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SOLUBLE GENE-EXPRESSED STIMULATING GROWTH FACTOR RECEPTOR 2 AS A POSSIBLE SERUM MARKER OF DIASTOLIC DYSFUNCTION IN PATIENTS WITH HYPERTENSIVE DISEASE AND TYPE 2 DIABETES MELLITUS

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We examined 60 patients with stage II hypertension (HT), grade 2, mean age 54.7±3.8 years. The first group consisted of 30 patients with hypertension of the II stage, the second group included 30 patients with HT with comorbid moderate, subcompensated type 2 diabetes mellitus (DM). The control group consisted of 20 healthy individuals. All subjects underwent clinical and laboratory examination including the level of soluble growth-stimulating receptor expressed by gene 2 (sST2) in serum, echocardiography with an assessment of mitral Doppler blood flow. It was determined that the serum level of sST2 was significantly ($p<0.05$) higher in patients with comorbidity of HT and DM compared with HT without DM. Significant ($p<0.05$) positive correlations were found between sST2 level and regurgitation rate on tricuspid valve, E/e ', E/A ratio. The significant ($p<0.05$) negative relationships were found between sST2 and values of e's, e'l, e'avg. Therefore, an increased level of the sST2 biomarker is associated with the progression of left ventricular diastolic dysfunction in case of comorbidity of HT and type 2 DM. The results of the study suggest sST2 as one of the possible serum markers of diastolic left ventricular dysfunction in comorbid patients with HT and DM.

Key words: comorbidity of hypertension and type 2 diabetes mellitus, diastolic dysfunction, soluble growth-stimulating receptor expressed by gene 2.

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РОЗЧИННИЙ РЕЦЕПТОР СТИМУЛЮЮЧИЙ ЧИННИК ЗРОСТАННЯ, ЩО ЕКСПРЕСУЄТЬСЯ ГЕНОМ 2, В ЯКОСТІ МОЖЛИВОГО СИРОВАТКОВОГО МАРКЕРУ ДІАСТОЛІЧНОЇ ДИСФУНКЦІЇ У ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ТА ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Обстежено 60 хворих на гіпертонічну хворобу II стадії (ГХ II), 2 ступеня, середній вік 54.7±3.8 років. Першу групу склали 30 пацієнтів з гіпертонічною хворобою II ст., до другої увійшли 30 хворих на ГХ II з коморбідним цукровим діабетом 2 типу (середнього ступеню тяжкості, стадія субкомпенсації). Контрольну групу склали 20 практично здорових осіб. Усім обстеженим особам проведено клініко-лабораторне обстеження, визначення рівня розчинного рецептору стимулюючого чинника зростання, що експресується геном 2 (sST2) в сироватці крові, ехокардіографія з оцінкою трансмітрального доплерівського кровотоку. Визначено, що сироватковий рівень sST2 достовірно ($p<0,05$) вище у пацієнтів з коморбідністю ГХ та ЦД 2 типу порівняно з хворими на ГХ без діабету. Встановлені достовірні ($p<0,05$) позитивні кореляційні зв'язки між рівнем sST2 і швидкістю регургітації на трикуспідальному клапані, E/e', співвідношенням E/A та негативні достовірні ($p<0,05$) зв'язки між рівнями sST2 і значеннями e'c, e'л, e'ср. Отже, підвищення рівня біомаркеру sST2 асоціюється з розвитком і прогресуванням діастолічної дисфункції лівого шлуночка при коморбідності гіпертонічної хвороби та цукрового діабету 2 типу. Отримані в ході дослідження результати дозволяють запропонувати показник sST2 в якості одного з можливих сироваткових маркерів наявності діастолічній дисфункції лівого шлуночка у коморбідних хворих на гіпертонічну хворобу та цукровий діабет 2 типу.

Ключові слова: коморбідність гіпертонічної хвороби та цукрового діабету 2 типу, діастолічна дисфункція, розчинний рецептор стимулюючий чинник зростання, що експресується геном 2.

The work is a fragment of the research project "Development of methods for early diagnosis and drug prevention of fibrosing processes in patients with comorbid pathology (hypertension and type 2 diabetes mellitus) based on the assessment of cardiohemodynamics and renal function", state registration No. 0120U102062.

