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ASSOCIATION BETWEEN ULTRASONOGRAPHIC PARAMETERS, CLINICAL AND BIOCHEMICAL INDICATORS AND RESULTS OF SURVEYS IN PATIENTS WITH HEART FAILURE WITH MODERATELY REDUCED LEFT VENTRICLE FRACTION

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The aim: *to evaluate the probable impact of type 2 diabetes on quality of life, clinical, biochemical and ultrasonographic parameters in patients with HFwmrLVEF and associations between them.*
Materials and methods: *the study included 68 patients with HFwmrLVEF, including 36 patients with concomitant DM type 2 and 32 patients without type 2 DM, and 18 healthy individuals. All study participants underwent anthropometric (height, weight, BMI), laboratory (clinical blood test, biochemical blood test to determine ACT, ALT, creatinine, glucose, lipid spectrum, potassium, sodium and magnesium, ELISA to determine glycated hemoglobin and NT-proBN), instrumental (EchoC, ECG) surveys and surveys to assess quality of life (EQ-5D-5L). Statistical processing of the obtained results was performed using the statistical software package SPSS v.19.0.*
Results: *between the group of patients with HFwmrLVEF with concomitant type 2 DM and the group with HFwmrLVEF without type 2 DM according to the results of the study there is a significant difference in quality of life in carbohydrate metabolism, NT-proBNP, BMI and echocardiographic data.*
Conclusions: *patients with HFwmrLVEF with concomitant type 2 DM compared with patients with HFwmrLVEF without type 2 DM had significantly worse carbohydrate metabolism, significantly higher mean serum NT-proBNP concentration, higher LVMM and iLVMM in transthoracic E quality of life according to the results of the EQ-5D-5L questionnaire in the absence of a significant difference in age and LVEF between groups. In addition, there was a stronger correlation between NT-proBNP and iLVMM in patients without type 2 DM and no correlation between NT-proBNP and LVMM in patients with concomitant type 2 DM, which may be due to certain influence of type 2 DM on the process of pro-BNP conversion*
Keywords: *heart failure, diabetes, NT-proBNP, echocardiography, body mass index, associations*

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1. Introductions

The medical space constantly publishes the results of recent studies on understanding the pathogenesis of heart failure (HF), timely and reliable prediction of its course and development of methods for personalized prevention and treatment of HF in different groups of patients. This is due to the high prevalence of HF and high mortality rates, which are the result of insufficiently effective methods of prevention and treatment. According to modern ideas, HF is not a separate diagnosis, but a clinical syndrome consisting of the main symptoms (e.g., shortness of breath, ankle edema and fatigue), which may be accompanied by symptoms (e.g., jugular venous pressure, pulmonary wheezing and peripheral edema). This is due to structural and / or functional abnormalities of the heart that lead to increased intracardiac pressure and / or insufficient cardiac output at rest and / or during exercise [1].

According to research, the incidence of HF in Europe is about 3/1000 person-years (all age groups) or about 5/1000 person-years in adults. The prevalence of HF is about 12 % in the adult population and increases with age: from about 1 % for people <55 years of age to >10 % for people aged 70 years and older [2]. By 2030, the number of patients with chronic HF is expected to increase by 46 % [3], which is associated with aging, unhealthy lifestyle, increased survival of patients with myocardial infarction (MI) and other diseases of the cardiovascular system. It is known that the annual mortality among patients with mild HF is about 10 %, and in severe cases increases to 50–60 %, and in 35–70 % of patients' death occurs suddenly [4]. According to the Framingham study, the five-year survival rate after the first clinical symptoms of CHF is 25 % in men and 38 % in women [5].

It is known that the course of HF could be significantly complicated by comorbid pathology, among which diabetes mellitus type 2 is more common [6]. It is detected in 30–50 % of patients with HF [7, 8] and in 44 % of

those hospitalized for HF decompensation [9]. In 2016, in the guidelines for the diagnosis and treatment of HF of the European Association of Cardiologists, patients with HF for LV EF are divided into three groups: HF with preserved LV EF (HFwpLVEF), HF with average LV EF (41–49 %) and HF with reduced LV EF (HFwrLVEF) [4, 10]. This distribution is related to differences in the phenotypes of these groups in terms of demographics, clinical manifestations, etiology, mechanical and electrical cardiac remodelling, and pharmacotherapy. In the updated recommendations from 2021, HF with moderate LV EF was renamed HF with moderately reduced LV EF (HFwmrLVEF), due to the proven effectiveness of HFwrLVEF treatment regimens in the treatment of patients with HFwmrLVEF [1].

