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ECHOCARDIOGRAPHIC FEATURES AND CAROTID SCORE IN PATIENTS OLDER THAN 65 YEARS WITH TYPE 2 DIABETES MELLITUS AND HEART FAILURE

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Abstract

Evaluation of arterial stiffness and carotid atherosclerotic burden, as well as echocardiographic structural changes, can provide important prognostic information regarding the risk of future cardiovascular events.

The aim of this study was to assess these vascular properties in patients with diabetes mellitus type 2 (DM type 2) and heart failure with preserved ejection fraction (HFpEF), older than 65 years.

In our research we analyzed 124 participants older than 65 years, 85 of them were with determined diabetes mellitus status, heart failure (HF) is accompanied by an preserved ejection fraction, diagnosed clinically and by echocardiography. In the control group were subjects older than 65 years, without DM type 2 and HFpEF. Carotid ultrasonography was performed to evaluate intima - media thickness (IMT) and carotid plaque burden. Echocardiographic measurements were performed according to criteria ESC/ASC(2015)

The carotid score - IMT and the presence of plaques in the carotid vessels were significantly correlated with the severity and duration of the diseases. Structural changes of the heart such as left atrial dilatation, left ventricular hypertrophy, the degree of diastolic dysfunction verified by echocardiography were correlated with the severity of heart failure and DM type 2.

Echocardiographic abnormalities are very common in elderly patients with DM type 2 and HFpEF and differed from the control group of patients. They, along with carotid score strongly correlate with disease severity and the possibility of future cardiovascular events.

Key words **:** elderly, diabetes mellitus type 2, heart failure, echocardiography, carotid score

Introduction

The aging process begins after the completion of the maturation of the organism, and the regeneration processes and compensatory mechanisms, which develop in this process, over time result in a reduced reserve physiological capacity and increased vulnerability to the changes that occur, especially certain diseases, and as a result and to the reduction of the organism's ability to survive [1, 2]

Multiple subsequent studies over the past two decades have specifically identified aging as an important factor in the emergence of an "epidemic" of heart failure with preserved ejection fraction (HFpEF). Aging itself independently contributes to the deterioration of diastolic function. [3,4,]

Specific changes in the structure and function of aging, including: ventricular stiffness, vascular dysfunction, impaired $Ca2^{+}$ regulation, reduced β-adrenergic reserve, which have been identified as important causes of HFpEF.[5]

As noted by Borlaug et al., left ventricular stiffness increases with normal aging, despite excellent blood pressure control and reduction in left ventricular mass.[6,7] Many of these processes are associated with greater adiposity, and the increase of body weight is associated with an increase in diastolic stiffness of the left ventricle. Aging leads to loss of sensitivity of β-adrenoceptors. [1]

Although aging may have no effects on resting heart rate, contractility and cardiac output decrease the capacity to improve heart rate, systolic function, and response to receptor stimulation during exercise. Aging is also associated with impaired vasodilation caused by endothelial dysfunction. [1,2] According to Borlaug et al, in HFpEF, these combined limitations are much more pronounced than what is seen in normal aging. [6,7]

The aging process causes structural and functional changes such as vascular stiffness, myocyte hypertrophy and myocardial thickening, increased myocardial fibrosis and extracellular matrix remodeling, leading together to diastolic dysfunction (DD), characterized by reduced active filling of the left ventricle. These changes may explain the high prevalence of HFpEF in the elderly population.

These patients are mostly women and usually have more comorbidities such as obesity, DM type 2 and hypertension, compared to patients without HFpEF.

DM type 2 is associated with an increased risk of HF and mortality even after accounting for known cardiovascular risk factors.[8,9]Mechanistic hypotheses related to hyperglycemia, advanced glycation end products, or inflammation and oxidative stress have been described [10] and theoretically related to cardiac structure and function. The concept of a specific diabetic cardiomyopathy affecting subjects with dysglycemia resulting in left ventricular (LV) concentric remodeling, increased LV mass and subtle impaired systolic and diastolic function [5] was reported nearly 5 decades ago.

