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LETTER TO THE EDITOR

Predictors of left ventricular diastolic dysfunction in type 2 diabetes patients: A 4-year prospective study

KEYWORDS
Left ventricular diastolic dysfunction;
Diabetic cardiomyopathy;
Type 2 diabetes;
hs-CRP;
Triglycerides

Patients with type 2 diabetes mellitus (T2DM) may develop a cardiomyopathy, often called diabetic cardiomyopathy, which is characterized by left ventricular diastolic dysfunction (LVDD) in the early stages.[1,2] In a study of T2DM patients with good glycemic control 47% were found to have diastolic dysfunction.[3] High-sensitivity C-reactive protein (hsCRP) has been associated with subclinical LVDD in patients with cardiovascular (CV) risk factors.[4] Therefore, the aim of the present study was to determine possible risk factors that could predict the new onset of LVDD within 48 months of follow up in a T2DM patient cohort.

We enrolled 48 patients (26 males) with T2DM [mean age (±standard deviation, SD): 55.4±10.0 years, HbA1c: 7.5±1.5%, body mass index (BMI): 29.4±5.1 kg/m^2, T2DM duration: 6.8±0.8 years] with normal both systolic and diastolic cardiac function that were followed up for 48 months. The exclusion criteria were coronary artery disease, inflammatory states and active malignancy. Demographic characteristics and medical history were recorded and fasting blood samples were analyzed for B-type Natriuretic Peptide (BNP), soluble ST2, hsCRP, HbA1c, glucose and lipid profile at the baseline visit. All subjects underwent resting transthoracic 2-dimensional echocardiography and Doppler imaging to assess LVDD, left ventricular myocardial index (LVMI) and left ventricular mass at baseline and annually for 48 months. Echocardiography, particularly tissue Doppler imaging, was used to diagnose subjects with left ventricular systolic and/or diastolic dysfunction (according to the A.C.C. / A.H.A. guidelines that were revised in 2009). Studies were performed using a Vivid 7 echocardiography machine (Vingmed, Norway). All measurements were performed according to the ASE recommendations for chamber quantification 20051 by a single experienced echocardiographer who was blinded to the diabetic status of the patients. The LV ejection fraction was estimated using the Simpson biplane method. The E- and A-wave peak velocities and DT were measured using the mitral inflow profile. The E' velocity from the septal and lateral mitral valve annulus and the mean value were determined, and the respective E/E' ratios were derived. An E/E' septal ratio >15 was considered to be indicative of elevated LV filling pressure. Diastolic function was categorized based on mitral inflow and Doppler tissue imaging parameters.

At baseline 41.7% of study recruits had arterial hypertension, 45.8% had dyslipidemia and 45.8% were current smokers. The majority of study patients were taking oral antihyperglycemic agents (OADs) (95.8%): 91.7% were on metformin, 27.1% were on sulfonylurea, 8.3% were on dipeptidyl peptidase 4 (DPP-4) inhibitors and 8.3% were on glinides. Regarding anti-hypertensive therapies, 18.8% of study participants were on angiotensin-converting-enzyme (ACE) inhibitors, 16.7% were on angiotensin receptor blockers (ARBs), 4.2% were on diuretics and 4.2% were on beta-blockers.

At the end of the study (48 months) 28 patients (58.3%) were diagnosed with LVDD. Univariate logistic regression analysis showed that LVDD was associated with **BMI** [odds ratio (OR): 1.14, 95% confidence interval (CI): 0.99-1.29, p=0.05], **ARBs** (OR: 0.17, 95% CI: 0.03-1.01, p=0.05), **hsCRP** (OR: 1.29, 95% CI: 1.04-1.59, p=0.02), **high density lipoprotein** cholesterol (OR: 0.95, 95% CI: 0.91-0.99, p=0.03), **triglycerides** (OR: 1.02, 95% CI: 1.00-1.04, p=0.003) and **LVMI** (OR: 1.05, 95%CI: 1.00-1.08, p=0.03). There was no correlation between LVDD and sex, age, diabetes duration, history of hypertension, dyslipidemia, smoking, OADs, total cholesterol, low-density lipoprotein

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cholesterol, BNP and soluble ST2. Multivariate logistic regression analysis controlling for the above factors indicated that LVDD was positively associated with **hsCRP** (OR: 1.12, 95% CI: 1.08-1.51, p=0.02) and **triglycerides** (OR: 1.07, 95% CI: 1.01-1.14, p=0.02) and negatively associated with **ARB** therapy (OR: 0.14, 95% CI: 0.05-0.43, p=0.05).

The results of the present study indicate that higher hsCRP and triglyceride levels might predict the new onset of LVDD, whereas ARB therapy might have a protective role in T2DM patients. Previous studies have demonstrated that CRP is a marker of left ventricular dysfunction. In patients with heart failure, CRP is increased and positively associated with parameters of left ventricular dysfunction.

A previous study on diabetic complications indicated that hypertriglyceridemia was closely associated with early stages of LV systolic longitudinal myocardial dysfunction in asymptomatic DM patients with preserved LVEF.[5] Elevated fasting triglycerides are thought to be a cause of myocardial steatosis, resulting in subclinical LV systolic and diastolic dysfunction.[6] Another study demonstrated that efficient modification of risk factor profile and, especially, of dyslipidemia, can be achieved by Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, reducing LDL levels substantially and eventually reducing the incidence of cardiovascular events and ischemic left ventricle dysfunction.[7]

We found that ARB therapy might have a protective role in the establishment of LVDD in T2DM patients. The same pattern was observed in another study in which ARBs and ACEs inhibited ventricular fibrosis in hypertensive diastolic heart failure.[8] In our study this protection was not found for ACE-I; however, a limitation of our study is the small sample size.

Despite recent findings of a favorable effect of DPP-4 inhibitors and pioglitazone on left ventricular function, we did not find any association.[9,10] A previous study by our research group found that the presence of LVDD in patients with T2DM was associated with higher sST2 levels.[11] In the present study, sST2 was not higher in the population that presented with LVDD at the follow-up examination. Furthermore, no association between BNP levels and LVDD was found despite the findings of previous studies.[12]

In conclusion, the results of the present 4-year prospective study demonstrate that baseline hsCRP and triglyceride levels can predict the presence of LVDD within 48 months in type 2 diabetes patients with previously normal systolic and diastolic cardiac function, whereas ARB therapy might have a protective role. HbA1c, LVMI, BNP and soluble ST2 did not show any predictive potential in this type 2 diabetes patient cohort.

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