The CHART-2 study demonstrated the analysis of changes in LV EF and its transition between groups in patients with HF after 1 year and 3 years. LV EF was less stable in the group with HFwmrLVEF, where after 1 year it increased in 44 % of cases and moved to the group HFwpLVEF, and in 16 % of cases decreased to the group HFwrLVEF. After 3 years, the changes were 45 % and 21 %, respectively. From the group of patients with HFwrLVEF 40 % of patients left after a year, and after three years – 47 %, from the group of patients with HFwpLVEF the number of patients who left was 10 % and 12 %, respectively [11]. In another study, patients with HF were conventionally divided into four groups according to the dynamics of LV EF changes, two of which had stable LV EF for some time, one group with increasing LV EF, one group with decreasing LV EF. It turned out that the highest 5-year mortality was in the group with a decrease in LV EF – 43 % [12].

Given the lack of awareness of the strategy for monitoring and treatment of patients with HFwmrLVEF, the results of the above studies and the prevalence of type 2 DM, we consider relevant studies of this group of patients.

The aim: to assess the likely impact of type 2 diabetes on quality of life, clinical biochemical and ultrasonographic parameters in patients with HFwmrLVEF and associations between them.

2. Materials and methods

The study is planned and started in March 2021 and was conducted until February 2022.

This study was conducted in accordance with the requirements of the Helsinki Declaration of Human Rights (1964), the Conference on the Harmonization of Good Clinical Practice (ICH GCP E6 (R2), 2016), the Council of Europe Convention for the Protection of Human Rights and Dignity in Biology and Medicine (Convention on Human Rights and Biomedicine) (ETS-164), including the Additional Protocol to the Convention on Biomedical Research of 25.01.2005, and the legislation of Ukraine. The study was reviewed and approved by the Ethics and Deontology Committee at the State Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine".

All patients were provided with information on the purpose and methods of examination, benefits, and risks before the study procedures. It was reported that they could take part in the study if they wished and focused on the possibility of opting out altogether or terminating the study at any time without losing preference. Patients signed an informed consent in case of a positive will and were included in the study.

Based on SI "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" examined 68 patients with HFwmrLVEF (main group), of which 53 men, 16 women, and 18 healthy individuals (control group). The main group was divided into two subgroups depending on the presence of patients with type 2 diabetes: the group with type 2 DM included 36 patients, the group without type 2 DM – 32 patients.

The mean age of patients was 63.6±4.1 years. The study group mainly included patients with coronary heart disease 91.7 % and hypertension 86.1 %.

All patients underwent a comprehensive examination based on the clinical-diagnostic therapeutic department – the base of the department of clinical pharmacology and pharmacogenetics of non-communicable diseases of the SI "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", which included anthropometric, laboratory, instrumental surveys and surveys to assess quality of life.

Prior to the examination, all patients completed the EQ-5D-5L Quality of Life Assessment Questionnaire.

Anthropometric studies were performed using standard methods with the calculation of body mass index (BMI) by the formula:

$$BMI=(\text{body weight (kg)})/(\text{height (m)})^2.$$

Laboratory studies were performed in the clinical diagnostic laboratory with bacteriological department and in the laboratory of immuno-biochemical and molecular genetic research SI "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine". To study laboratory parameters, blood sampling was performed in the morning on an empty stomach from the ulnar vein. Laboratory tests included clinical blood tests, biochemical blood tests to determine ACT, ALT, creatinine, glucose, lipid spectrum, potassium, sodium and magnesium. The content of NT-proBNP and glycated hemoglobin in the blood was also determined by enzyme-linked immunosorbent assay (ELISA).

To assess the lipid spectrum, the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), triglycerides (TG), low-density lipoprotein cholesterol content (LDLC) were determined according to the formula W.T. Friedewald: LDLC = TC – (HDLC + TG /2,22).

Instrumental techniques included standard-lead electrocardiography (ECG) and transthoracic Doppler echocardiography (DECG). ECG at rest were recorded in 12 standard leads. DECG was performed in accordance with the recommendations of standard accesses on the device Toshiba Aplio 500 with measurement: end-diastolic size (EDS), end-diastolic volume (EDV), end-systolic size (ESS), end-systolic volume (ESV), stroke volume (SV), left ventricular ejection fraction (LVEF), the thickness of the interventricular septum (TIS), the thickness of the posterior wall of the left ventricle (TPWLV), the size of the left atrium (SLA), LP volume,

size of the right ventricles of the heart (right ventricle (RV) and right atrium (RA)).

