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"THE IMPORTANCE OF PROGNOSTIC MARKERS GALECTIN 3 AND H-FABR IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CHRONIC HEART FAILURE

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Abstract

Relevance. It is known that among the macrovascular complications of type 2 diabetes mellitus (T2DM), cardiovascular diseases remain the main cause of death and disability in patients. Type 2 diabetes aggravates the mechanisms underlying atherosclerosis and heart failure.

Target. To study the features of the course of CHF in patients with type 2 diabetes mellitus and

Material and methods. 80 patients (prospectively) with type 2 diabetes were examined at the Center of Surgery named after Acad. V.V. Vakhidov.

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.

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

Results.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. Thus, the average values of galectin -3 in group 1 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.

Conclusion. An increase in the concentration of Galectin-3 and H-FABR in all patients with type 2 diabetes 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 diabetes.

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

Introduction

Type 2 diabetes mellitus (DM 2) is known to be a known risk factor for cardiovascular disease and mortality[17]. The worldwide prevalence of diabetes is estimated to increase by almost 50% in the next 25 years, from 415 million people in 2015 to 642 million people in 2040 [21]. Many people are unaware of their metabolic status, and more than a third of patients admitted for acute coronary syndrome have previously unknown disorders of glucose metabolism.

Atherosclerotic cardiovascular disease remains the leading cause of death and disability among patients with diabetes, especially in patients with DM 2, in whom it usually occurs 14.6 years earlier[8] with greater severity and more diffuse distribution than in persons without DM 2 [6]. In addition, about two-thirds of deaths in people with diabetes are related to cardiovascular disease: of these, approximately 40% are due to coronary heart disease, 15% due to other forms of heart disease, predominantly congestive heart failure, and about 10% due to stroke.

Key manifestations of atherosclerotic cardiovascular disease in DM 2 include advanced atherosclerosis manifested as coronary artery disease, ischemic stroke, peripheral arterial disease, and heart failure.[eleven].

Several studies have shown that patients with acute myocardial infarction (AMI) and impaired glucose metabolism below the threshold for DM 2 have a worse prognosis compared with patients with normal glucose tolerance (NGT) [18, 13, 12].

In patients with type 2 diabetes and multivessel coronary artery disease, the recommended method of revascularization is CABG [15, 19, 22]. The prognosis in patients with established T2DM after CABG is worse than in patients without DM 2, researchers note [14, 10, 4]. However, there have also been reports of similar long-term mortality after CABG in patients with an established diagnosis of DM 2 and in patients without diabetes [15]. Less is known about the prognostic significance of prediabetes or new-onset diabetes after CABG in patients without a history of diabetes.

In 2018, the World Health Organization reported that 17.9 million people die each year from cardiovascular diseases, including coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions, accounting for approximately 31% of all deaths worldwide. Additionally, 85% of all cardiovascular disease deaths are due to heart attack and stroke, and 60% of cardiovascular disease deaths occur in low- and middle-income countries. Diabetes mellitus, hypertension, dyslipidemia, tobacco

use, physical inactivity, and a family history of premature coronary heart disease are known to increase the risk of cardiovascular disease. However, traditional risk factors often lack sufficient sensitivity, specificity and therefore researchers have developed the use of cardiac biomarkers such as creatine kinase-myocardial band or fraction (CK-MB), cardiac troponin I and troponin T, B-type natriuretic peptide and high-sensitivity C-reactive peptide. protein (hsCRP) to provide information beyond traditional risk factors[18].

Recent research progress has revealed the key role of galectin-3 in cardiovascular disease and in the diagnosis and treatment of heart failure. Compared with other HF biomarkers, galectin-3 provides information about the fibrotic state of the myocardium and the risk of adverse cardiac remodeling and its progression [9]. Among patients at increased risk of HF, there was no association between dynamic changes in galectin-3 and incident HF or atrial fibrillation. Although peak galectin-3 concentrations were independently associated with increased risk of all-cause mortality, cardiovascular mortality, and HF hospitalizations for all HF phenotypes [5], there was no significant effect of HF medications on galectin-3 concentrations [7].Thus, galectin-3 remains an alternative biomarker.

Galectin-3is considered as a possible profibrotic molecule, a potential marker of fibrosis in the heart and liver. Perhaps studying galectin-3 will help in assessing the risk of development and progression of fibrosis. Galectin-3 correlates with the severity of CHF and is closely associated with key indicators of the central nervous system and endogenous inflammation, being both a marker and a mediator of these pathogenic processes [20]. Galectin-3 has been considered in studies as a risk factor for adverse cardiovascular events. At baseline, the level of galectin-3 in patients with CHF with preserved ejection fraction ranged from 15.9 to 31.6 ng/ml and averaged 22.2±0.77 ng/ml. Moreover, this level was two times higher than that in patients with coronary artery disease without heart failure [1]. According to the literature, clinical studies have confirmed the high diagnostic potential of exceeding the level of galectin-3 more than 19-25 ng/ml in relation to the stratification of patients into a group at high risk of adverse clinical outcomes. Circulating galectin-3 levels greater than 19 pg/mL are associated with the risk of new-onset diastolic HF and mortality from it [2].

