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THE PREVALENCE OF PREVIOUSLY UNKNOWN HEART FAILURE WITH REDUCED EJECTION FRACTION AND LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

[1]*Intessar Mohammed Housh, [2]Akram Jahjah and [3]Ruba Salman

[1]Department of Internal Medicine, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[2]Department of Cardiology, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[3]Department of Endocrinology, Lecturer, Tishreen University, Faculty of Medicine, Lattakia, Syria.

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Corresponding Author: Intessar Mohammed Housh*

Department of Internal Medicine, Tishreen University, Faculty of Medicine, Lattakia, Syri.

ABSTRACT

Aim & Objective: The aim of this study was to assess the prevalence of previously unknown heart failure with reduced ejection fraction (HFrEF) and left ventricular dysfunction in patients with type 2 diabetes mellitus. **Materials & Methods:** In total 85 patients with newly or previously diagnosed type 2 diabetes mellitus were included in this observational descriptive (cross sectional) study between November 2021 and December 2022, patients were not known for previously having heart failure with reduced ejection fraction or left ventricular dysfunction. A full medical history was taken, and a full physical exam was performed, and the following was documented: gender, age, BMI, duration of diabetes, and clinical symptoms. FPG, 2h postprandial glucose and creatinine were measured, and an ECG was recorded. A 2D echocardiography was also performed and systolic function was evaluated based on ejection fraction (EF), diastolic function was evaluated based on E wave, A wave, E/A ratio, IVRT, E/e' ratio, LAVI, and TR velocity. **Results:** Of the patients studied, 59 were found to have previously unknown diastolic dysfunction (69.4%), 64.7% had a grade I diastolic dysfunction, and 4.7% had grade II diastolic dysfunction. Previously unknown heart failure with reduced ejection fraction (HFrEF) was found in 6 patients (7.1%), and previously unknown asymptomatic left ventricular systolic dysfunction was found in 4 patients (4.7%) The prevalence of left ventricular dysfunction increased steeply with age, higher BMI, longer diabetes duration, and with poor glycemic control. **Conclusion:** Left ventricular dysfunction is common in patients with type 2 diabetes mellitus, especially left ventricular diastolic dysfunction. It is important to be vigilant to these patients to avoid progression of the disease, and to improve prognosis and reduce morbidity and mortality.

KEYWORDS: Diabetes mellitus, heart failure with reduced ejection fraction, asymptomatic left ventricular systolic dysfunction, left ventricular diastolic dysfunction, diabetic cardiomyopathy.

Abbreviations
A: Atrial Contraction.
BMI: Body Mass Index.
Ca^{2+}: Ionized Calcium.
CAD: Coronary Artery Disease.
CKD: Chronic Kidney Disease.
COPD: Chronic Obstructive Pulmonary Disease.
E: Early Diastolic Mitral Flow Velocity.
e': Early Diastolic Mitral Annular Velocity.
E\A: Early-to-Atrial Left Ventricular Filling Ratio.
E\e': Early Filling to Early Diastolic mitral annular velocity ratio.
ECG: Electrocardiography.
ESC: European Society of Cardiology.
FPG: Fasting Plasma Glucose.
HF: Heart Failure.
HFrEF: Heart Failure with Reduced Ejection Fraction.
LAVI: Left Atrial Volume Index.
LVDD: Left ventricular diastolic dysfunction.
LVEF: Left Ventricular Ejection Fraction.
RAAS: Renin-Angiotensin-Aldosteron System.
SD: Standard Deviation.
SGLT2is: Sodium–Glucose Co-transporter 2 Inhibitors.
T2DM: Type 2 Diabetes Mellitus.
TRVmax: Peak Velocity of the Tricuspid Regurgitated signal.

INTRODUCTION

Cardiovascular diseases are of major importance in patients with type 2 diabetes mellitus (T2DM), accounting for up to 80% of the excess mortality in these patients.[1] Heart failure (HF) is an important manifestation of T2DM. The development of HF in T2DM may be preceded by Stage B HF. Asymptomatic left ventricular dysfunction, especially left ventricular diastolic dysfunction (LVDD), is a defining early feature of Stage B HF. Detection of Stage B HF is crucial as it provides an opportune target for intervention with cardio-protective therapy to prevent the development of symptomatic HF in T2DM. Processes underlying the excess cardiovascular mortality risk include coronary atherosclerosis, generalized microvascular disease and autonomic neuropathy.[1] In addition, myocardial abnormalities ('diabetic cardiomyopathy') and heart failure seem to play a role.[2] In general, underdiagnosis of heart failure in T2DM patients is common; a prevalence of unrecognized heart failure of up to 20.5% has been reported in specific patient groups, such as patients with chronic obstructive pulmonary disease.[3] In the Framingham Heart Study, it was shown that HF was twice as common among men and five times as common among women with diabetes as among those without diabetes.[4]

PATIENTS AND METHODS

Participants: This observational descriptive (cross sectional) study was conducted between November 2021 and December 2022, at Tishreen University Hospital in the city of Lattakia, in Syrian Arab Republic.