However, little is known about the underlying dysglycemia - related cardiac mechanisms leading to HF in these patients.

Chronic low-grade inflammation is associated with the aging process, metabolic syndrome, and cardiovascular disease. Serum IL-6 levels increase with age. Increased levels of IL-6 are associated with increased cardiovascular mortality indicating that systemic inflammation may contribute to the cardiac aging process. [11,12] Measurement of serum CRP concentration is a well -known useful marker in patients at high risk for atherosclerotic disease and has great prognostic value.

These immunological changes, immunosuppression, accompanied by a chronic inflammatory state also contribute to the development of metabolic syndrome and diabetes and their cardiovascular consequences. Insulin resistance is increasingly recognized as a chronic, low - grade inflammatory condition. The similarities between insulin resistance and another type of inflammatory condition, atherosclerosis, have been amply demonstrated in the last few decades. [10]

DM type 2 is an important risk factor for cardiovascular disieses (CVD) and each 1% increase in hemoglobin A1c level is associated with an 8% increase in CVD prevalence. [14,15] Patients with HF show a high prevalence of insulin - dependent diabetes mellitus, ranging from 26-45%. About 75% of normotensive, well - controlled patients with insulin - dependent diabetes mellitus without coronary artery disease show evidence of LV DD on echocardiographic tissue by Doppler analysis. [16,17]

In a left ventricular endomyocardial biopsy study, compared with non - diabetics, diabetic HF patients had higher left ventricular DD as well as greater cardiomyocyte hypertrophy. [18,19] Diabetes causes left ventricular DD by multiple mechanisms, altering the myocardial extracellular matrix as evidenced by increased interstitial and perivascular fibrosis, increased expression of type I collagen, and downregulation of collagen - degrading metalloproteinases.

These pathological mechanisms are mediated by hyperglycemia, oxidative stress, and elevated levels of aldosterone and angiotensin - 2. [17]

The development of atherosclerosis is associated with altered lipid accumulation and chronic inflammation in the arterial wall. The blood vessel endothelium responds to stresses, such as blood flow turbulence and high level of circulating modified low - density lipoprotein (LDL), and activates the recruitment of circulating immune cells. Penetrating monocytes are differentiated into macrophages which take up lipid through phagocytosis and turn into foam cells in plaques. Later stages of atherosclerosis are characterized by the formation of unstable plaques leading to thrombus formation and potentially embolism, which are precursors to more serious CVD such as myocardial infarction and stroke. [18]

Material and methods

Study design - clinical prospective cross - sectional study. The patients were examined in one act for a period of 3 months. 124 patients were included, of which: the examined group - 85 patients - were selected from patients who are on a long - term hospital stay in the Specialized Hospital for geriatric and palliative Medicine "13 November ", and part of the outpatients who are examined on an outpatient basis in the specialist - consultative outpatient clinics within the hospital. A control group - 39 patients - were selected from outpatients who use a specialist-consultative service.

Inclusion criteria include: age over 65 years, on ECG - sinus rhythm, symptoms and signs of HF (ESC/ASC criteria) and presence of type 2 diabetes. Patients were examined, who were found to have symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue and/or exertion intolerance, and who by echocardiography had preserved LV EF (LVEF >50%) and signs of DD and had a good echocardiographic examination window. Exclusion criteria - age under 65 years, on ECG - signs of absolute arrhythmia, data on implanted permanent pace-maker, data on advanced valvular heart disease (of moderate and severe degree), data on the existence of another serious disease.

In the studied group were patients diagnosed DM type 2, with oral or insulin therapy.

Laboratory analyzes of blood - complete laboratory analyzes were taken from the patients, with glicemia, lipid profile, enzymes, degradation products, electrolytes. Hg A1 C.