A 2015 study reported that levels of galectin-3, a member of the soluble β-galactoside-binding lectin family, are higher in patients with type 2 diabetes and metabolic syndrome. There are conflicting results about the effect of galectin-3 in patients with diabetes. The authors examined the relationship between galectin-3 levels and coronary artery disease (CAD), coronary plaque burden, and plaque structure in patients with type 2 diabetes. This study included a total of 158 patients with type 2

diabetes who underwent elective coronary computed tomography angiography (CCTA). The study population was divided into groups with and without CAD depending on the presence of coronary atherosclerosis. Galectin-3 concentrations were significantly higher in the CAD group than in the non-CAD group (1412.0 ± 441.7 vs. 830.2 ± 434.9 pg/mL, P < 0.001). Galectin-3 levels were positively correlated with BMI, high-sensitivity C-reactive protein, total number of affected vessels, number of plaques (all, P < 0.001), and type of calcified plaque (P = 0.001). . The authors concluded that Galectin-3 is a promising new biomarker that may help identify patients with type 2 diabetes who may require early intervention for CAD due to the potential risk of coronary atherosclerosis. [24].

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 features of the course of CHF in patients with type 2 diabetes mellitus and

Material and research methods. 80 patients (prospectively) with type 2 diabetes were examined at the Center of Surgery named after Acad. V.V. Vakhidov on the basis of a scientific agreement jointly with the RSNPMCE Ministry of Health of the Republic of Uzbekistan named after academician. Y.H. Turakulova. At the same time, 300 patients with type 2 diabetes who underwent CABG at this center were retrospectively analyzed.

All observed 80 patients were divided into 4 groups: 1 gr. – 15 patients with coronary artery disease and type 2 diabetes, subjected to ER; 2 gr. – 15 patients with coronary artery disease without type 2 diabetes, subjected to ER; 3 gr. – 15 patients with coronary artery disease and type 2 diabetes who underwent CABG; gr. – 20 patients with coronary artery disease without type 2 diabetes who underwent CABG. The control group consisted of 10 patients with type 2 diabetes without coronary artery disease.

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. 10 patients with type 2 diabetes without coronary artery disease of the same age formed 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 examination methods - ultrasound of internal organs, ECG, Echo-ECG, as well as statistical techniques.

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For echocardiography we usedVivid e9 or Vivid I (General Electric, Fairfield, CT)with M4S-RS sensor (1.5–3.6 MHz). All M-mode measurements were performed in accordance with the recommendations of the American Society of Echocardiography.

Results of own research and their discussion. Table 1 shows the distribution of patients by gender and age. As can be seen from Table 1, patients in the age category from 60 to 74 years predominated among both men and women - 47 out of 80 patients (58.7%).

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

Indicators		Number of patients (n=80)									
		1 group (n= 15)		2nd group (n=15)		3 group (n=15)		4 group (n=20)		Control (n=10)	
		abs	%	abs	%	abs	%	abs	%	abs	%
Age periods, years	18-44	4	26.6	-	-	-	-	-	-	-	-
	45-59	1	6.6	4	26.6	6	40.0	9	45.0	4	40
	60-74	10	66.6	eleven	73.3	9	60.0	eleven	55.0	6	60
	75 and >	-	-	-	-	-	-	-	-	-	-
Total		15	18.7	15	18.7	15	18.7	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	
Floor	Male	9	60.0	8	53.3	eleven	73.3	13	65	5	50.0
	Female	6	40.0	7	46.6	4	26.6	7	35	5	50.0
Total		15	18.7	15	18.7	15	18.7	20	25.0	10	12.5

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

Table 2. Clinical and anamnestic characteristics of patients included in the study (absolute numbers)

Sign/indicator	1 group (n=15)	2 group (n=15)	3 group (n=15)	4 group (n=20)	control (n=10)
Women/men	9/6	8/7	11/4	13/7	5/5
Main disease: __SD 2, n=40 Concomitant disease: __obesity 1st degree: n =14 __obesity level 2: n =5 — CHF, n =80 Complication of diabetes 2: DPR: n =22 DNP: n =34	 9/6 4/3 1/- 9/6 6/3 9/6	 -/- 1/- 2/- 8/7 -/- -/-	 11/4 4/2 -/1 11/4 9/4 11/4	 -/- -/- -/1 13/7 -/- -/-	 5/5 -/- -/- -/- -/- 2/2