LV myocardial mass (LVMM) was calculated by the formula:

$$LVMM=0.8\times1.04\times[(TIS_D+EDS+TPWLV_D)^3-EDS^3]+0.6.$$

The surface area of the body was calculated by the formula:

$$SAB=0.007241*\text{weight (kg)}^{0.725}*\text{height (cm)}^{0.425}$$

Index LVMM (iLVMM) by the formula:

iLVMM=LVMM/SAB

LP volume index (LAVi) by the formula:

LAVi=Volume LA/SAB

Diastolic LV function was assessed using the latest recommendations of the American Society of Echocardiography (2021) [13].

Patients received standard therapy.

Statistical processing of the obtained data was performed using the statistical software package SPSS v.19.0. The mean value (M) and the standard error of the mean (m) were calculated. Differences between the compared values were considered significant if the value of Student's t-test was greater than or equal to 95 % ($p<0.05$).

3. Results

According to the data obtained, groups of patients are expected to differ significantly in terms of carbohydrate metabolism (HbA1c and fasting blood glucose), due to the presence of type 2 DM in patients in one group (Table 1).

Table 1

Clinical characteristics, laboratory and echocardioscopic parameters of the studied groups

Indicator	HFwmrLVEF + DM type 2 (n=36)	HFwmrLVEF (n=32)	p
Age, years	64.94±2.61	62.33±2.43	0.162
BMI, kg/m^2	32.92±0.97	29.18±0.88	0.036
EQ-5D-5L, points	64.17±1.16	71.94±1.21	0.020
EDS, mm	59.46±0.88	57.88±0.98	0.231
EDV, ml	180.94±5.94	162.65±5.84	0.034
KCP, mm	45.00±0.97	41.93±1.19	0.047
ESS, ml	99.17±4.15	87.86±4.21	0.064
EF, %	45.06±0.51	46.19±0.83	0.238
SV, ml	81.78±1.97	74.79±1.89	0.014
TIS, mm	12.68±0.21	12.23±0.24	0.159
TPWLV, mm	12.06±0.11	11.78±0.18	0.173
LVMM, g	326.06±8.87	291.57±12.17	0.022
iLVMM, g/m^2	156.56±4.87	142.14±4.15	0.033
SLA, mm	43.22±0.69	42.50±0.71	0.470
LAVi, ml/m^2.	35.03±0.92	34.31±0.63	0.544
RA, mm	40.06±0.64	39.44±0.70	0.516
RV, mm	30.56±0.73	28.81±0.63	0.079
NT-proBNP, pg/ml	964.82±63.10	449.35±77.54	0.011
HbA1c, %	7.32±0.25	5.24±0.12	0.00001
Glucose, mmol/l	9.72±0.88	5.79±0.78	0.000048

It is known that BMI is an independent risk factor for type 2 DM and that its increase is associated with the progression of microvascular complications in patients with DM, which adversely affects the course of coronary heart disease and HF [14, 15]. On the other hand, in a study by Francesco Gentile et al., it was shown that mild obesity (BMI 30–34.9 kg / m^2) is associated with better survival in all patients with HF, including patients with HFwmrLVEF, but not patients with DM were studied [16]. Therefore, the possible prognostic role of BMI on survival in patients with HFwmrLVEF with concomitant type 2 DM is controversial and needs further study. We found the difference in mean body mass index (BMI) between groups. In the group of patients with DM type 2 BMI was significantly higher. Similar results have been obtained in other studies involving patients with HFwpLVEF and HFwrLVEF [17, 18]. Therefore, regardless of LVEF, BMI is higher among patients with HF in those with type 2 DM.

4. Discussion of research results

The RECODE-HF study of 3.778 patients with HF demonstrated the reliability and validity of using the EQ-5D-5L Visual Analog Scale (VAS) questionnaire to assess quality of life in HF patients [19]. According to the study, patients with comorbid pathology and higher NYHA scores had lower scores for VAS, but the dependence of quality of life on LVEF and diabetes mellitus as concomitant diseases in HF patients was not studied separately. Agnieszka Jankowska et al. in their work,

they assessed the quality of life of patients using the EQ-5D-5L questionnaire, showed a significantly lower mean score for VAS (difference of 18.5 points on a 100-point scale) in patients with DM, which was considered the main disease [20]. In our study, there was no significant difference in age and LVEF among patients with HFwmrLVEF between the two groups, but the quality of life was significantly worse in those with type 2 DM. This confirms the results of the RECODE-HF study and the work of Agnieszka Jankowska, but the novelty is that previously the dependence of quality of life on type 2 DM has not been studied among patients with HFwmrLVEF, most of whom, regardless of comorbid pathology, have quite severe HF and a number of symptoms that impair quality of life and affect the results of the assessment.

