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Original Research Article

Effect of type 2 diabetes on the left ventricular diastolic dysfunction in patients with chronic kidney disease, 3 and 4 stages

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ABSTRACT

Introduction: Patients with chronic kidney disease (CKD) and coexisting diabetes mellitus (DM) are likely to have cardiological complications.
Aim: We assessed whether patients with moderate kidney dysfunction, with coexisting type 2 DM and preserved left ventricular (LV) systolic function, demonstrate a more advanced LV diastolic dysfunction.
Material and methods: The study group consisted of 58 ambulatory patients with CKD, stages 3 and 4. The patients were assigned to groups based on the presence of type 2 DM. The first group (DM+) consisted of 21 patients with type 2 DM while second one (DM−) consisted of 37 patients without type 2 DM. Standard echocardiography was performed in all patients with tissue Doppler echocardiography for evaluation of the systolic velocity and both diastolic velocities of LV. The following laboratory parameters were measured: serum creatinine concentration, estimated glomerular filtration rate, and the levels of urea, phosphorus, calcium, parathormone, platelets count, hemoglobin level and N-terminal pro-B-type natriuretic peptide levels. LV diastolic dysfunction was defined as EmLV less than 8 cm/s.
Results and discussion: Patients in DM+ group, as compared to patients in DM− group, were characterized by higher values of left and right ventricular end-diastolic dimension, left atrial diastolic dimension, interventricular septal diastolic diameter, LV posterior wall dimension at diastole and of LV mass index, smaller LV ejection fraction and LV fractional shortening. In tissue Doppler echocardiography patients of DM+ group, as compared to patients of DM− group, did not differ in value of EmLV (7.4 ± 2.4 cm/s vs. 7.6 ± 2.1 cm/s, $P = .723$), respectively, and were characterized by similar estimated LV diastolic filling pressure as indicated by E/EmLV (10.1 ± 3.7 vs. 8.8 ± 2.6, $P = .119$).

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Conclusions: CKD patients in the moderate stage, with coexisting type 2 DM were not characterized by higher risk of developing LV diastolic dysfunction.

1. Introduction

Heart failure with preserved ejection fraction is the most frequent clinical type of heart failure found in patients with chronic kidney disease (CKD),[1,2] whereas cardiovascular complications are the main cause of death in this group of patients.[3–5] Type 2 diabetes mellitus (DM) is a risk factor for cardiovascular complications in the general population, and CKD is also associated with increased cardiovascular morbidity and mortality.[6–11] Consequently, the comorbidity of these two diseases may worsen prognosis for patients. Both type 2 DM and end-stage renal disease (ESRD) can lead to diastolic cardiac dysfunction. Additionally, type 2 DM also contributes to an increased left ventricular (LV) stiffness, which directly affects LV diastolic and systolic function.[12–15] Numerous previous studies with tissue Doppler imaging (TDI) confirmed its efficacy in diagnosing LV diastolic dysfunction.[16–19] The majority of these studies assessed LV diastolic dysfunction in patients with ESRD or type 2 DM, or in dialysis patients with DM.[20–23] However, there are limited reports that assess patients with moderate kidney dysfunction (MKD). We assessed whether patients with MKD, CKD, stages 3 and 4, with coexisting type 2 DM and preserved LV systolic function, demonstrate a more advanced LV diastolic dysfunction.

2. Aim

We assessed whether patients with MKD, with coexisting type 2 DM and preserved LV systolic function, demonstrate a more advanced LV diastolic dysfunction.

3. Material and methods

The study group consisted of 58 ambulatory patients with CKD, stages 3 and 4. The patients were assigned to groups based on the presence of type 2 DM. DM was defined as fasting glucose more than or equal to 7.0 mmol/L or therapy with insulin or hypoglycemic therapy. Insulin therapy was used in the majority of the subjects. Mean reported duration of DM was 6.5 years. The type 2 DM group (DM+) consisted of 21 patients while non-type 2 DM group (DM−) consisted of 37 patients. Inclusion criteria included preserved LV systolic function defined by LV ejection fraction more than 50% and lack of regional wall motion abnormalities, and presence sinus rhythm.[24] Exclusion criteria comprised: non-sinus rhythm, LV systolic dysfunction, previous myocardial infarction, cardiomyopathy, significant valvular heart disease, pericardial fluid more than 10 mm at diastole. Diagnostic criteria for CKD were consistent with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative standards.[25] Body mass index (BMI) was also calculated for each patient.

