Original Research Article

A Study on Heart Failure with Preserved Ejection Fraction among Patients of Type 2 Diabetes Mellitus in a Tertiary Care Hospital, India

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Abstract

Introduction: Diabetes is associated with several diabetic-related abnormalities and increased retention of sodium (up regulation of sodium-glucose co transporters) which increases the risk of onset or worsening of heart failure. With this background, the current study was planned to study the prevalence of type 2 diabetes mellitus among patients presenting with heart failure with preserved ejection fraction. **Materials and Methods:** It was a prospective observational study among patients visiting outpatient department and IPD of Nil Ratan Sircar Medical College & Hospital, India from October 2016 to September 2017. The study was pre-approved by Institutional Ethics Committee and the study was conducted after obtaining permission accordingly. Sample size was 100 patients between 30 and 90 years both male and female. The patients who satisfied inclusion and exclusion criteria have been identified and included in this study. Quantitative data thus obtained have been analyzed and exported to statistical software SPSS ver. 20.0. The continuous variables have been presented as mean ± standard deviation. **Results:** A total of 100 patients between 30 and 90 years, both male and female who met the inclusion criteria were selected for the study. Majority belonged to the age group of 61–70 years with mean age 63.5 ±7.2 years. 53 were men and 47 were female. Diabetes was present in 51 patients. Majority had ejection fraction between 55 and 60% and mean was 57.3± 6.7%; mostly with normal or near normal systolic function. The elevated mean LVMI indicated LV hypertrophy and decreased mean E/A indicated LV diastolic dysfunction, often produced by diabetes. Mean E/E' was 9.2 ± 5.4. Grade-2 (DD2) diastolic dysfunction patients were maximum in number comprising 47% followed by Grade-1 (DD1) diastolic dysfunction among 44%, and only 9% had Grade-3 (DD3) diastolic dysfunction. **Conclusion:** Etiology and treatment approach of HFpEF differs from that of HFrEF. Moreover, diabetes mellitus is the modern day epidemics. Hence, if further studied by multicenter, prospective, longitudinal studies, this association may be used to identify the population at risk.

Key Words: Heart Failure, Preserved Ejection Fraction, Type 2 Diabetes Mellitus

Introduction

Heart failure is a clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which, in turn, leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of heart failure, that is, edema and rales[1]. Based on underlying mechanism, it could be divided into heart failure with preserved ejection fraction (left ventricular ejection fraction [LVEF] >50%, that is, heart failure with preserved ejection fraction [HFpEF]) or heart failure with mid-range ejection fraction (LVEF 40–49%, i.e., HFmrEF) or heart failure with reduced ejection fraction (LVEF < 40%, i.e., HFrEF)[2]. The number of cases of HFpEF has been increasing in the Western countries and consists more than 50% of total heart failure hospitalizations. The prevalence of HFpEF sharply increases with advancement of age, with a female predominance[3]. There are limited data on heart failure in Indian population. Comparative data from Asian Heart Failure Registry showed that Indian patients with HFpEF were younger with mean age of 63.4 years in males and 46.4 years in females. Risk factors included hypertension (40.3%) and DM (28.8%). It has also been proved that HFpEF is prognostically as bad as HFrEF[4].

Diabetes is associated with several diabetic-related abnormalities, such as ischemia from either coronary artery atherosclerosis, or microvascular dysfunction, myocardial hypertrophy, dysfunction of mitochondria, dysfunction of autonomic nervous system, proinflammation, and increased retention of sodium (upregulation of sodium-glucose cotransporters) which increase the risk of onset or worsening of heart failure[5, 6]. Unfortunately, outcomes in HFpEF are poor and could be compared to those of HFrEF, with 1-year mortality ranging between 10 and 30%[7]. A subanalysis of I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction) showed that in HFpEF, patients with diabetes have more signs of congestion, worse quality of life, higher levels of heart failure biomarkers (N-terminal pro-B-type natriuretic peptide: NT-proBNP), and a poorer prognosis[8]. In addition, comparing in-patient costs of heart failure admissions, patients with diabetes have the highest cost, and cost per day alive appears to be the highest for HFpEF patients with diabetes[9]. Data on this aspect of heart failure is limited may be due to multiple pathophysiologic mechanisms in HFpEF, such as impaired diastolic function and impaired systolic reserve, impaired longitudinal ventricular systolic and atrial function, impaired autonomic heart function, and peripheral mechanisms such as endothelial and skeletal muscle dysfunction[6, 10–13].

