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PREDICTING HEART FAILURE IN PATIENTS WITH DIABETES MELLITUS: GALECTIN-3, SST2, AND CAROTID THICKNESS

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Heart failure and Type 2 Diabetes Mellitus are two of the most common chronic conditions affecting adults worldwide. Soluble suppression of tumorigenicity 2 and galectin-3 are two biomarkers that have been studied extensively in recent years as predictors of risk of heart failure in patients with Type 2 Diabetes Mellitus. Carotid Intima Media Thickness is a well-established measure of arterial stiffness and vascular aging. We enrolled 154 patients with diabetes mellitus who presented to a private medical clinic: 83 patients in the diabetes mellitus with heart failure group and 71 patients in the diabetes mellitus–only group. We found that the diabetes mellitus with heart failure group had a significantly higher body mass index, mean Carotid Intima Media Thickness, and Galectin-3 compared to the diabetes mellitus group. However, there was no significant difference in age, gender composition, left ventricular ejection fraction, HbA1c, and soluble suppression of tumorigenicity 2 levels between the two groups.

Key words: heart failure, diabetes mellitus, galectin-3, low-grad inflammation, carotid intima media thickness

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ПРОГНОЗУВАННЯ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ: ГАЛЕКТИН-3, SST2 ТА ТОВЩИНА СОННОЇ АРТЕРІЇ

Серцева недостатність та цукровий діабет 2 типу є двома поширеними хронічними захворюваннями, що впливають на дорослих у всьому світі. Розчинна форма стимулюючого фактору росту 2 та галектин-3 – це два біомаркери, які активно досліджуються як показники ризику розвитку серцевої недостатності у пацієнтів з цукровим діабетом 2 типу. Товщина інтими сонної артерії є визнаним показником ступеня жорсткості артерій та старіння судин. У нашому дослідженні ми залучили 154 пацієнтів з цукровим діабетом, які звернулися до приватної медичної клініки: 83 пацієнтів із цукровим діабетом та серцевою недостатністю, і 71 пацієнтів з цукровим діабетом без серцевої недостатності. Ми виявили, що у групі пацієнтів з цукровим діабетом та серцевою недостатністю спостерігається значно вищий індекс маси тіла, середня товщина інтими сонної артерії та рівень галектину-3 у порівнянні з групою пацієнтів з цукровим діабетом без серцевої недостатності. Проте, між двома групами не було значних різниць у віці, статевому складі, відсотку викиду лівого шлуночка, рівнів HbA1c та розчинної форми стимулюючого фактору росту 2.

Ключові слова: серцева недостатність, цукровий діабет, галектин-3, запалення низького ступеня, товщина інтими сонних артерій

The study is a fragment of the research project "Structural and functional changes of internal organs in chronic non-infectious diseases: possibilities", state registration No. 0121U108893.

Heart failure (HF) and Type 2 Diabetes Mellitus (T2DM) are two of the most common chronic conditions affecting adults worldwide. According to the World Health Organization, the prevalence of T2DM is estimated to have increased from 4.7 % in 1980 to 8.5 % in 2014, while the global burden of HF is enough to constitute it as an epidemic, that affects 64 million people [12, 14]. HF and T2DM are both

associated with increased risk of cardiovascular disease and stroke, and the co–occurrence of both conditions has been identified as a significant risk factor for adverse cardiovascular outcomes [15].

The underlying mechanisms of this increased risk are multifactorial, and they involve multiple pathways such as inflammation, oxidative stress, and endothelial dysfunction. In recent years, there has been a growing interest in exploring the role of biomarkers in predicting the risk of HF in patients with T2DM [5].

Two such biomarkers that have been studied extensively in recent years are soluble suppression of tumorigenicity 2 (sST2) and galectin-3. sST2 is a member of the interleukin-1 receptor family, and it is a decoy receptor for the pro-inflammatory cytokine, interleukin-33 (IL-33). Elevated levels of sST2 have been shown to be associated with adverse cardiovascular outcomes in patients with HF, and it has been proposed as a prognostic biomarker for these patients [4]. Galectin-3 is a beta-galactoside-binding lectin that is involved in the regulation of cell proliferation, differentiation, and apoptosis. Elevated levels of galectin-3 have been shown to be associated with inflammation, fibrosis, and adverse outcomes in patients with HF [13].