3.1. *Echocardiography*

3.1.1. *Standard echocardiography*

Standard echocardiography was performed for all patients using a GE 6S device with 2.5–3.5 MHz transducer. In order to increase the credibility of the obtained echocardiographic results, the physician who performed the examination was unaware of the biochemical parameters of the patients. The examinations were conducted in stable patients and particular attention was placed on retaining optimal hydration.

Using the M-MODE in the parasternal long-axis view the following parameters were measured: LV end-diastolic dimension, right ventricular end-diastolic dimension, left atrial diastolic dimension, interventricular septal diastolic diameter and LV posterior wall dimension at diastole. Additionally, LV fractional shortening was assessed. In a four-chamber view LV ejection fraction was calculated with the modified Simpson's rule.[26] LV mass was calculated with the formula recommended by the American Society of Echocardiography modified by Devereux.[27] The obtained results of LV mass were indexed by the body surface area of the patient and presented as LV mass index.

Mitral flow velocities were recorded via a pulsed-wave Doppler with the sample volume placed at the tip of the mitral valve in the apical four-chamber view. The mitral inflow velocity curve yielded the following measurements: peak mitral inflow velocity at early and late diastole and deceleration time of early diastole. Early and late diastole ratio was also calculated.[26]

3.1.2. *Tissue Doppler echocardiography*

Pulsed-wave TDI of the mitral annulus was obtained from the apical four-chamber view immediately after standard echocardiography. In pulsed wave TDI diastolic and systolic velocities were measured by placing the Doppler gate on the lateral mitral annulus at the posterior leaflet of the mitral valve. The following parameters were measured: peak mitral annular systolic velocity, peak early diastolic velocity and peak late diastolic velocity of the lateral part of the examined annulus.[10] Next a combination of transmitral flow velocity with annular velocity was calculated to evaluate and estimate LV filling pressures. Additionally isovolumetric contraction time, isovolumetric relaxation time and ejection time were also measured. Myocardial performance index was calculated as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time (IVCT + IVRT/ET).[28] All parameters were calculated as the mean of measurements taken in three consecutive cardiac cycles. LV diastolic dysfunction was defined as EmLV less than 8 cm/s.[29]

3.2. Biochemical tests

On the day of echocardiographic examination, the following laboratory parameters were recorded for all patients: serum creatinine concentration, estimated glomerular filtration rate (eGFR) evaluated by the modified MDRD formula, as well as the serum levels of urea, phosphorus (P), calcium (Ca), parathormone (PTH), platelets (PLT), and hemoglobin (Hb). Additionally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were calculated by immunoassay with the Stratus CS Acute Care Siemens.

3.3. Statistical analysis

Values of parameters with a normal distribution were presented as a mean ± standard deviation, whereas values with non-normal distributions were expressed as median and range. In order to compare both groups, Student's *t*-test and the Mann–Whitney *U* test were used, depending on the parameter distribution. To compare qualitative variables in contingency tables χ^2 test was used.

In order to determine potential and independent echocardiographic and laboratory parameters indicating LV diastolic function, as a diagnostic criterion of LV diastolic dysfunction we used a decreased early diastolic velocity of the LV basal lateral wall (EmLV) less than 8 cm/s, univariate and multivariate logistic regression were performed. Additionally in group with type 2 DM, the correlation between the parameter indicating the diastolic dysfunction (EmLV < 8 cm/s) and the another echocardiographic and laboratory parameters has been also presented.

3.4. Ethics approval

All patients consented in writing for the inclusion in the research. The study protocol was approved by the Local Bioethics Committee (no 555/2011).

4. Results

The study group consisted of 58 ambulatory patients with CKD, stages 3 and 4. CKD etiology in the study group included: hypertensive and ischemic nephropathy in 35 patients, glomerulonephritis in 3 patients, interstitial nephritis in 7 patients, diabetic nephropathy in 2 patients, polycystic kidney disease in 4 patients, autoimmune disease in 1 patient, whereas unknown etiology was present in 6 cases. The DM+ group consisted of 21 patients while DM− group consisted of 37 patients.

Patients of DM+ group, as compared to patients of DM− group, were characterized by significantly higher BMI (32.9 ± 5.9 vs. 28.1 ± 4.0, $P = .0005$), however did not differ in age, sex, presence of arterial hypertension, and CKD severity.

Table 1 – Echocardiographic parameters in both groups.