85 patients were enrolled in this study; all participants gave written informed consent. Patients who were admitted to the hospital or who were seen as outpatients at hospital's clinics, and who were recently or previously diagnosed with type 2 diabetes mellitus were included. The exclusion criteria were the presence of any of the following: CAD evident clinically or by ECG, hypertension or treatment with antihypertensive drugs, valvular heart disease, congenital heart disease, atrial fibrillation, any arrhythmia during evaluation, COPD, CKD, alcoholism, previously known heart failure with reduced ejection fraction or left ventricular dysfunction, use of insulin or $SGLT2i_s$, poor acoustic windows.

Measurements: A full medical history was taken, and a full physical exam was performed, and the following was documented: gender, age, BMI, duration of diabetes, and clinical signs and symptoms.

FPG, 2h postprandial glucose, and creatinine were measured, and an ECG was recorded. Echocardiography was performed with a Siemens Acuson ×300 Premium imaging system device by a well-trained and experienced cardiac sonographer. Variables from Doppler analysis, M-mode echocardiography and two-dimensional transthoracic echocardiography were used. Where image quality was adequate, left-ventricular ejection fraction (LVEF) was calculated from the endocardial surface tracings in the apical four-chamber view and two-chamber view, using Simpson's rule (disc summation method).[5]

Left atrial (LA) volume was assessed by the biplane area–length method from apical four- and two-chamber views.[6] Indexed values were corrected for body surface area. The cut-off values 28 and 34 ml/m^2 were used for normal and definitely increased LA volume index, respectively.

Mitral inflow was assessed by means of pulsed-wave Doppler echocardiography. From the mitral inflow profile, the early diastolic mitral flow velocity (E) and atrial contraction (A)-wave velocity were measured, and the early-to-atrial left ventricular filling ratio (E/A) was calculated.

We also measured the peak velocity of the tricuspid regurgitated signal with continuous-wave Doppler and calculated the systolic pulmonary artery pressure with the modified Bernoulli's equation.[7]

Diastolic function was assessed by an approach that integrates Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus using the early diastolic septal annular velocity (e').[8] e' (early diastolic mitral annular velocity) is a measure of the relaxation of the ventricle. We calculated the early filling to early diastolic mitral annular velocity ratio (E/e') as a measure of filling pressures.

Criteria to establish diastolic and systolic dysfunction and heart failure: An E/e' value below 8 was considered normal, and 8–14 indeterminate. An E/e'>14 was considered abnormal, and these patients were classified as having diastolic dysfunction. When E/e' was between 8 and 14 and a septal e' <8 cm/s, a combination of elevated values of the indexed volume of the left atrium, the mitral inflow, the average E\e', and the TRV_{max} were used to classify the presence or absence of diastolic dysfunction. Diastolic function was categorized as normal, impaired relaxation (grade I), pseudo-normal filling (grade II) or restrictive filling (grade III) by a combination of age-corrected values of E/A velocity ratio, average E\e', LAVI, and TRV_{max} (see Figure 1).

Diastolic dysfunction was graded as I, II or III regardless of presence or absence of signs or symptoms, and regardless of the ejection fraction.

Asymptomatic left ventricular systolic dysfunction was defined as an LVEF<50% by echocardiography in the absence of any signs or symptoms suggestive of heart failure.

To be classified as heart failure with reduced ejection fraction, an ejection fraction of ≤40% had to be present in combination with one or more suggestive symptoms (e.g.

orthopnea, paroxysmal nocturnal dyspnea, fatigue, peripheral edema, nocturia more than twice a night) and\or one or more signs indicative of heart failure (e.g. peripheral or pulmonary fluid retention or raised jugular venous pressure).[9]

Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by height squared (m^2), and categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obesity (≥30 kg/m^2).

Good glycemic control was defined as fasting blood glucose (80- 130 mg/dl), or 2h postprandial glucose <180 mg/dl.