The pathological changes in the arterial wall that lead to increased cardiovascular risk are believed to reflect the cumulative impact of cardiovascular risk factors, such as hypertension, dyslipidemia, and hyperglycemia.

Arterial stiffness and vascular aging are two mechanisms by which HF and T2DM contribute to the development of cardiovascular disease. Carotid Intima Media Thickness (CIMT) is a well–established measure of arterial stiffness and vascular aging, and has been proposed as a potential marker for the early detection of cardiovascular disease [2]. CIMT is determined by the thickness of the intima and media layers of the carotid artery, and it has been shown to increase with age and in the presence of cardiovascular risk factors. Previous studies have demonstrated a relationship between CIMT and cardiovascular risk in patients with T2DM, but the impact of HF on CIMT in this population is less well established. Furthermore, the use of non-invasive imaging techniques, such as ultrasound, to measure CIMT has facilitated more accurate and reproducible assessments of vascular health.

The purpose of the study was to assess the impact of heart failure with preserved and mid-range ejection fraction on Galectin-3 and sST2 levels, and atherosclerotic burden by measuring Carotid Intima Media Thickness and calculating vascular age in patients with type 2 diabetes mellitus.

Materials and methods. We enrolled 154 patients with diabetes mellitus who attended clinical bases of Ivano-Frankivsk National Medical University. The diagnosis of diabetes mellitus was established based on the measurement of glycated hemoglobin (HbA1c). To determine the presence of heart failure, the biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) was used. The patients were divided into two groups: 83 patients in the diabetes mellitus with heart failure group and 71 patients in the diabetes mellitus-only group.

Inclusion criteria for the study were: a diagnosis of diabetes mellitus, age between 45 and 75 years, left ventricular ejection fraction (LVEF) greater than 40 %, estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m², and signed informed consent. Exclusion criteria included age below 45 or above 75 years, LVEF less than 41 %, and a history of alcoholism.

Ultrasound measurements were performed using the Siemens NX3 Elite machine. Two-dimensional echocardiography was used to obtain left ventricular end-systolic and end-diastolic dimensions. The LVEF was calculated using the modified Simpson's biplane method. CIMT was measured using high-resolution B-mode ultrasound, and the maximum CIMT value among six measurements was used for analysis. Vascular age was calculated based on mean CIMT.

Laboratory tests were conducted at the Ivano-Frankivsk National Medical University interdepartmental scientific laboratory. ELISA tests were performed using specific kits for HbA1c, NT-proBNP, Galectin-3, and sST2. The measurements were performed by certified technicians who were blinded to the patients' clinical status.

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Categorical variables were presented as frequencies and percentages and analyzed using appropriate tests. Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR 25-75 %). Independent t-tests or Mann-Whitney U tests were used for comparisons. Receiver operating characteristic (ROC) curves were constructed, and logistic regression analysis was conducted to evaluate the impact of study variables on the outcomes.

The results were reported with a significance level of $p < 0.05$ considered statistically significant.

Results of the study and their discussion. We found that the DM+HF group had a significantly higher body mass index (BMI) compared to the DM group (28.50 [25.82;31.40] vs. 25.15 [22.80;27.80],

p<0.001). The DM+HF group also had significantly higher levels of NT–pro BNP (219.47±53.31 pg/mL vs. 64.71±31.35 pg/mL, p<0.001), CIMT right (0.81 [0.57;1.05] mm vs. 0.70 [0.4075;0.92] mm, p=0.015), CIMT left (1.05 [0.75;1.25] mm vs. 0.90 [0.62;1.18] mm, p=0.019), mean CIMT (0.94 [0.66;1.12] mm vs. 0.80 [0.49;1.04] mm, p=0.013), and Galectin-3 (13.38 [12.08;14.71] ng/mL vs. 11.36 [10.27;12.28] ng/mL, p<0.001) compared to the DM group. However, there was no significant difference in age, gender composition, LVEF, HbA1c and sST2 levels between the two groups (Table 1).