With this background, the current study was planned to study the prevalence of type 2 diabetes mellitus among patients presenting with heart failure with preserved ejection fraction.

Materials and Methods

It was a prospective observational study among patients visiting outpatient department and IPD of Nil Ratan Sircar Medical College & Hospital, India from October 2016 to September 2017. The study was pre-approved by Institutional Ethics Committee and the study was conducted after obtaining permission accordingly. Sample size was 100 patients between 30 and 90 years both male and female.

The risk factors in study, that is, hypertension and diabetes were based on the following criteria:

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- Hypertension, that is, systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg at least on two occasions or receiving antihypertensive drug
- Diabetes, that is, history of type 2 diabetes diagnosed with American Diabetic Association criteria, that is, symptoms of diabetes plus random blood glucose concentration more than or equal to 200 mg/dl or, fasting plasma glucose more than or equal to 126 mg/ dl or, glycosylated hemoglobin more than or equal to 6.5% or, 2 h plasma glucose more than or equal to 200 mg/dl during an oral glucose tolerance test or were on medications for diabetes[14].

Inclusion criteria considered for the study:

- The diagnosis of HFpEF has been made based on: Signs and symptoms of heart failure by clinical examination, LVEF >50% by echocardiography, Echocardiographical evidence consistent with structural or functional anomaly including left diastolic dysfunction/increased left ventricular filling pressure or raised serum NTproBNP[15, 16].
- Age more than 30 years and < 60 ml/min)
- History of cocaine or heroin use in the past 6 months
- History of significant alcohol intake
- Body mass index (BMI) < 18.5 or > 40
- Severe anemia (Hb < 8 g %).

The patients who satisfied inclusion and exclusion criteria have been identified and included in this study. Proper history including demographic details, specific co morbidities, duration of HTN and DM, and medication details was taken and detailed clinically examination was done. For further clinical evaluation, a 12-lead ECG with long rhythm strip, straight X-ray skiagram of chest, and routine blood investigations such as complete blood count, renal function test, glycosylated hemoglobin, fasting plasma glucose, and ser. NTproBNP was performed. Finally, transthoracic echocardiogram was performed with M-mode, 2D (two-dimensional), Doppler, and tissue Doppler imaging using standard techniques. At first, the following parameters were measured by M-mode: Interventricular septal thickness, left ventricular posterior wall thickness, end-systolic dimension of left atrium (LAD), and left ventricular internal diameter (LVID) at end diastole (LVIDd) and end systole (LVIDs). The LVEF was estimated by 2D approximation and wall motion abnormalities were noted, if any. Next, the following LV diastolic function parameters were measured by recording transmitral flow velocity using Doppler echocardiography, that is, peak early-diastolic transmitral flow velocity (E), peak latediastolic transmitral flow velocity (A), deceleration time, and E/A ratio. Then, tissue Doppler echocardiography was performed at medial mitral annulus. Peak early (E') and late (A') diastolic mitral annular velocities and their ratio (E'/A') were measured. The ratio of transmitral flow velocity and annular velocity (E/E') was calculated to assess LV end-diastolic pressure (LVEDP) which was used as a parameter of LV diastolic dysfunction. Elevated filling pressure was based on E/E' ratio>10. Diastolic dysfunction was classified into four grades as per ASE guidelines[17].

Quantitative data thus obtained have been analyzed and exported to statistical software SPSS ver 20.0. The continuous variables have been presented as mean ± standard deviation. Percentage analysis was used to describe distribution of demographic variables. The association between HFpEF with diabetes was obtained by Chi-square test. P value < 0.05 has been considered significant.