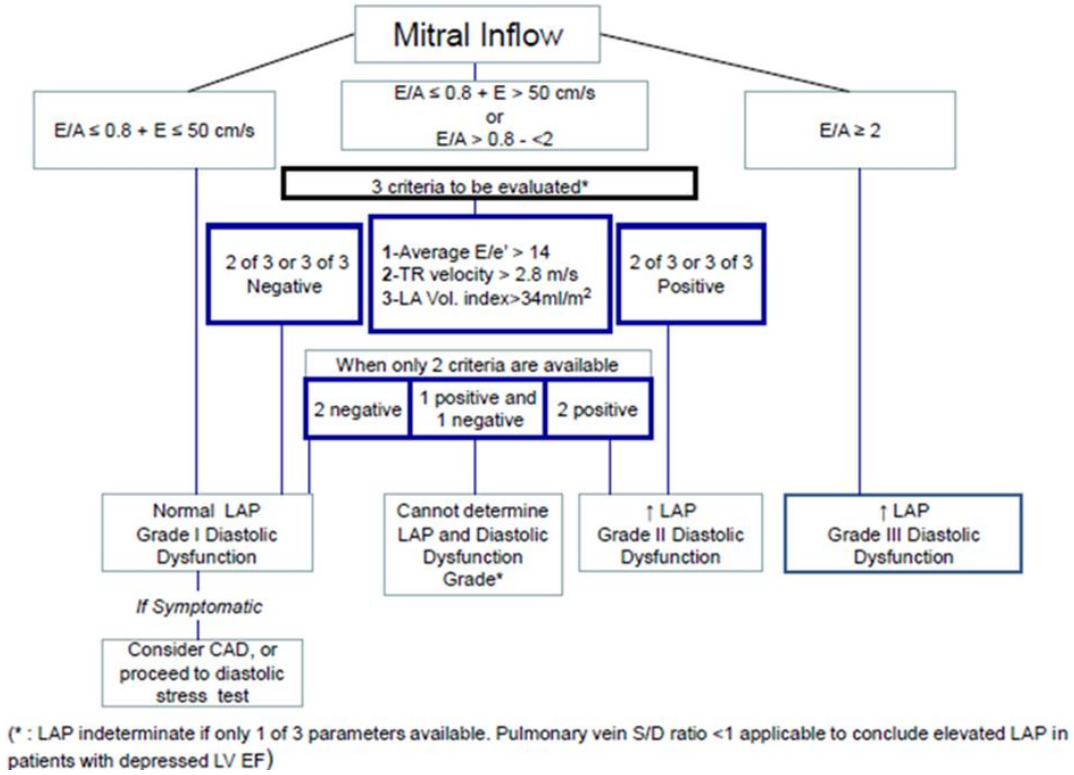

Figure 1: Assessment of left ventricular diastolic function.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD), median, frequency and percentages. Inferential statistics included chi-square test and One-way ANOVA test. All tests were considered significant at a 5% type I error rate ($p<0.05$).

RESULTS

Participants

The baseline characteristics of the participants were as shown in (Table 1). Males represented 51.8% of the study population and females 48.2%. Ages ranged from 45 years to 76 years (30.6% were 45-55 years of age, and 30.6% were 56-65 years of age, and 38.8% were 66 years or older).

The majority of the patients were in the overweight category (45.9%), with 28.2% being of normal weight, and 25.9% being obese.

Diabetes duration ranged from one year to 13 years, 52.9% of the patients had diabetes for 5 years or less, and 47.1% had it for more than 5 years (mean 5.28±2.9).

As for glycemic control, 56.5% and 67.1% of patients had poor glycemic control based on FPG and 2h postprandial glucose, respectively.

Exertional dyspnea was the most common symptom in this patient population (42.4% of patients) and orthopnea was the least common symptom (9.4% of patients).

Table 1: Demographic and lab characteristics of the study population.

Variable	Result
Gender	44 (51.8%) Males 41 (48.2%) Females
Age (years)	33 (38.8%) ≥ 66 26 (30.6%) 56-65 26 (30.6%) 45-55
BMI (kg/m^2)	39 (45.9%) Overweight 24 (28.2%) Normal weight 22 (25.9%) Obese
Diabetes Duration (years)	45 (52.9%) ≤ 5 40 (47.1%) > 5
Symptoms	36 (42.4%) Exertional Dyspnea 25 (29.4%) Fatigue 14 (16.5%) Palpitations 9 (10.6%) Pedal Edema 8 (9.4%) Orthopnea
Glycemic Control Based on FPG	48 (56.5%) Poor Glycemic Control 37 (43.5%) Good Glycemic Control
Glycemic Control Based on 2h Postprandial Glucose	57 (67.1%) Poor Glycemic Control 28 (32.9%) Good Glycemic Control

Prevalence of left ventricular dysfunction: As shown in (Table 2) 59 patients (69.4%) had diastolic dysfunction, 6 patients (7.1%) had HFrEF, 4 patients (4.7%) had asymptomatic left ventricular systolic dysfunction, and 26 patients (30.6%) had a completely normal echocardiographic study.