Table 1

Baseline characteristics of enrolled patients

Variable	DM + HF	DM	p-value
Age, years	60.71±8.45	59.01±9.39	0.131
Male sex	64 (45.7 %)	58 (50.9 %)	0.450
BMI, kg/m^2	28.50 [25.82;31.40]	25.15 [22.80;27.80]	<0.001
HbA1c, %	7.76 [6.88;8.56]	7.71 [6.89;8.99]	0.555
NT–pro BNP, pg/mL	219.47±53.31	64.71±31.35	<0.001
CIMT right, mm	0.81 [0.57;1.05]	0.70 [0.4075;0.92]	0.015
CIMT left, mm	1.05 [0.75;1.25]	0.90 [0.62;1.18]	0.019
Mean CIMT, mm	0.94 [0.66;1.12]	0.80 [0.49;1.04]	0.013
Vascular age, years	76.00 [45.60;94.10]	58.65 [29.88;82.25]	0.008
Galectin-3, ng/mL	13.38 [12.08;14.71]	11.36 [10.27;12.28]	<0.001
sST2, ng/mL	30.62 [26.92;34.87]	30.76 [26.17;35.71]	0.887
LVEF, %	53.49±7.05	53.60±7.73	0.905

The univariable regression analysis showed that several variables were significantly associated with heart failure. Mean CIMT had a statistically significant odds ratio of 2.12 (95 % CI 1.11–4.08, p=0.024), indicating that participants with a higher mean CIMT had more than twice the odds of having the heart failure compared to those with lower mean CIMT. BMI also had a statistically significant odds ratio of 1.24 (95 % CI 1.15–1.34, p<0.001), meaning that for every one unit increase in BMI, the odds of having the heart failure increased by 24 %. Vascular age also had a statistically significant odds ratio of 1.01 (95 % CI 1.00–1.02, p=0.017), indicating that with each one year increase in vascular age, the odds of having the heart failure increased by 1 %. Galectin-3 was also significantly associated with the heart failure, with an odds ratio of 2.19 (95 % CI 1.78–2.70, p<0.001), meaning that participants with higher Galectin-3 levels had more than twice the odds of having the heart failure compared to those with lower levels. Age, gender, sST2, and ejection fraction were not significantly associated with the heart failure.

The ROC analysis was conducted to evaluate the diagnostic accuracy of various variables in predicting the presence of DM+HF. The AUC values were calculated for each variable, along with their 95 % confidence intervals and associated p–values. An AUC of 1 represents perfect discrimination, while an AUC of 0.5 indicates random chance.

The results of the ROC analysis showed that BMI, mean CIMT, Vascular age, and Galectin-3 had statistically significant AUC values, indicating that they could be useful in predicting the presence of DM+HF. Galectin-3 had the highest AUC value of 0.820, indicating excellent diagnostic accuracy. The AUC value for mean CIMT was 0.591, indicating fair diagnostic accuracy. The AUC value for Vascular age was 0.596, indicating fair diagnostic accuracy. The AUC value for BMI was 0.723, indicating good diagnostic accuracy.

In contrast, the AUC values for Age, sST2, and LVEF were not statistically significant, indicating that they may not be useful in predicting the presence of DM+HF (Table 2, Fig. 1).

Table 2

ROC analysis for age, BMI, mean CIMT, vascular age, Galectin-3, sST2, LVEF

Variable	AUC	95 % CI	p value
Age, years	0.553	0.481–0.625	0.145
BMI, kg/m^2	0.723	0.662–0.785	<0.001
Mean CIMT, mm	0.591	0.520–0.661	0.013
Vascular age, years	0.596	0.526–0.666	0.008
Galectin-3, ng/mL	0.820	0.770–0.871	<0.001
sST2, ng/mL	0.495	0.423–0.567	0.887
LVEF, %	0.490	0.418–0.563	0.789

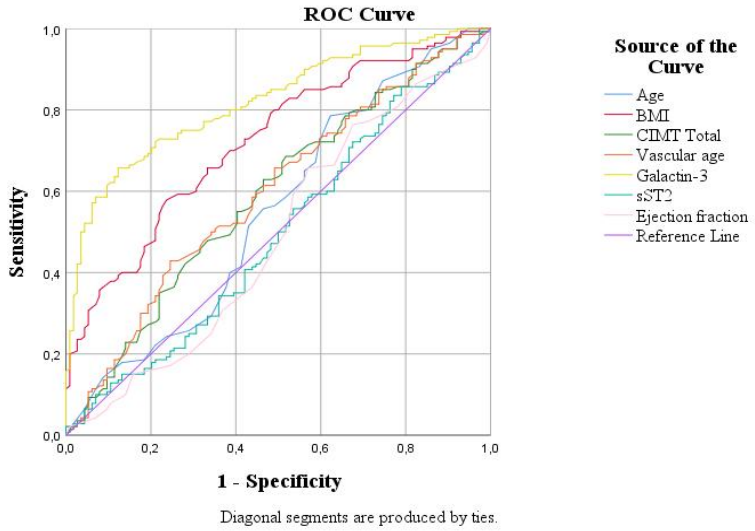

Fig. 1. ROC curve for age, BMI, mean CIMT, vascular age, Galectin-3, sST2, LVEF.