One of the most important medical and social problems today is the problem of comorbidity of arterial hypertension (AH) and type 2 diabetes mellitus (DM), which is preconditioned by the increasing number of patients with both HT and DM [1, 2, 3]. Hemodynamic disorders together with metabolic disturbances in case of the comorbidity of HT and type 2 DM lead to the damage of target organs and early development of cardiovascular complications with macro- and microangiopathy. Therefore, untoward changes in the heart and kidneys are known to worsen the prognosis of patients with HT and type 2 DM significantly, as well as to increase the risk of cardiovascular complications [4]. For that reason, the study of target organ damage in patients with HT and type 2 DM is important for optimization of the prognosis and individualization of treatment strategies for this cohort of patients.

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Based on the latest scientific data, the progression of comorbid pathology may be based on the progression of fibrotic changes in the heart. These processes can be a trigger for the development of heart remodelling, specifically the development of diastolic dysfunction.

A number of biomarkers have been verified to study the processes of fibrosis in modern medical science. From a significant number of fibrosis markers, we selected the following probable markers that may reflect the processes of cardiac and renal fibrosis, especially: soluble gene-expressed stimulating growth factor receptor 2 (sST2), cystatin C, the terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP), neutrophil gelatinase-associated lipocalin (NGAL).

Currently, among the biomarkers of myocardial fibrosis the soluble gene-expressed stimulating growth factor receptor 2 (sST2) is being actively studied, but the information on the possibility of its use as a predictor of diastolic dysfunction in patients with HT and type 2 DM was not found. The study of sST2 relationship with clinical and instrumental and other biochemical parameters in case of HT in combination with type 2 DM is a promising direction in the management strategy of this cohort of patients.

The purpose of the study was to provide a comparative analysis of the level of soluble gene-expressed stimulating growth factor receptor 2 in patients with hypertension and type 2 diabetes mellitus as well as without it, and also the search of correlations between sST2 and structural-functional indicators of the myocardium.

Materials and methods. The study included 60 patients over 35 years old with stage II grade 2 HT, who matched the following inclusion criteria: presence of type 2 DM (medium severity, subcompensation stage) – group 1 (n = 30), or without DM – group 2 (n = 30).

Main clinical-anamnestic data are presented in table 1.

Table 1

Clinical characteristics of patients

Index	Group 1 (n=30)	Group 2 (n=30)
Age, years	54.5±3.4	54.9±3.7
Hypertensive disease, n (%)	30 (100 %)	30 (100 %)
Arterial pressure (mm Hg)	162/102	164/102
Duration of HT (years)	8	10
Type 2 Diabetes Mellitus, n (%)	30 (100 %)	0
Body mass index (kg/m²)	25.9	25.9

The standard method of patient examination included clinical and laboratory-instrumental examination in accordance with the recommendations of the European Society of AH/European Society of Cardiology (ESH/ESC) 2019, the American Diabetes Association (ADA) 2019 and the International Diabetes Federation (IDF) 2018. All patients signed informed consent to participate in the study.

The study did not include pregnant women; patients with resistant and symptomatic AH; with a high functional class of chronic heart failure (CHF) (NYHA functional class III-IV); type 1 DM, acute or chronic inflammatory diseases; patients with a history of alcohol abuse, mental illnesses; as well as the patients with a high probability of the study protocol violation.

Patients enrolled in the study had not received regular antihypertensive and/or hypolipidemic therapy until the work started. The control group included 20 healthy individuals comparable by age.

All examined individuals underwent general clinical examination, measurement of office blood pressure (BP), heart rate (HR), determination of fasting serum glucose, glycosylated hemoglobin level (HbA1c) in whole blood, insulin, indicators of lipid profile; insulin resistance was assessed by the HOMA-IR index.

According to the results of standard clinical and laboratory blood tests, statistically, significant differences were found only in the indicators of carbohydrate metabolism. The blood glucose index was 7.8 mmol/l in group 1 against 5.15 mmol/l in group 2 ($p<0.01$). Similarly, the level of HbA1c was also higher in group 1 – 7.5 % against 5.5 % ($p<0.01$). No other statistically significant differences, including the showings of lipid spectrum, were observed.

Enzyme immunoassay kits were used to measure the concentration of fibrosis marker in blood serum and hemodynamic overload of the myocardium – soluble gene-expressed stimulating growth factor receptor 2 (sST2, Critical Diagnostics, USA).