Table 2: Prevalence of left ventricular dysfunction.

Left Ventricular Function	Number of Patients	Percentage of Patients
Normal	26	30.6%
Diastolic Dysfunction **Grade I** **Grade II** **Grade III**	59 55 4 0	69.4% 64.7% 4.7% 0%
Asymptomatic Systolic Dysfunction	4	4.7%
HFrEF	6	7.1%

Prevalence of left ventricular dysfunction in specific subgroups: As shown in (Table 3) 54.2% of the patients who had diastolic dysfunction were males. 55.9% of them were 66 years of age or older. 52.5% of them were overweight. 67.8% of them had diabetes for more than 5 years. 71.2% and 76.3% of them had poor glycemic control based on FPG and 2h postprandial glucose, respectively. And exertional dyspnea was seen in 47.5% of them. 66.7% of the patients who had HFrEF were males. 100% were 66 years of age or older. 83.3% of them were obese. 100% of them had diabetes for more than 5 years. 66.7% and 83.3% of them had poor glycemic control based on FPG and 2h postprandial glucose, respectively. And exertional dyspnea was seen in 83.3% of them.

75% of the patients who had asymptomatic left ventricular systolic dysfunction were males. 100% of them were 66 years of age or older. 50% of them were overweight and 50% were obese. 100% of them had diabetes for more than 5 years. 50% and 7% 5of them had poor glycemic control based on FPG and 2h postprandial glucose, respectively.

Older age, higher BMI, longer duration of diabetes and poor glycemic control were associated with increased left ventricular dysfunction.

Table 3: Characteristics of patients with type 2 diabetes, previously not known to have left ventricular dysfunction, categorized as left ventricular diastolic dysfunction, asymptomatic left ventricular systolic dysfunction, HFrEF, and normal left ventricular function, after the diagnostic assessment.

Variable	Left Ventricular Diastolic Dysfunction	Asymptomatic Left Ventricular Systolic Dysfunction	HFrEF	Normal	*p* value
Gender:					
Male	32(54.2%)	3(75%)	4(66.7%)	12(46.2%)	>0.05
Female	27(45.8%)	1(25%)	2(33.3%)	14(53.8%)	
Age (years):					
45-55	3(5.1%)	0(0%)	0(0%)	23(88.5%)	
56-65	23(39%)	0(0%)	0(0%)	3(11.5%)	0.0001
≥66	33(55.9%)	4(100%)	6(100%)	0(0%)	
BMI (kg\m^2):					
Normal	11(18.6%)	0(0%)	0(0%)	13(50%)	
Overweight	31(52.5%)	2(50%)	1(16.7%)	8(30.8%)	0.0001
Obesity	17(28.8%)	2(50%)	5(83.3%)	5(19.2%)	
Diabetes Duration (Years):					
≤5	19(32.2%)	0(0%)	0(0%)	26(100%)	0.0001
>5	40(67.8%)	4(100%)	6(100%)	0(0%)	
Glycemic Control Based on FPG:					
Controlled	17(28.8%)	2(50%)	2(33.3%)	20(76.9%)	<0.05
Uncontrolled	42(71.2%)	2(50%)	4(66.7%)	6(23.1%)	
Glycemic Control Based on 2h Postprandial Glucose: Controlled	14(23.7%)	1(25%)	1(16.7%)	14(53.8%)	<0.05
Uncontrolled	45(76.3%)	3(75%)	5(83.3%)	12(46.2%)	
Symptoms:					
Exertional Dyspnea	28(47.5%)	0(0%)	5(83.3%)	8(30.8%)	
Fatigue	18(30.5%)	0(0%)	3(50%)	7(26.9%)	
Orthopnea	8(13.6%)	0(0%)	4(66.7%)	0(0%)	>0.05
Palpitations	7(11.9%)	0(0%)	1(16.7%)	7(26.9%)	
Pedal Edema	4(6.8%)	0(0%)	4(66.7%)	5(19.2%)	

DISCUSSION

This observational descriptive (cross sectional) study of 85 T2DM patients assessed the prevalence of left ventricular dysfunction (diastolic dysfunction, HFrEF, and asymptomatic left ventricular systolic dysfunction) in this patient population. It showed that the prevalence of previously unknown left ventricular dysfunction is very high (81.2%), steeply increases with age, higher BMI, longer duration of diabetes, and with poorer glycemic control. It is overall higher in men than women. The majority (69.4%) of patients with newly detected left ventricular dysfunction had diastolic dysfunction. Only 26 (30.6%) of all investigated patients had 'normal' left ventricular function.