Echocardiographic analysis

Echocardiographic measurements were performed according to criteria ESC/ASC (2015)

Analyses of 2 - dimensional, doppler, and tissue doppler echocardiography were overread LV dimensions (body surface area - BSA) - indexed LV end - diastolic diameter) and interventricular septum were obtained from the parasternal long - axis view. LV mass was calculated by the linear method and indexed to BSA. LV volumes (BSA - indexed LV end-diastolic volume, BSA - indexed LV end - systolic volume), LV ejection fraction and BSA-indexed left atrial (LA) volume index were assessed by the modified Simpson's rule. Right ventricular function was assessed by the fractional area change. LV hypertrophy (LVH) was defined as LV mass index (LV mass/BSA) >115 g/m^2 in men and > 95 g/m^2 in women. Pulsed - wave Doppler of mitral inflow was used to measure early and late mitral inflow peak velocities (E wave and A wave) and their ratio. The average ratio of E wave and the early mitral annulus tissue Doppler velocity (E/e′) was then calculated.

Carotid doppler ultrasonography was performed on all patients. Grading of the carotid score was performed as follows: - score 0: no plaques and thickening of the intimo - median complex (IMT) < 1 mm - score 1: thickened IMT (≥ 1 mm) - score 2: non-stenotic internal carotid artery plaque (ACI) - score 3: stenotic internal carotid artery plaque (ACI) (≥ 50% stenosis) Determination of peak-systolic velocity and end - diastolic velocity (PSV/EDV) of common carotid artery (ACC), internal carotid artery (ACI) and external carotid artery (ACE)

Statistical analysis

The obtained data were processed with statistical computer program SPSS 23 for Windows. Numerical features are shown with descriptive statistics (arithmetic mean, standard deviation, median, interquartile range); Qualitative features are shown with absolute and relative representation; Independent parametric and non-parametric tests were used to compare the analyzed groups (Chi-square test, Fisher exact test, Student t test, Mann-Whitney Z test, Analysis of Variance with Post Tukey test, Kruskal-Wallis ANOVA test); To analyze the relationship between two variables, Pearson's linear correlation coefficient, Spearman's rank correlation coefficient were used; For all analyses, a p value < 0.05 was considered statistically significant.

Results

Out of a total of 124 respondents who were included in the research, 34.7% (43) were male, 65.3% (81) were female patients.

Table 1 - distribution by gender in the examined (EG) and control group (CG) of patients

gender	**groups**			**p value**
	N (%)	**EG n (%)**	**CG n (%)**	
men	43 (34.68)	28 (32.94)	15 (38.46)	0.55
female	81 (65.32)	57 (67.06)	24 (61.54)	
In total	124	85	39	

Pearson Chi-square: ,359656, df=1, p=,548699

The gender structure of the studied group consisted of 32.9% (28) male patients, and 67.1% (57) female patients. In the CG, 38.5% (15) were male patients, 61.5% (24) were female patients. Out of the total number of examined patients, women predominate both in the examined and in the control group of patients, although both groups were completely homogeneous in terms of gender structure,

that is, the statistical analysis as insignificant confirmed the tested difference in the distribution of males and females respondents between the examined and control group (p=0.55).

Table 2 - presence of LVH in EG and CG

LVH	groups			p value
	n	**EG**	**CG**	
There is none	52 (	15 (18.52)	37 (97.37)	0.000000
There is	67 (	66 (81.48)	1 (2.63)	
In total	119	81	38	

Pearson Chi-square: 65.3642, df=1, p=,000000

The echocardiographic finding LVH was significantly associated with HF and the presence of type 2 diabetes (p<0.001). In EG, i.e. in the group of patients with HF and diabetes, LVH was present in 81.5% (66/81) patients against only one patient from CG.

