF medications. Diastolic dysfunction (E/E' ratio) was associated with increased levels of galectin-3 in CHF without DM 2 after adjusting for sex and age was attenuated. On the contrary, in T2DM, a corresponding relationship between diastolic dysfunction and galectin-3 levels was observed significantly. In general, an increase in the level of galectin-3 was associated with the occurrence of disturbances in systolic and diastolic function of the heart in T2DM, as well as with a violation of systolic heart function in CHF without type 2 diabetes.

Table 7. Relationship between the level of galectin-3,H-FABRand systolic, diastolic function

Indicators	**R**	**p**
EF LV	0.56	< 0.005
E/E' ~Gal-3 With SD2	0.65*	> 0.005
E/E' ~Gal-3 With CHF	0.33	< 0.005
E/E' ~H-FABR For DM 2	0.59*	< 0.005
E/E' ~ H-FABR For CHF	0.38	> 0.005

Note:R - correlation, p - criterion of significance when compared with control.

All the above data indicate the need for timelydiagnosing CHF in patients with type 2 diabetes mellitus, developing measures to prevent their development and organizing long-term monitoring of patients with a high risk of developing this complication of diabetes.

Thus, a significant difference was found in the parameters of central hemodynamics in all the studied groups compared with the normal values, but in patients with DM 2 and CHF, these changes were most pronounced. So,in the groups of patients with type 2 diabetes and CHF, we detected Echo-ECG changes according to the type of LV diastolic dysfunction of 2-3 degrees with a tendency to increase the mean pressure in the pulmonary artery.

CONCLUSION

1) An increase in the concentration of Galectin-3 and H-FABR in all patients with type 2 DM with concomitant CHF, as well as the high sensitivity and specificity of the test, prove the value of this marker for diagnosing CHF in patients with type 2 DM. The dynamics of their concentration can help in assessing the effectiveness of the therapy and the need to titrate the dose of drugs. 2)An increase in the level of galectin-3 was associated with the occurrence of violations of systolic and diastolic function of the heart in T2DM, as well as with a violation of systolic function of the heart in CHF without type 2 diabetes.

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