The high prevalence of previously unknown heart failure could be due to patients with symptoms of heart failure not going to a physician or physicians not asking the patient about these symptoms. A further possibility is that when patients do present with these symptoms, physicians do not recognise heart failure.

The exact reason for the high prevalence of diastolic dysfunction may be related to early stages of so-called 'diabetic cardiomyopathy'. Our finding that the majority of the patients (64.7%) had an E/A ratio <0.80, supports this idea. A low E/A ratio has been linked to early stages of diabetic cardiomyopathy.

From a pathophysiologic standpoint, there are several mechanisms involved in the development of diabetic cardiomyopathy, including: Resistance or lack of insulin shifts metabolism from glucose to fatty acid, the increase in myocardial oxygen utilization changes calcium homeostasis, which leads to cardiac dysfunction.[10] Depletion of myocardial catecholamine stores through autonomic dysregulation blunts contractile reserve, which causes systolic and diastolic dysfunction.[11] Insulin resistance stimulates glycation of proteins, lipids, and nucleic acids, advanced glycation end-products increase free radicals, which inactivate nitric oxide leading to impaired endothelium-dependent relaxation and microvascular dysfunction,[12,13] also inactive nitric oxide decreases intracellular Ca^{2+} sensitization and impairs

sarcoplasmic Ca^{2+} uptake.[14] Activation of RAAS by hyperglycemia increases angiotensin II and aldosterone levels, inducing fibrosis and left ventricular hypertrophy, which are precursors to diastolic dysfunction.[15]

LJM Boonman-de Winter et al.[16] demonstrated in a cross sectional study conducted on 581 patients in 2012 that 53.3% of the patients had diastolic dysfunction, 4.5% had asymptomatic left ventricular systolic dysfunction, and 4.8% had HFrEF. Older age, female gender, and higher BMI were associated with increased left ventricular dysfunction.

Sachinkumar K. Khade et al.[17] found in a cross sectional study conducted on 54 patients in 2020 that 44.4% of the patients had diastolic dysfunction. Male gender, longer duration of diabetes and poor glycemic control were associated with increased left ventricular diastolic dysfunction.

Mikael Kjaer Poulsen et al.[18] demonstrated in an observational prospective study conducted on 305 patients in 2010 that 40% of the patients had diastolic dysfunction, and 9% had asymptomatic left ventricular systolic dysfunction. Older age was associated with increased left ventricular dysfunction.

Fawad Ahmad Randhawa et al.[19] found in a descriptive case series conducted on 150 asymptomatic patients in 2014 that 48% of the patients had diastolic dysfunction. Male gender was associated with increased left ventricular diastolic dysfunction.

Virendra C. Patil et al.[20] demonstrated in a case control prospective study conducted on 127 diabetic patients and 100 non-diabetic patients in 2011 that 54.33% of the diabetic patients had diastolic dysfunction as compared to 11% of the control group. Longer duration of diabetes and poor glycemic control were associated with increased left ventricular diastolic dysfunction.

NR Shrestha et al.[21] found in a cross sectional study conducted on 100 asymptomatic patients in 2009 that 71% of the patients had diastolic dysfunction, none of the patients had systolic dysfunction.

Female gender, older age, and longer duration of diabetes were associated with increased left ventricular diastolic dysfunction.

Ying Wang et al.[22] demonstrated in an observational prospective study conducted on 310 asymptomatic patients in 2018 that 10% of the patients had diastolic dysfunction and 23% of them had asymptomatic left ventricular systolic dysfunction. Higher BMI was associated with increased left ventricular systolic and diastolic dysfunction, and poor glycemic control was associated with increased left ventricular diastolic dysfunction.

In summary, left ventricular dysfunction is common in patients with type 2 diabetes mellitus, especially left ventricular diastolic dysfunction. It is important to be vigilant to these patients to avoid progression of the disease, and to improve prognosis and reduce morbidity and mortality.

Screening of patients with type 2 diabetes should be considered in the light of the high rates of prevalence of previously unknown left ventricular dysfunction in patients with type 2 diabetes observed in our study. Physicians should be constantly alert for signs and symptoms indicative of heart failure in these patients. In addition, echocardiography and/or ECG or B-type natriuretic peptide measurements could be part of the yearly monitoring. We need to determine which screening strategy is the most efficient.

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