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Hereditary burden of T2DM n =39 Hereditary burden of CVD: n =5	9/6 -/2	-/- -/-	11/4 -/1	-/- 1/-	5/4 -/1
PIX, n =17	6/2	3/3	7/4	7/5	-/-
ONMC, n =0	-/-	-/-	-/-	-/-	-/-
Duration of diabetes mellitus 2, years Up to 5 years, n =11 From 5 to 10 years, n =17 Over 10 years, n =12	 2/3 2/3 3/2	 -/-	 1/1 3/3 7/-	 -/-	 1/3 4/2 -/-
SBP, mmHg	136.3±7.3*	141.7±8.2*	138.6±6.5*	139.8±8.7*	118.4±6.7
DBP, mmHg	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 nonproliferative retinopathy– * – reliability criterion, where $p < 0.005$, DNP - diabetic neuropathy

As can be seen from Table 2,the significance of the differences compared with the control regarding SBP, DBP, BMI in the studied patients was established ($p<0.05$). It should be noted that out of 40 patients with type 2 diabetes, 39 (98%) had a hereditary burden of T2DM, while in general, among the 80 examined, hereditary burden of CVD was only 5 cases (6.3%). 19 (23.8%) patients out of 80 had 1-2 degrees of obesity. Diabetic nonproliferative retinopathy was detected in 22 out of 40 patients with type 2 diabetes, that is, in more than half of the cases.

ext, we studied the biochemical characteristics of the patients (Table 3).

Table 3. Average biochemical blood parameters of patients in the study groups in the preoperative period

Index	1 Group (n=15), M± m	2 group (n=15), M± m	3 group (n=15), M± m	4 group (n=20), M± m	control (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
Total bilirubin, 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.($p<0.05$). Average values of total bilirubin, urea,blood creatinine levels were normal ($p<0.05$) against the background of dyslipidemia (decreased LDL, normal HDL levels, 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 type 2 diabetes and CHF, approaching critical threshold values. Thus, the average values of galectin -3 in group 1 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 in our patients (Table 4).

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

Indicators	1 group (n=15), M± m	2 group (n=15), M± m	3 group (n=15), M± m	4 group (n=20), M± m	Norm
LV EDV, cm	2.8±0.3 *	3.7±0.6	2.6±0.5*	3.8±0.3	4.6-5.7
ESR, ml	26.9±4.5*	32.3±7.6	27.5±4.6*	31.6±6.8	33-68
EDV, ml	73.8±7.6*	82.4±6.4*	76.5±8.2*	87.6±6.5*	96-157
LV ESD, 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
PV, %	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, msec	105.9±7.9*	98.6±8.3*	108.8±7.9*	95.6±5.9*	70-75
LVMM, 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, PA - pulmonary artery, LV - left ventricle, LA - left atrium, n/a - unreliable difference in the compared parameters, RV - right ventricle, SBP - systolic blood pressure, LV TZ - thickness posterior wall of the left ventricle, TMZH - thickness of the interventricular septum, EF - ejection fraction, CHF - chronic heart failure, HR

- heart rate, DT - blood flow slowdown time of early diastolic filling, IVRT - LV isovolumic relaxation time, E/A - peak ratio velocities of waves E and A., EDV - end-diastolic volume, ESV - end-systolic volume, LVMM - LV myocardial mass, LVMI - LVMM index, MPAP - mean pressure in the pulmonary artery

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 norm. Indicators such as KDO, DT, PV, E/A,IVRT, LVMM, LVMI were significantly different from the norm in all 4 observation groups($p < 0.05$).At the same time, the average values end diastolic dimension of the left ventricle (LVED), end systolic volume (ESV), mean pressure in the pulmonary artery MPAP, blood flow deceleration time of early diastolic filling (LVDT), 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 left atrium (LA) and right ventricle (RV) volumes and interventricular septal thickness (IVS) were significantly increased in all study groups ($p > 0.05$).

Next, we assessed 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 study groups

eGFRml/min/1.73 m2	**Glycemia On an empty stomach mmol/l**	**HbA1C %**	**Left ventricular ejection fraction**	**Mean pulmonary artery pressure**	**Blood flow velocity in the renal artery (right)**	**peak systolic blood flow velocityin the right renal artery**
1 g	0.65	0.68	0.67	0.58	0.57	0.44
2 g	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 study groups

eGFRml/min/1.73 m2	**Glycemia On an empty stomach mmol/l**	**HbA1C%**	**Left ventricular ejection fraction**	**Mean pulmonary artery pressure**	**Blood flow velocity in the renal artery (right)**	**peak systolic blood flow velocityin the right renal artery**
1 g	0.62	0.71	0.69	0.58	0.68	0.74
2 g	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 biomarkersGalectin-3 and H-FABRas factors predicting the outcome of CHF with type 2 diabetes and without type 2 diabetes, as indicated in the literature.

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

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

Conclusions.An increase in the concentration of Galectin-3 and H-FABR in all patients with type 2 diabetes 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 diabetes. The dynamics of their concentrations can help in assessing the effectiveness of therapy and the need to titrate the dose of drugs.

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