Table 3 - values of speed of early diastolic movement of the mitral annulus laterally e' - lat in EG and CG

groups	Descriptive Statistics (e'-lat)			**p value**
	mean ± SD	median	IQR	
EG	3.01 ± 9.8	0.5	0.4 – 0.8	Z=4.4
CG	3.84 ± 4.1	0.9	0.7 – 8.2	p=0.00001 sig

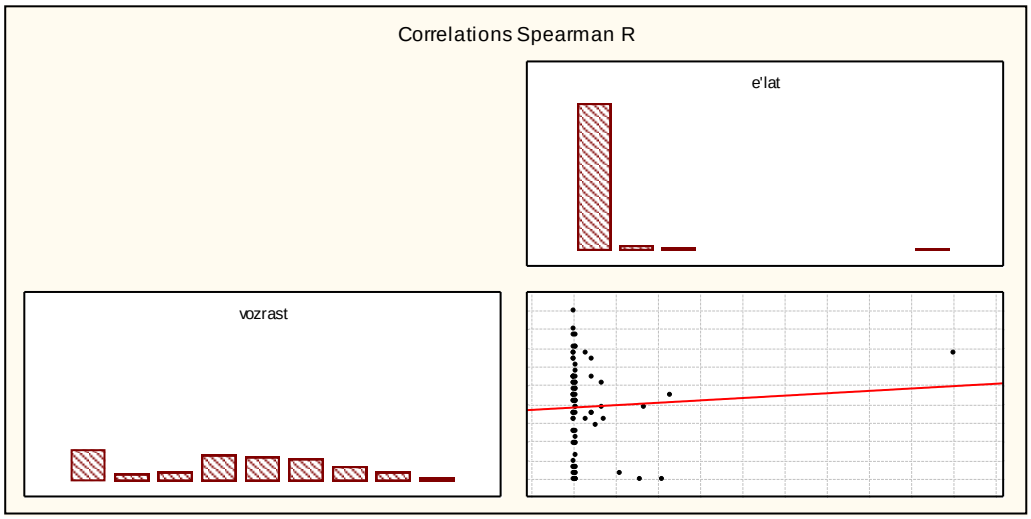
Z (Mann-Whitney U Test)

Patients from the study group had significantly lower values of the echocardiographic parameter e'-lat compared to patients from CG (p=0.000011). Average values for e'lat of 3.0 ± 0.8, median 0.5 were recorded in IG (0.4 – 0.8), in CG the average e'-lat had a value of 3.8 ±4.1, median 0.9 (0.7 – 8.2).

Table 4 - correlation of age with e' - lat

correlation	Spearman R	p-level
age & (e' lat) (EG)	-0.176	p=0.121 ns
age & (e' lat) (CG)	-0.079	p=0.629 ns

Ilustration1 - correlation of age with e' - lat



e' lat. parameter was negatively, that is, indirectly correlated with the age of patients from the examinated and CG. The Spearman value of this coefficient was R = - 0.176 for the association between these two parameters in EG, and R = - 0.0796 for the association between age and e'-lat in CG. These results show that the e' parameter decreases with aging.

Table 5- values of LAVI max in EG compared to CG

groups	Descriptive Statistics **(LAVI max)**				**p value**
	n	**mean ± SD**	**std err**	**min - max**	
EG	56	37.56 ± 9.4	1.25	3.7 – 69.6	t =5.78
CG	39	27.58 ± 6.3	1.01	13.2 – 39	p=0.00000 sig

t (Student t-test)

LAVI max (left atrial volume maximal index) averaged 37.56 ± 9.4 in the group of patients with diabetes, and 27.58 ± 6.3 in CG. The difference of 9.98 between the two groups was statistically significant for p<0.001.

Table 6 - degree of DD in EG patients

Levels of DD	Descriptive Statistics				p value
	n	mean ± SD	std err	min - max	
1	15	14.53 ± 7.0	1.817	3 – 25	F=0.055
2	29	14.93 ± 7.6	1.411	4 – 35	p=0.095 ns
3	13	15.38 ± 3.8	1.053	10 – 20	

Analysis of Variance

In the EG the majority had degree 2 of DD – 49.4% (42), followed by degree 1 of DD – 29.4% (25), and degree 3 of DD –70 21.2% (18). All patients in the CG had echocardiographic finding of grade 1 DD.