Results

A total of 100 patients between 30 and 90 years, both male and female who met the inclusion criteria were selected for the study. Majority belonged to the age group of 61–70 years with mean age 63.5 ±7.2 years [Table 1]. 53 were men and 47 were female. Diabetes was present in 51 patients. Majority had ejection fraction between 55 and 60% and mean was 57.3± 6.7%; mostly with normal or near normal systolic function. The elevated mean LVMI indicated LV hypertrophy and decreased mean E/A indicated LV diastolic dysfunction, often produced by diabetes. Mean E/E' was 9.2 ± 5.4. Grade-2 (DD2) diastolic dysfunction patients were maximum in number comprising 47% followed by Grade-1 (DD1) diastolic dysfunction among 44%, and only 9% had Grade-3 (DD3) diastolic dysfunction. The prevalence of diabetes mellitus in study population is progressively increasing along with the severity of diastolic dysfunction (from Grade-1 to Grade-2) to a fact that all patients having DD-3 were having diabetes mellitus. [Figure 1]. Chi-square test was done to find association between severity of diastolic dysfunction and presence of diabetes mellitus and the association was found to be statistically significant. Apart from this, age of the patient and duration of diabetes seemed to be an important determining factor, both having p value < 0.05.

Table 1: Table showing age distribution of the study participants

Age group (in years)	Number
30-40	4
41-50	16
51-60	24
61-70	37
>70	19

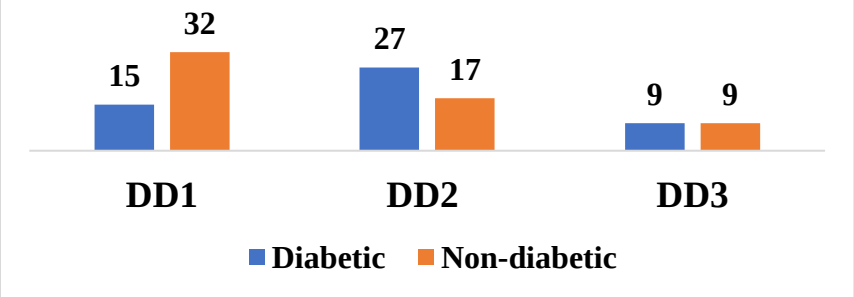

Figure 1: Column distribution of diabtetic patients according to severity of disease

Discussion

In the absence of coronary artery disease and HTN, maladaptive cardiac remodeling associated with diabetes is properly referred to as diabetic cardiomyopathy[18-20]. Accumulating evidence supports the notion that there are two distinct HF phenotypes associated with diabetic cardiomyopathy. Type 1 diabetes leads to HFrEF with a dilated left ventricular phenotype. In contrast, type 2 diabetes, which is a common outcome of obesity, is associated with HFpEF and

concentric remodeling of the LV. Seferović and Paulus recently presented evidence attributing the etiology of the two phenotypes to the differential principal involvement of either microvascular endothelial cells (HFpEF) or cardiac myocytes (HFrEF) in the remodeling process[19]. An ancillary study of the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) trial indicated that compared to non-diabetic HFpEF patients, those with diabetes were younger, more obese and more often male, with a higher prevalence of renal dysfunction, HTN, pulmonary disease, and vascular disease[20]. Analysis of the I-Preserve [Irbesartan in heart failure with preserved ejection fraction (HFpEF)] trial showed that HFpEF patients with diabetes had more signs of congestion, worse quality of life, and a poorer prognosis with a higher risk of cardiovascular mortality and hospitalization[21]. On the basis of 11 clinical features, HFpEF patients who were enrolled in the I-Preserve or CHARM-Preserved (effects of candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) trials were found to fall into one of six subgroups; patients with obesity and or diabetes constituted a distinctive subgroup with (along with another subgroup characterized by advanced age) the worst event-free survival[22].

In our study, high prevalence of diabetes mellitus in HFpEF was the most significant finding and signifies a strong etiological association. Patients having longer duration of HTN/DM or having both together were shown to have advanced DD with elevated LVEDP along with advancement of age. These findings are consistent with other large scale trials where hypertension and diabetes mellitus has been identified as the commonest risk factor[23] presenting in 50–90% of patients of HFpEF, and prevalence is even more than that of HFrEF[24-25]. To study individual etiological association of DM with HFpEF, we also excluded certain other confounding risk factors such as chronic kidney disease, atrial fibrillation, and coronary artery disease which are a complication of HTN/DM itself and also being an important risk factor for HFpEF[26-27].

Conclusion

Etiology and treatment approach of HFpEF differs from that of HFrEF. Moreover, diabetes mellitus is the modern day epidemics. Hence, if further studied by multicenter, prospective, longitudinal studies, this association may be used to identify the population at risk for HFpEF and to establish new targets for the management of diastolic dysfunction at the herald of its onset and prevention of symptomatic HFpEF resulting in longer survival and better prognosis.

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