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Left ventricular diastolic dysfunction in normotensive postmenopausal women with type 2 diabetes mellitus

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Abstract

Background: *The prevalence of heart failure among diabetic patients is high, also in those with normal blood pressure and without coronary artery disease, even when electrocardiogram (ECG) is normal. The goal of our study was to assess the prevalence of left ventricular diastolic dysfunction (LVDD) among diabetic women (DW) and its correlation with glycosylated hemoglobin (HbA1c) levels, obesity status, and ECG parameters.*

Methods: *A group of 456 consecutive normotensive postmenopausal women affected by type 2 diabetes, diagnosed over 5 years, were enrolled. One hundred normotensive non-diabetic postmenopausal women were included as a control group (CG). Rest ECG and trans-thoracic echocardiogram and Doppler were performed.*

Results: *LVDD was present in 103 (23.3%) out of 456 DW, and 8 out of 100 women in CG (8%), $p < 0.001$. There was no difference in mean age between the two groups: 56 ± 13 and 55 ± 3, respectively ($p = 0.3$). There were 191 (41.9 %) DW with body mass index (BMI) > 30 kg/m^2. Among those, there were 56 (12.3%) with significant prevalence of LVDD, while there were 49 (10.7%) with BMI < 30 kg/m^2, $p < 0.005$. DW with HbA1c > 7.5% comprised a group of 243 (53.3%) patients. Among those, there were 45 (9.9%) with higher prevalence of LVDD, and 15 (3.3%) with HbA1c < 7.5%, $p < 0.01$. Out of a group of 147 (32.2%) DW with abnormal ECG , 21 had LVDD (4.6%), $p = 0,1$, and 84 (18.8%) had LVDD with normal ECG.*

Conclusions: *Our data prove a high prevalence of LVDD in asymptomatic diabetic postmenopausal women. This finding is closely related with HbA1c levels and obesity status, not with abnormal ECG, which is a unique cardiologic test recommended by current guidelines in all diabetic patients. We conclude that early detection of high level of HbA1c and obesity (30 kg/m^2) may identify women with major risk to develop LVDD. Furthermore, a simple ECG, when normal, is not enough to assess a normal LV diastolic function.* (Cardiol J 2017; 24, 1: 51–56)

Key words: left ventricular, diastolic function, type 2 diabetes, postmenopausal women

Introduction

Diabetes mellitus (DM) is the most common metabolic disease, especially in Western countries and its prevalence will double in the next 25 years [1].

Cardiovascular diseases are the leading cause of death among diabetic patients because, as widely demonstrated, chronic hyperglycemia results in morphological and functional changes on vascular wall, which leads to development of atherosclerotic plaque [2].

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It is mandatory to detect "diabetic cardiomyopathy" at an early stage, to improve cardiovascular risk stratification on diabetic patients. Left ventricular (LV) diastolic dysfunction (LVDD), without impairment of systolic function, i.e. with preserved LV ejection fraction (LVEF), is the first stage of "diabetic cardiomyopathy" [3]. The gold standard for LVDD assessment is echocardiogram with pulse wave (PW) tissue Doppler that allows to perform a non-invasive, rapid, free of radiation, reproducible assessment of LV filling and pressure [4, 5]. Early LVDD of lower degree, as impaired relaxation pattern, can be considered a preclinical stage of disease, the heart reduces LV compliance and elevates filling pressure, increases left atrial contribution to LV filling, preserving LVEF [6]. It is quite clear that an impaired ventricular relaxation can determine, with time, a diastolic heart failure with a preserved ejection fraction (heart failure with normal ejection fraction, HFpEF), with a mortality rate similar to systolic heart failure [7].

Pathogenesis of impaired LV relaxation in diabetic patients is not fully understood, although microvascular disease, autonomic dysfunction, other concomitant metabolic disorders, long duration of DM and poor blood glucose control are universally recognized as concurrent factors [8]. Microcirculation plays an important role in impairment of LV compliance, similarly to prolonged hyperglycemia causing fibrosis and autonomic dysfunction, with an additive and adverse effect of DM on cardiovascular system. Mishra et al. [9] found that DM represents the most common risk factor involved in the development of LVDD [9].