Structural and functional parameters of the heart were determined by echocardiography using the diagnostic system "GE Medical Systems" (Germany) by phase sensor with a modulated frequency of 2.25-3 MHz in M- and B-modes according to the recommendations of the American Society of Echocardiography (ASE, 2016).

Mathematical computer processing of the study results was performed using the software package "Statistica 9.0" (Statsoft Inc, USA). Mean (M), variance, standard deviation, median (m), reliability and

significance level (p) were calculated. Differences were considered significant at the level of statistical significance p<0.05. The method of correlation analysis with the calculation of the Pearson's correlation coefficients (with normal distribution) and Spearman's (with a distribution that differs from normal) were used to assess the relationship between the indices.

Results of the study and their discussion. Statistically significant differences of sST2 levels in the groups of examined patients were established. This index was significantly lower in the patients of group 2. Figure 1 shows the difference in sST2 levels in the examined persons.

Thus, in patients with stage II hypertension, a significant increase in sST2 levels was found compared to controls. It was noticed that the level of sST2 in the group of patients with comorbidity of HT and DM significantly exceeded the corresponding values in patients with HT without concomitant DM. Taking into account that sST2 is one of the known markers of fibrosis, the data may indicate more pronounced fibrotic changes in the myocardium of patients with diabetes compared with patients with essential hypertension without impaired carbohydrate metabolism.

Echocardiography in patients with comorbid HT stage II and type 2 diabetes revealed the highest values of left ventricular myocardial mass (LVMM) and left ventricular myocardial mass index (LVMMI) compared to other groups (p <0.05 for all groups), which clearly shown in fig. 2 and 3.

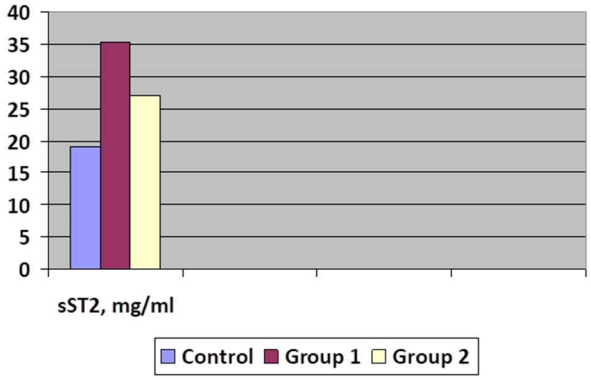

Fig. 1. Blood serum sST2 levels in the examined patients

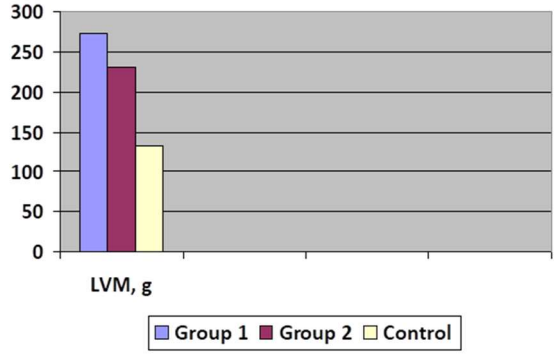

Fig. 2. Comparison of left ventricular myocardial mass in the examined patients.

The value of LVM in patients with stage II HT and concomitant DM not only significantly (p <0.05) exceeded the corresponding values of the control group, but was also significantly (p<0.05) greater than in patients with HT without comorbid DM. It creates conditions for progression of various cardiovascular complications and, in turn, increases cardiovascular risk.

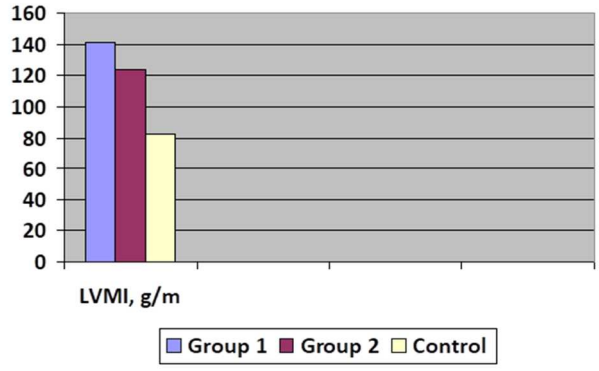

Fig. 3. Comparison of left ventricular myocardial mass index (LVMI) in the examined patients.