Parameter	In total $n = 58$	DM+ group $n = 21$	DM− group $n = 37$	*P*
LVEDD, cm	4.7 (3.7–6.1)	4.7 (4.1–6.1)	4.5 (3.7–5.5)	.018
RVEDD, cm	2.7 (2.3–3.3)	2.8 (2.5–3.3)	2.7 (2.3–3.3)	.035
LADD, cm	4.1 ± 0.5	4.4 ± 0.4	3.9 ± 0.5	.0005
IVSDD, cm	1.1 (0.9–1.5)	1.2 (1.0–1.5)	1.1 (0.9–1.5)	.004
LVPWD, cm	1.1 (0.9–1.5)	1.2 (1.1–1.5)	1.1 (0.9–1.4)	.002
LVEF, %	58.9 ± 4.8	57.0 ± 4.4	60.0 ± 4.8	.022
LVMI, g/m^2	93.8 (57.8–198.0)	103.6 (83.6–166.1)	90.1 (57.8–198.0)	.009
LVFS, %	30.5 ± 3.2	28.8 ± 2.6	31.6 ± 3.1	.0009
E, cm/s	61 (35–120)	64 (35–120)	60 (38–111)	.427
A, cm/s	84 (50–141)	79 (58–132)	84 (50–141)	.789
DT, ms	226 (101–457)	230 (101–355)	222 (154–457)	.903
E/A	0.73 (0.42–1.90)	0.73 (0.53–1.90)	0.73 (0.42–1.65)	.987
SmLV, cm/s	7 (4–10)	7 (4–10)	7 (5–10)	.884
EmLV, cm/s	7.5 ± 2.2	7.4 ± 2.4	7.6 ± 2.1	.723
Patients with EmLV < 8 cm/s, *n*/%	29/50	11/52	18/49	.785
AmLV, cm/s	9.7 ± 2.3	9.9 ± 2.7	9.7 ± 2.0	.718
Em/AmLV	0.76 (0.25–2.25)	0.63 (0.25–2.25)	0.76 (0.37–2.00)	.668
E/EmLV	9.3 ± 3.1	10.1 ± 3.7	8.8 ± 2.6	.119
Patients with E/EmLV ≥ 12, *n*/%	9/16	4/19	5/13	.575
IVCT, ms	71 ± 17	71 ± 20	72 ± 16	.800
IVRT, ms	64 ± 16	68 ± 18	62 ± 15	.380
ET, ms	273 ± 40	266 ± 41	276 ± 40	.380
MPI	0.51 ± 0.17	0.53 ± 0.20	0.48 ± 0.15	.362

Comments: (DM+) – group with diabetes mellitus, (DM−) – group without diabetes mellitus, LVEDD – left ventricular end-diastolic dimension, RVEDD – right ventricular end-diastolic dimension, LADD – left atrial diastolic dimension, IVSDD – interventricular septal diastolic diameter, LVPWD – left ventricular posterior wall dimension at diastole, LVEF – left ventricular ejection fraction, LVMI – left ventricular mass index, LVFS – left ventricular fractional shortening, *E* – early transmitral peak velocity, A – late transmitral peak velocity, DT – deceleration time, E/A ratio – ratio of early transmitral peak velocity to late transmitral peak velocity, SmLV – peak mitral annular systolic velocity, EmLV – peak early diastolic velocity, AmLV – peak late diastolic velocity, Em/AmLV – ratio of peak early diastolic velocity to peak late diastolic velocity, E/EmLV – ratio of early transmitral peak velocity to peak early diastolic velocity, IVCT – isovolumetric contraction time, IVRT – isovolumetric relaxation time, ET – ejection time, MPI – myocardial performance index.

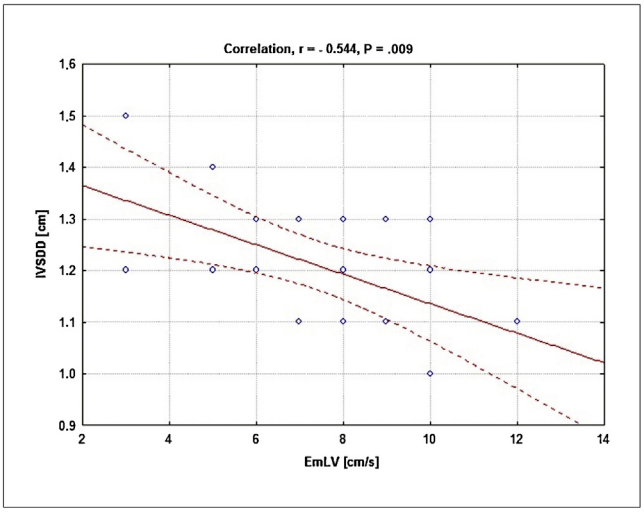

Fig. 1 – Correlation between EmLV and IVSDD.