A significant amount of scientific evidence suggests a higher prevalence of LVDD in postmenopausal women [7–10] — a drop in estrogen causes a lack in physiological protection of endothelium with growth of atherosclerotic plaques and activation of the renin–angiotensin–aldosterone system (RAAS), with increase of angiotensin II and production of reactive oxygen species (ROS), with impaired ventricular relaxation [11].

It may be observed that in such patients, occur unfavorable changes in arteries structure and function [12]; aortic stiffness is an early marker of cardiovascular disease and atherosclerosis, [13] whose increase is often associated to abnormal LV filling [14]. Therefore, aortic stiffness increases with age and its association with mortality is twice higher in women than in men [15]. Postmenopausal women present a close correlation between aortic stiffness and hypertension, DM and hypercholesterolemia, independently of age when the menopause started [16]. According to these, aortic stiffness plays a prognostic role in identifying risk of developing adverse cardiac events along time.

The goal of our study is to evaluate the prevalence of LVDD in asymptomatic and normotensive postmenopausal women with DM, over 5 years. Our secondary endpoint was the correlation between LVDD and long-term glycemic control, assessed by glycosylated hemoglobin (HbA1c), obesity (body mass index [BMI] > 30 kg/m^2), being LVDD often associated with metabolic disorders.

Methods

Patients

A group of 456 consecutive normotensive postmenopausal women affected by type 2 DM over 5 years were enrolled. Menopause was assessed if occurred 12 months after last menstrual period, DM duration average time was 7 ± 3 years, all of them were on oral antidiabetic therapy, 45 of them were also on insulin treatment. Subjects with systolic dysfunction (LVEF < 50%), mild-severe valvular diseases and atrial fibrillation were excluded. One hundred normotensive and non-diabetic postmenopausal women were included as a control group (CG). None of the enrolled women was physically active. Electrocardiogram (ECG), PW tissue Doppler and transthoracic echocardiogram (TTE) were performed, baseline characteristics: demographic and clinical conditions are described in Table I.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Echocardiography

Transthoracic echocardiogram was performed with patient in left lateral decubitus, after 10 min of resting, with the exam table elevated by 30°. The examination was carried out with 3.5 MHz probe, with ECG trigger. We used echo-Doppler system equipped with a multifrequency transducer, GE Vivid T8, Health Care, via Galeno 126, Miland (Italy). We assessed: intraventricular septum thickness in diastole (IVSd), LV diastolic diameter (LVDD), LV posterior wall thickness during diastole (LVPWd), intraventricular septum thickness in systole (IVSs), LV systolic diameter (LVSD), LV posterior wall thickness during systole (LVPWs), ejection fraction (EF), and fractional shortening (FS). Peak velocities of early (E wave) and late (A wave) trans-mitral flow and deceleration time (DT)

Table 1. Baseline characteristics (demographics, diseases and clinical conditions).

Demographic variables	All	Diabetic	Control group	P
Age [%]		56 ± 13	55 ± 3	0.3
Postmenopausal women	556	456	100	
Body mass index > 30 kg/m^2	230	191 (41.9%)	39 (39%)	0.6
HbA1c > 7.5%	234	234 (53.3%)	0 (0%)	
Abnormal electrocardiogram	173	147 (32.2%)	26 (26%)	0.1