Carotid intima-media thickness (CIMT) is a non-invasive imaging technique used to assess the degree of atherosclerosis and vascular damage in the carotid arteries. Several studies have shown that CIMT is a strong predictor of cardiovascular disease (CVD) and stroke in both diabetic and non-diabetic populations [7, 8]. In the present study, we found that CIMT was significantly higher in diabetic patients with heart failure (HF) compared to those without HF. Additionally, our univariable regression analysis revealed that CIMT was a significant predictor of the presence of HF in diabetic patients.

Moreover, our ROC analysis showed that CIMT had a modest ability to discriminate between diabetic patients with and without HF, with an AUC of 0.591 (95 % CI: 0.520–0.661, p=0.013). This result is consistent with previous studies that reported similar AUC values for CIMT in diabetic patients with and without CVD [9].

Vascular age is a composite measure of arterial stiffness, blood pressure, and other risk factors for CVD, and has been shown to be a better predictor of CVD than chronological age alone [3]. In our study, we found that vascular age was significantly higher in diabetic patients with HF compared to those without HF. Additionally, our univariable regression analysis revealed that vascular age was a significant predictor of the presence of HF in diabetic patients.

Our ROC analysis showed that vascular age had a moderate ability to discriminate between diabetic patients with and without HF, with an AUC of 0.596 (95 % CI: 0.526–0.666, p=0.008). This result is consistent with previous studies that reported similar AUC values for vascular age in diabetic patients with and without CVD [6].

Taken together, our results suggest that CIMT and vascular age may serve as useful markers for the presence of HF in diabetic patients. These findings are consistent with previous studies that have shown that CIMT and vascular age are strong predictors of CVD in both diabetic and non-diabetic populations [10].

In a review conducted by Katerenchuk I.P., it was found that galectin-3, a biomarker for heart failure, plays a significant role in the prognosis and diagnosis of patients with ischemic heart disease [1]. This aligns with our findings that galectin-3 levels were significantly higher in diabetic patients with heart failure compared to those without. Katerenchuk's study also highlighted the importance of other markers such as neopterin, fractalkine, vascular endothelial growth factor, and endothelin-1 in assessing cardiovascular risk. This suggests that a comprehensive approach, considering multiple biomarkers, could enhance the prediction and management of heart failure in diabetic patients.

Another study analyzed the use of suppressor of tumorigenesis 2 (ST2) as a biological marker for heart failure in patients with type 2 diabetes mellitus [11]. While our study found a lower predictive value for sST2 compared to galectin-3, the mentioned study emphasizes the potential of ST2 in slowing down the processes of left ventricular myocardial remodeling, thus contributing to the control of blood pressure and fluid volume. This could potentially lead to a decrease and gradual regression of heart failure, regardless of its origin. This suggests that while galectin-3 may have a higher predictive value, the combined use of multiple biomarkers, including sST2, could provide a more comprehensive assessment of heart failure risk in diabetic patients.

However, it should be noted that our study has some limitations. First, it is a cross–sectional study and therefore, we cannot establish a cause–and–effect relationship between CIMT, vascular age, and HF in diabetic patients. Second, our sample size was relatively small, which may limit the generalizability of our findings. Future prospective studies with larger sample sizes are needed to confirm our results and establish the clinical utility of CIMT and vascular age in predicting HF in diabetic patients.

Overall, our study adds to the growing body of evidence supporting the potential utility of Galectin-3 as a biomarker for identifying patients with DM who are at higher risk of developing HF.

Conclusion

Heart failure has a profound impact on patients with type 2 diabetes mellitus. It leads to more severe atherosclerotic burden and changes of processes of fibrosis. CIMT and vascular age are reliable methods of assessing the atherosclerotic burden in patients with T2DM and should be routinely used. Galectin-3 is a well–grounded marker of the presence of HF with preserved and mid–range LVEF in patients with T2DM. On the contrary, sST2 did not show to be detrimental in this comorbidity.

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