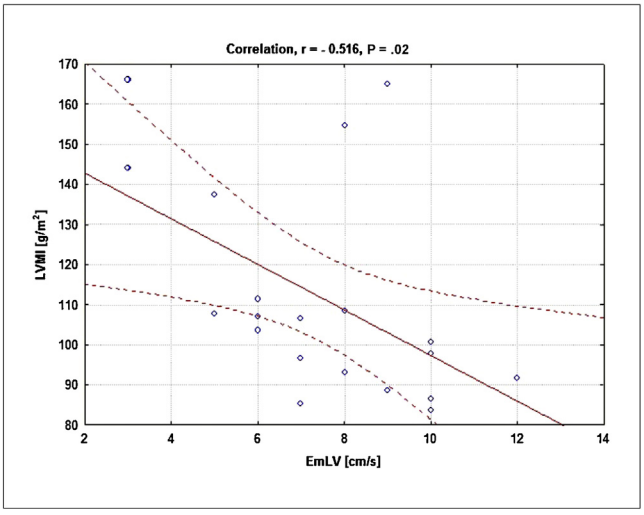

Fig. 3 – Correlation between EmLV and LVMI.

Both groups did not differ in the eGFR level (38 ± 9.0 mL/min/1.73 m^2 in DM+ group vs. 36 ± 13.2 mL/min/1.73 m^2 in DM− group, $P = .419$) and concentrations of creatinine, urea, P, Ca, PLT, Hb, PTH and NT-proBNP.

Parameters obtained in standard echocardiography and TDI in both groups of patients are presented in Table 1.

In standard echocardiography, patients with DM+ group, as compared to patients with DM− group, were characterized by higher values of LVEDD, RVEDD, LADD, IVSDD, LVPWD and of LVMI, smaller LVEF and LVFS. No differences were noted as concerns: *E*, A, DT and *E*/A ratio.

In TDI patients with DM+ group, as compared to patients with DM− group did not differ in values of EmLV, AmLV, SmLV and MPI, and were characterized by similar estimated LV diastolic filling pressure as indicated by *E*/EmLV (10.1 ± 3.7 vs. 8.8 ± 2.6, $P = .119$). The prevalence of patients with diastolic dysfunction defined as EmLV less than 8 cm/s and ratio of *E*/EmLV more or equal to 12 were similar in diabetic and non-diabetic patients.

In order to determine potential and independent parameters indicating LV diastolic function (EmLV < 8 cm/s), univariate and multivariate logistic regression were performed. To assess the diagnostic value, odds ratio (OR) for particular laboratory and echocardiographic parameters was calculated. Only those parameters with $P < .1$ in univariate logistic regression were considered.

Among the examined parameters, only a serum Ca level (OR = 0.21, 95%CI = 0.07–0.840, $P = .021$), IVSDD (OR = 1594.9, 95%CI = 5.4–474, 323, $P < .0001$) and BMI (OR = 0.81, 95% CI = 0.69–0.96, $P = .014$) were found to be an independent predictive factor for LV diastolic dysfunction. The presence of DM and other parameters did not reach statistical significance in multivariate analysis.

In DM+ group of patients, EmLV correlated negatively with: IVSDD ($r = -0.544$, $P = .009$), LVPWD ($r = -0.505$, $P = .017$), and LVMI ($r = -0.516$, $P = .02$). The relationship between EmLV and IVSDD, LVPWD and LVMI in DM+ group of patients is shown in Figs. 1–3, whereas other parameters did not show statistically significant correlation with EmLV.

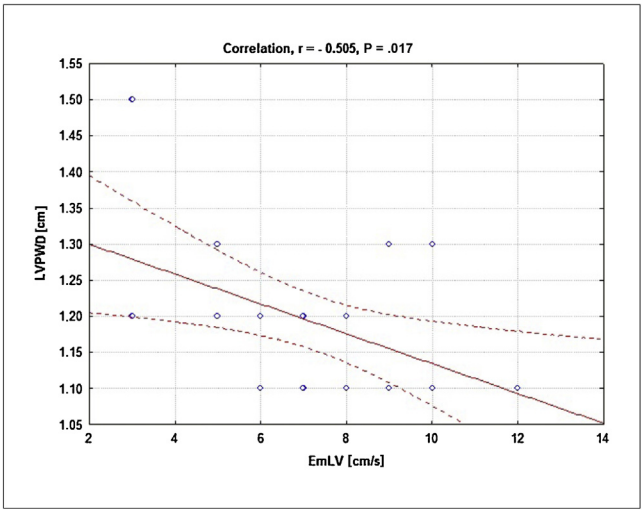

Fig. 2 – Correlation between EmLV and LVPWD.