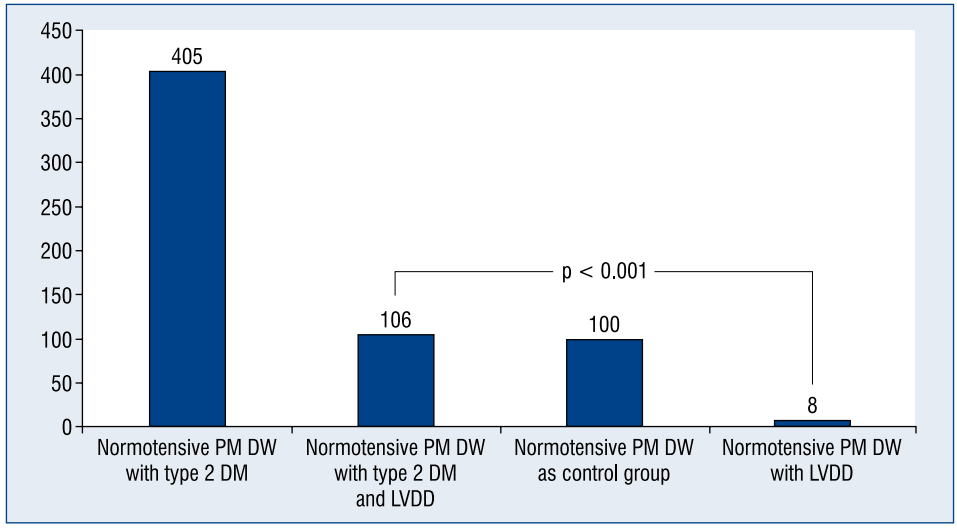

Figure 1. Left ventricular diastolic dysfunction (LVDD) in postmenopausal (PM) diabetic (D) normotensive women (W) according to diabetes status; DM — diabetes mellitus.

were determined, and E/A ratio was calculated. LV mass (LVM) was determined according to the formula by Devereux et al. [17] and indexed according to body surface area (BSA) to obtain LVM index (LVMI). Listed normal values of the above echocardiogram parameters are in accordance with the American Society of Echocardiography. LVDD was diagnosed by at least two expert cardiologists according to current guidelines [18, 19], by PW Doppler of mitral inflow and Doppler tissue imaging of the mitral annulus. LVDD was assessed as mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormal pattern), and grade III or severe (restrictive filling). Mild LVDD for mitral E/A ratio < 0.8, DT > 200 ms, IVRT ≥ 100 ms, E'< 8 cm/s, E/E' ratio < 8 (septal and lateral). Moderate LVDD for mitral E/A ratio from 0.8 to 1.5 (pseudonormal), E/E' (average) ratio from 8 to 15, and E'< 8 cm/s. Severe LVDD (grade III) for E/A ratio ≥ 2, DT < 160 ms, IVRT ≤ 60 ms, E/E' > 15 [18]. All subjects with abnormal diastole, for all different degrees of severity, were assessed as having LVDD.

Electrocardiogram

It was assessed as abnormal according to observation of ST-T abnormalities at rest.

Statistical analysis

Statistical analysis was performed by IBM SPSS version 20.0 (Chicago, IL, USA). Results are described as mean with 95% confidence interval (CI 95%). Student's t test was used for continuous variables and χ^2 test for categorical variables. A p value < 0.05 was considered significant.

Results

Left ventricular diastolic dysfunction was present in 103 (23.3%) out of 456 diabetic women (DW), and 8 out of 100 women in CG (8%), p < 0.001 (Fig. 1). There was no differ-