Table 7- values of the right carotid score right in EG compared to a CG

Carotid score	groups			p value
Right	N (%)	CG n (%)	DM	
0	21	21 (53.85)	0	p=0.000000
1	43	15 (38.46)	28 (49.12)	
2	32	3 (7.69)	29 (50.88)	
In total	96	39	57	

Pearson Chi-square: 44.24, df=2, p=0.00000

Right carotid score - 0 had more than half of patients from CG – 53.85% (21/39) and none of the group with diabetes. Only 7.7% (3/39) of CG patients had a right carotid score of 2, and about half of the patients with DM – 50.9% (29/57). Right carotid score 0 had 41% (16/39) and only one of the group with diabetes. Only 10.3% (4/39) of CG patients had right carotid score 2, and more than half of patients with DM – 56.1% (32/57). Only patients with diabetes mellitus had a carotid score of 3 – 12.3% (7/57)

Table 8 - left carotid score values in EG compared to a CG

Carotid score left	groups			p value
	N (%)	CG n (%)	DM	
0	17	16 (41.03)	1 (1.75)	p < 0.001
1	36	19 (48.72)	17 (29.82)	
2	36	4 (10.26)	32 (56.14)	
3	7	0	7 (12.28)	
In total	96	39	57	

Discussion

With the aging process, the incidence of cardiovascular diseases are greater in the elderly, compared to younger individuals. Although age is the most powerful independent risk factor for cardiovascular disease, the mechanisms by which aging predisposes atherogenesis, are still being clarified, as well as the specific strategies for optimal prevention and treatment of atherosclerotic diseases in the elderly. Research in science to date suggests that aging potentiates atherosclerosis through a combination of several factors[7,8]

First, the specific biological changes associated with aging increase the occurrence of atherosclerosis. Second, the increased age the time of exposure to known risk factors for CVD and modifies their effects.

Finally, the elderly have an increased number of comorbidities, which can contribute to the occurrence or worsen the severity of atherosclerosis, in particular conditions that create and maintain pro - inflammatory conditions for a longer time biological milieu.[8]

HF is one of the major cardiovascular complications in patients with DM typ 2 and increases the risk of morbidity and mortality. Although active management for HF is needed in patients with diabetes mellitus. Traditional treatment and some new class of antihyperglycemic drugs, such as

glucagon - like peptide -1 receptor agonists or dipeptidyl peptidase - 4 inhibitors, could not reduce the risk of HF. Recent major trials demonstrated sodium - glucose co – transporter - 2 (SGLT2) inhibitors improve prognosis of DM typ 2 patients through prevention of HF. Both, heart failure with reduced ejection fraction and HFpEF is observed DM typ 2 patients. HFpEF is often overlooked and misdiagnosed in these population. LVH, LA dilatation, DD and subclinical systolic dysfunction indicated as reduced global longitudinal strain are major abnormalities on echocardiography in patients with diabetic cardiomyopathy.[20,21] These structural and functional changes are also prevalent in the general patients with DM typ 2, and those with these abnormalities have higher incidence of HF than those without them. Glycemic control might improve some of these abnormalities on echocardiography, but it is still unclear whether their improvement could be associated with risk reduction for HF. At now, there are only limited data on the effects of DPP- 4 inhibitors or SGLT2 inhibitors on echocardiography in DM typ 2. Large - scale trials are needed to clarify how antihyperglycemic drugs affect echocardiographic parameters. [21]

Echocardiography is suggested in the diagnostic work - up of patients with DM typ 2. We investigated which echocardiographic parameters are the specific for the diabetic cardiomyopathy and that best predicted CVD and whether this was persistent in both genders.[22]