5. Discussion

In our study, patients with MKD and coexisting type 2 DM did not exhibit a more significant LV diastolic dysfunction as compared to patients with CKD without DM. Values of EmLV and *E*/EmLV were similar in patients of two groups; also no statistical differences occurred as regards MPI. In standard echocardiography, patients with coexisting DM did not display a different mitral flow profile than those without DM. They demonstrated, however, larger values of LVEDD, RVEDD, LADD, IVSDD, LVPWD and LVMI, as well as smaller values of LVEF and LVFS. The results that we obtained in this study partially not correspond to previous studies.[22,23,30] Hung et al.[22] reported that patients on chronic dialysis with coexisting type 2 DM were characterized by smaller EmLV and larger *E*/EmLV ratios, larger values of LADD and IVSDD. They did not differ as regards diastolic mitral flow velocities and values of LV MPI. In the study by Nardi et al.,[30] the effect of type 2 DM on CKD patients with arterial hypertension was

evaluated. These researchers concluded that the coexistence of both type 2 DM and kidney dysfunction worsens LV diastolic function in these patients, through a decrease in EmLV, increase in E/EmLV and increase in left atrial volume. In another study, chronic dialysis patients with coexisting DM demonstrated larger values of LADD, IVSDD and LVPWD as compared to patients without DM.[23]

Many studies indicated that DM not only affects LV diastolic function, but also results in reduced systolic function.[20,31] These studies proved that in patients with type 2 DM, increased LV stiffness caused by collagen deposits and cardiac fibrosis as well as LV hypertrophy can also lead to systolic dysfunction.[20,31] In the Hung et al. study,[22] LV global contractility in dialysis patients with type 2 DM did not differ from LV global contractility in patients without DM. However, TDI showed that patients with DM demonstrated statistically significantly smaller values of mitral annular lateral systolic velocity (SmLV) than in the group of patients without DM (7.6 ± 1.6 vs. 8.5 ± 2.1 cm/s, $P = .035$), respectively. In the study by Fang et al.[20] the presence of LV systolic dysfunction in patients with DM was also demonstrated. In our study, mitral annular lateral systolic velocities (SmLV) did not differ between the researched groups. However, when LV global contractility combined with the assessment of LVEF was evaluated, patients with type 2 DM demonstrated decreased values of LVEF and LVFS, when compared to patients without DM (57 ± 4.4 vs. $60 \pm 4.8\%$, $P = .022$ and 28.8 ± 2.6 vs. $31.6 \pm 3.1\%$, $P = .0009$), respectively.

To sum up, according to our results, it should be stressed that in the group of CKD patients with coexisting DM a good correlation was demonstrated between the values of IVSDD, LVPWD, LVMI and the EmLV parameter. Consequently, we can claim that, apart from the already documented role of E/EmLV, LV hypertrophy determined both by the effect of type 2 DM and CKD maybe is not closely associated with LV diastolic dysfunction.

The most significant limitation of this study is that it is a single-center study, conducted on a relatively small group of subjects. In TDI movement velocities were measured only within the lateral portion of the mitral annulus at the posterior leaflet of the mitral valve. The analysis of systolic and diastolic movement velocities concerning the remaining portions of this annulus could improve the precision of this study. Additionally, Doppler techniques are also angle dependent. In our study, these parameters were recorded at an angle of more than 20° to the Doppler beam. Other limitation of this study includes the fact that the assessed diastolic dysfunction was not compared directly with invasive parameters evaluating the increase of LV filling pressure.

6. Conclusions

CKD patients in the moderate stage, with coexisting type 2 DM were not characterized by higher risk of developing LV diastolic dysfunction.

Conflict of interest

There are no financial or other relationship considerations that could lead to any conflict of interest.

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The authors of this manuscript declare that they have complied with the Principles of Ethical Publishing present in the Declaration of Helsinki and that the study protocol was approved by a local ethics committee.

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