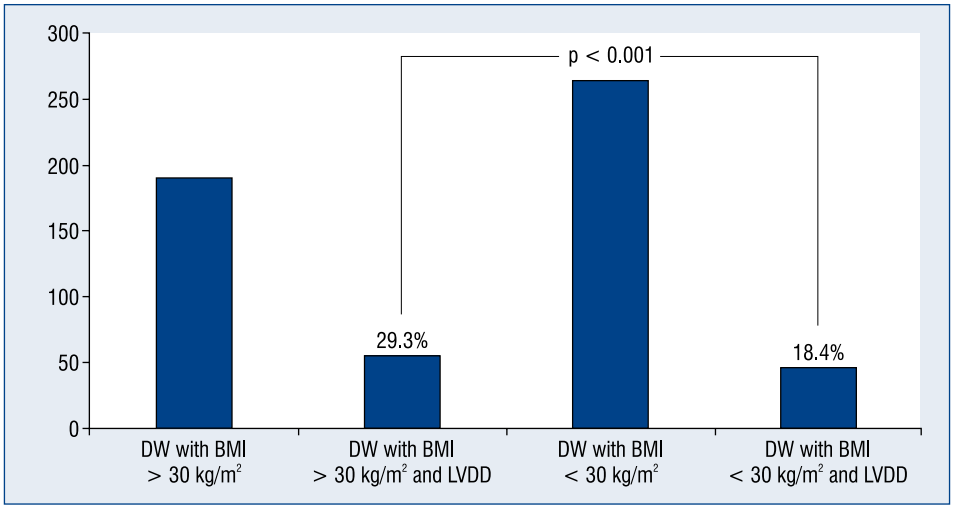

Figure 2. Left ventricular diastolic dysfunction (LVDD) in postmenopausal (PM) diabetic (D) normotensive women (W) according to different body mass index (BMI) and LVDD.

Table 2. Results according to left ventricular diastolic dysfunction distribution.

Clinical variables	Affected	Free	Control group	P
Diabetic women	105 (23.3%)	351 (76.7%)	8 (8%)	< 0.001
Body mass index > 30 kg/m²	56 (12.3%)	135 (29.6%)	39 (39%)	< 0.005
Body mass index < 30 kg/m²	49 (10.7%)	216 (47.4%)		
HbA1c > 7.5%	45 (9.9%)	198 (43.4%)	0 (0%)	< 0.01
HbA1c < 7.5%	15 (3.3%)	198 (43.4%)	100 (100%)	
Abnormal electrocardiogram	21 (4.6%)	126 (27.7%)	14 (14%)	0.1
Normal electrocardiogram	84 (18.4%)	225 (49.3%)	86 (86%)	

ence in mean age between the two groups: 56 ± 13 and 55 ± 3, respectively (p = 0.3). There were 191 (41.9 %) DW with BMI > 30 kg/m^2. Among those, there were 56 (12.3%) with significant prevalence of LVDD, while there were 49 (10.7%) with BMI < 30 kg/m^2, p < 0.005. Then, the number of DW with BMI > 30 kg/m^2 and normal diastolic function were 135 (29.6%), DW with BMI < 30 kg/m^2 and normal diastolic function were 216 (47.4%). DW with HbA1c > 7.5% comprised a group of 243 (53.3%) patients. Among those, there were 45 (9.9%) with higher prevalence of LVDD, and 15 (3.3%) with HbA1c < 7.5%, p < 0.01. A group of 198 (43.4%) DW had poor glycemic control with normal diastolic function and equally, 198 (43.4.%) DW had good glycemic control and normal diastolic function. Out of a group of 147 (32.2%) DW with abnormal ECG, 21 had LVDD (4.6%), p = 0,1, and 84 (18.8%) had LVDD with normal ECG. Normal diastolic function was found in 126 (27.7%) DW with abnormal ECG and in 225 (49.3%) DW with normal ECG. All results are described in Table 2. 105 DW affected by LVDD, 90 were on impaired relaxation pattern (85.7%), 84 with normal ECG and 6 with abnormal. Eleven (10.4%) DW were on pseudonormal pattern and 4 (3.9%) on restrictive filling; all 15 DW had abnormal ECG. 8 women of CG affected by LVDD, all of them had abnormal ECG.