For the correctness of the study, we compared also the meanings of LVMI in patients of the study groups and obtained similar results. In the group of patients with comorbid course of HT and type 2 DM, the value of LVMI significantly exceeded not only the control group, but also the corresponding values of LVMI in patients with stage II HT without diabetes. This once again confirms the more severe progression of the disease and the increase in cardiovascular risk, including the development of heart failure in this category of patients.

According to Doppler echocardiography of intracardiac hemodynamics in patients with HT both with type 2 DM and without DM, a decrease in the rate of early and late LV diastolic filling was observed. Moreover, in group 1, these indicators were reduced more significantly in comparison with those in group 2 and control group (p<0.05). Similar tendency was observed for LV (E/A) (0.92± 0.02, 0.88±0.02 and 1.14±0.01, respectively; p<0.05).

Diastolic dysfunction (DD) was found in 63.3 % of patients with HT without DM (group 2), which was represented only by initial changes in transmitral blood flow (TMF), that is relaxation disorders. In patients of group 1 and group 2, the percentage of patients with diagnosed TMF disorders was approximately the same (66.7 and 63.3 %, respectively). At the same time, 16.7 % of comorbid patients with DM (group 1) had a pseudonormal type of DD, which was not found in patients without DM (group 2). Thus, more pronounced diastolic dysfunction was revealed in patients with comorbidity of HT and type 2 DM in comparison to the patients with HT without diabetes. It may worsen the prognosis of disease progression and increase the cardiovascular risk of the initially severe disease.

The analysis of correlations of sST2 with geometrical indices of the myocardium of a left ventricle has been done. There was a significant positive relationship between sST2 and tricuspid valve regurgitation rate ($r=0.46$; $p<0.05$) and E/e' ($r=0.48$; $p<0.05$). A negative significant relationship was observed between the levels of sST2 and the values of e's, e'l, e'avg (respectively $r=0.52$, $r = 0.50$ and $r=0.51$; all $p<0.05$). A weak positive relationship was found between sST2, on the one hand, and the E/A ratio on the other hand ($r=0.29$; $p<0.05$). The correlation between sST2 levels and the progression of diastolic myocardial dysfunction indicates the feasibility to use sST2 as a biomarker of LV diastolic dysfunction in patients with comorbid HT and type 2 DM.

Metabolic disorders caused by hyperglycemia lead to persistent structural and functional changes in internal organs, including the myocardium. A distinctive form of heart disease in case of diabetes is diabetic cardiomyopathy (DC), which is characterized by accelerated development and progression of heart failure [5, 6]. Today there are no clear diagnostic criteria for DC [7]. Left ventricular diastolic dysfunction is the earliest preclinical manifestation of diabetic myocardial disease [8]. It is known that myocardial fibrosis is the main mechanism of the development of diabetic cardiomyopathy [9]. However, to date, the diagnosis of myocardial fibrosis has been associated with certain difficulties.

Among the biomarkers of myocardial fibrosis, soluble gene-expressed stimulating growth factor receptor 2 (sST2) is being actively studied [10]. The study of the relationship of this biomarker with clinical and instrumental and other biochemical indicators, as well as their prognostic value is a promising direction in the management strategy of such patients.

In the present study, at the first stage, the analysis of routine examinations and standard echocardiography have been made. It was observed that patients in group 1 had significantly higher dimensions of left ventricular myocardium. To confirm the suggestion that the above changes may be associated with myocardial fibrosis, the patients were tested for sST2. It turned out to be significantly higher in patients of group 1. To confirm the relationship between sST2 levels and possible fibrotic heart disease, a correlation analysis was performed between myocardial mass and serum fibrosis marker. The obtained results, confirming the presence of a correlation between sST2 and the main indicators characterizing the presence and severity of LVDD, suggest that changes in the biomarker of myocardial stress and sST2 fibrosis are associated with the development of progression of LV diastolic dysfunction.

Conclusion

1. It was found that more pronounced diastolic dysfunction was revealed in patients with comorbidity of HT and type 2 DM compared to the patients with HT without diabetes.

2. Increase of the levels of soluble gene-expressed stimulating growth factor receptor 2 (sST2) in blood serum of the patients with HT and type 2 DM compared to the HT patients without diabetes is associated with left ventricular diastolic dysfunction.

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