Studies have shown that DM is a factor in the development of certain negative structural changes in the LV myocardium, which is manifested by an increase in LV myocardial mass (LVMM) and LVMM index (iLVMM) [21]. This is associated with myocardial deposition of triglycerides and collagen and the development of fibrosis. In addition, it is believed that hyperinsulinemia, as a consequence of insulin resistance, directly contributes to myocardial hypertrophy. Independent studies involving patients with HFwpLVEF and HFwrLVEF have shown an increase in LVMM and iLVMM in patients with type 2 DM compared to patients without diabetes [22, 23]. However, patients with HFwmrLVEF with concomitant type 2 DM have not been studied separately. Our study demonstrates significantly higher LVMM and iLVMM in those patients with HFwmrLVEF who have concomitant type 2 DM. Therefore, it could be said that type 2 DM leads to a significant increase in LVMM and iLVMM in all patients with HF, regardless of LVEF.

NT-proBNP is a well-known and actively studied biomarker for the diagnosis of HF and prediction of a number of cardiovascular diseases. NT-proBNP, like other natriuretic peptides, has low sensitivity but high prognostic value for heart failure [24]. It is known that in addition to the pathological increase in the volume of the chambers of the heart, pressure in them and increase in the rigidity of the vascular wall, the level of NT-proBNP is influenced by certain factors, the main of which are age, sex, and comorbidities. According to the results of the PROVE-HF study, it was found that among patients with HFwrLVEF, the mean NT-proBNP was significantly higher in the group with type 2 DM [15]. Another study among patients with HFwpLVEF found no significant difference between NT-proBNP levels in patients with and without type 2 DM [18]. According to our results, it was found that among patients with HFwmrLVEF the level of NT-proBNP is significantly higher in the group of patients with type 2 DM. These results in patients with HFwmrLVEF and HFwrLVEF demonstrate the similarity of these groups in the possibility of concomitant DM influencing the level of natriuretic peptide.

According to many studies, serum NT-proBNP levels are directly correlated with LVMM in both patients with HF [25] and patients without HF [26]. In patients with HFwmrLVEF and concomitant DM 2 type, positive correlations were found between blood levels of NT-proBNP and iLVMM (r=0.49, p=0.005), NT-proBNP and DAC (r=0.41, p=0.02), NT-proBNP and ESS (r=0.45, p=0.01). Positive correlations between NT-proBNP and iLVMM (r=0.73, p <0.001), NT-proBNP and LVMM (r=0.59, p=0.003) were also found in patients with HFwmrLVEF without concomitant DM 2 type. , NT-proBNP and DAC (r=0.41, p=0.046), NT-proBNP and ESS (r=0.44, p=0.03). Comparing these data, the stronger correlation between NT-proBNP and iLVMM in patients without type 2 DM and the lack of correlation between NT-proBNP and LVMM in patients with concomitant type 2 DM are noteworthy. One of the probable reasons for this situation may be the peculiarities of the conversion of pro-BNP to BNP and NT-proBNP, which are characteristic of patients with DM.

Study limitations. A limitation of our study is the relatively small sample (enrollment stopped after martial law was imposed) and the fact that we cannot say for sure which component increases BMI: adipose tissue, muscle tissue, or fluid retention due to HF.

Prospects for further research. The results we obtained indicate the need for further research to identify factors influencing the level of NT-proBNP and determine their importance in the progression of HFwmrLVEF in patients with concomitant type 2 DM.

5. Conclusions

1. According to our study, BMI is significantly higher among patients with HFwmrLVEF and type 2 DM compared with those without carbohydrate metabolism disorders (32.92 kg/m^2 vs. 29.18 kg/m^2, p-value 0.036).

2. Our data indicate that according to the EQ-5D-5L questionnaire, significantly lower quality of life is observed in the group of people with HFwmrLVEF and concomitant DM type 2 (64.17 points for YOU) compared to patients with HFwmrLVEF without disorders of carbohydrate metabolism (71.94 points for YOUR). At the same time, there is no significant difference in age and LVEF between these groups of patients.

3. In the group of patients with HFwmrLVEF and concomitant type 2 DM compared to the group of people with HFwmrLVEF without diabetes found significantly higher concentrations of NT-proBNP in the blood (964.82 pg/ml and 449.35 pg/ml, respectively, p-value 0.01) and higher LVMM (326.06 g and 291.57 g, p-value 0.02) and iLVMM (156.56 g/m^2 and 142.14 g/m^2, p-value 0.03) according to the results of transthoracic echocardioscopy. The correlation between NT-proBNP and iLVMM in patients without type 2 DM and the lack of association between NT-proBNP and LVMM in patients with concomitant type 2 DM may be due to some influence of pathogenic factors of type 2 DM on pro-BNP conversion process.

Conflict of interests

The authors declare that they have no conflicts of interest.

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