Diabetic cardiomyopathy is a form of nonischemic HF in patients with diabetes, and it is defined as structural or functional changes in the myocardium that arise from longstanding DM without any specific cause of ventricular dysfunction, such as uncontrolled hypertension, significant valvular heart disease or coronary artery disease. In the early stages of DM type 2, LVH, myocardial fibrosis, and abnormal cell signaling can be found without symptoms of HF.The estimated prevalence of LVH is approximately 70% in adult patients with DM type 2. [25]Chronic hyperglycemia, insulin resistance, hyperinsulinemia, impaired insulin metabolic signaling, increased oxidative stress, metabolic imbalance, inflammation, inadequate immune response, microvascular dysfunction, activation of renin-angiotensin-aldosterone system, and sympathetic nervous system, and accumulation of advanced glycation end-products can all adversely affect cardiac function, resulting in DM type 2. Abnormal LV remodeling is associated with longstanding glycemic abnormalities, and the longer duration of abnormal glucose control, the worse the degree of LVH and DD. The prevalence of DD is about 20% to 60%, depending on the diagnostic criteria and study populations. [23]

In our study, it was shown that women over 65 years old, who suffer from DM typ 2 and HFpEF are dominant in the studied, but also in the CG. Echocardiographic parameters such as : LVH, LAVI max, DD, e' - lat , as a levels of carotid scores proved to be the most dominant in the studied group, compared to the control group, and as confirmed in other studies, they best reflect the structural changes of the heart and carotid vessels in the presence of these diseases in the elderly. The echocardiographic finding LVH was significantly associated with HF and the presence of type 2 diabetes ($p<0.001$). In EG, i.e. in the group of patients with HF and diabetes, LVH was present in 81.5% (66/81) patients against only one patient from CG.

In the literature, inconsistent results have been established. Our findings are in agreement with those of Zhi et al.'s case–control study, where 48 patients with diabetes were compared with 48 controls, and statistically significant measurements were obtained.[24] Although Zheo et al.'s case–control study reported statistically significant differences in carotid score and echocardiography parameters between diabetic and healthy populations, statistically significant differences were observed in a study among the Sudanese population [25,26]

Our results show significantly higher DD in the diabetic group than in the control. In the EG the majority had degree 2 of DD – 49.4% (42), followed by degree 1 of DD – 29.4% (25), and degree 3 of DD –70 21.2% (18). All patients in the CG had echocardiographic finding of grade 1 DD. Patients from the study group had significantly lower values of the echocardiographic parameter e'- lat compared to patients from CG ($p=0.000011$). Average values for e'-lat of 3.0 ± 0.8, median 0.5 were recorded in IG (0.4 – 0.8), in CG the average e'- lat had a value of 3.8 ±4.1, median 0.9.

This finding is supported by the majority of studies in the literature. Virendra et al. studied similar patients, with a mean HbA1c of 8.3 ± 1.91% in males and 8.1 ± 1.3% in females, along with a disease duration of 11 ± 5 years in males and 10 ± 4 years in females. The results showed 54.33% DD among 127 diabetics with normal systolic function compared to 11% among 100 controls (p-value < 0.05); patients with a longer disease duration (defined as 11 to 15 years) and an HbA1c of >7.5% were

significantly associated with higher DD (p-value < 0.05) [27]Similarly, significantly higher LV DD was observed among asymptomatic Indian patients with diabetes than the healthy population [28]

E.J.Lee and collaborators in their research showed that increased IMT and plaque score are associated with acute ischemic stroke in patients with DM type 2. The IMT and plaque score found in ischemic stroke in patients with DM type 2 seem to be induced by cerebrovascular risk factors. Therefore, to prevent ischemic stroke in patients with DM type 2 strict control of hyperglycemia, hypertension, smoking, and low HDL, together with monitoring of IMT and carotid plaque, may be important.[25]

Conclusion

Echocardiographic abnormalities are very common in elderly patients with DM type 2 and HFpEF. They, along with carotid score strongly correlate with disease severity and the possibility of future cardiovascular events.

Conflict of interest statement

Declaration of competing interest None declared.

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