Discussion

Our study evaluated the prevalence of LVDD in asymptomatic and normotensive postmenopausal women, diabetic over 5 years. We found a higher prevalence of LVDD in our diabetic population compared with the CG (23.3% for DW vs. 8% for CG). Other authors found LVDD as early subclinical myocardial damage in diabetic patients [20, 21]. Furthermore (Fig. 2), we found a higher prevalence

of LVDD in obese women with BMI > 30 kg/ /m^2 (29.3% for DW vs. 18.4% for CG) and with poor glycemic control, assessed by HbA1c > 7.5 (35.4% for DW vs. 28% for CG) [22]. Bhuiyan et al. [23] observed a similar correlation between LVDD and uncontrolled DM. Our data are in accordance with Patil et al. [24], who found a strong correlation between LVDD and DM duration, HbA1c levels, obesity and microcirculation impairment. They underline that diabetic patients, although asymptomatic, within 10 years since first diagnosis, develop microcirculation impairment, which leads to cardiovascular events. Several mechanisms have been proposed to explain DM and LVDD correlation, such as increased cardiac lipid accumulation and impaired calcium homeostasis. LVDD but not systolic dysfunction was associated with increased cardiac triglyceride content in ob/ob mice [24]. Furthermore, these mice also exhibit impaired calcium reuptake that was associated with LV contractile dysfunction [25, 26]. Impaired contractility in cardiomyocytes isolated from sedentary db/db mice was associated with increased diastolic sarcoplasmic reticulum (SR)-Ca^{2+} leak, reduced synchrony of Ca^{2+} release, lower peak systolic and diastolic Ca^{2+} and caffeine-induced Ca^{2+} release, consistent with a role for calcium in the LVDD seen in type 2 DM [27]. This finding is in agreement with data concerning Indian population, genetically more prone to DM than others. It was assessed that LVDD is statistically associated with DM duration, poor glycemic control and mixed therapy consisting of insulin and oral hypoglycemic agents [28].

Another study, on 486 patients affected by DM, found that the most important determinant of LVDD is DM duration over 4 years, regardless of hypertension and coronary artery disease affections [29]. Although DM duration seems to be a clear determinant for impaired LVDD, the prevalence of LVDD in newly-diagnosed (within 1 month) diabetic patients is high [30]. The prevalence of LVDD among diabetic population was 41%, lower in women, regardless of confounding factors as hypertension, previous ischemia, and obesity. Poor glycemic control (HbA1c > 7.24 ± 0.64) was statistically associated with LVDD. Age over 50 years at diagnosis was considered a major risk factor for LVDD development. However, in our opinion, high LVDD prevalence in newly-diagnosed diabetics seems due to a delay in diagnosis. Beyond diabetes, there are others determinants of LVDD: we found a strong correlation between LVDD and hypercholesterolemia in a population of postmenopausal women affected by a mild-moderate hypertension [31]. This finding can be easily explained by an increased aortic stiffness and high peripheral resistance that compromise LV diastolic function in postmenopausal women.

The main finding of this study consists in the evaluation of LVDD impact on asymptomatic postmenopausal women with normal blood pressure, assessing diabetes as a major determinant of LVDD. It is clear that hypertension is the most important factor for aortic stiffness, but it also plays an important role in determining LVDD [32]. Therefore, the diagnosis of LVDD in diabetic patients, without a confounding factor such as hypertension, requires LVDD monitoring, because it represents the first marker of "diabetic cardiomyopathy". Our study has found that poor glycemic control and obesity are additional factors for LVDD increase in diabetic population. The evidence of LVDD in diabetic normotensive post-menopausal women allows us to affirm that a complete echocardiographic examination in all diabetics is essential for an early diagnosis of "diabetic cardiomyopathy" [33]. LVDD diagnosis is often neglected in clinical practice in this subset of patients who are at high risk of developing adverse cardiac events. LVDD early diagnosis and treatment may be useful to reduce morbidity and improve the outcomes.

Conclusions

There is a high prevalence of LVDD in asymptomatic diabetic postmenopausal women; this finding is closely related with HbA1c levels and obesity status, not with abnormal ECG, which is a unique cardiologic test recommended by current guidelines in all diabetic subjects. We conclude that early detection of high level of HbA1c and obesity (30 kg/m^2) may identify women with major risk to develop LVDD. Furthermore, a simple ECG, when normal, is not enough to assess a normal LV diastolic function.

Conflict of interest: None declared

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