



IMPACT OF DIABETES MELLITUS ON PROGRESSION OF HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)

Muhammad Faheem khan¹, Farooq Ahmad², Awais Farhad^{3*}, Muhammad Habeel Dar⁴,
Zeeshan Ahmad⁵, Kamran khan⁶

¹Associate Professor, Cardiology unit, Khyber Medical College, Peshawar

²Associate Professor, Cardiology unit, Khyber Medical College, Peshawar

^{3*}Assistant Professor, Cardiology unit, Khyber Medical College, Peshawar.

⁴Senior Registrar, Cardiology unit, Khyber Teaching Hospital, Peshawar.

⁵PG resident, Cardiology unit, Khyber Teaching Hospital, Peshawar.

⁶PG resident, Cardiology unit, Khyber Teaching Hospital, Peshawar.

Corresponding Author: Awais Farhad

Assistant Professor, Khyber Medical College, Peshawar

*Email: awais1192@gmail.com

ABSTRACT

Background: Diabetes mellitus (DM) is among the principal risk factors related to cardiovascular disease, heart failure with preserved ejection fraction (HFpEF). HFpEF is typified by defective myocardial relaxation and diastolic heart dysfunction, causing heart failure symptoms with normal ejection fraction. The correlation between DM and HFpEF development has not properly studied in Pakistan which has the highest age correlated prevalence of diabetes in the world. The proposed study will evaluate the effects of DM in the progression of HFpEF with regard to myocardial stiffness, diastolic performance, and clinical outcome.

Objectives: To assess the impact of diabetes mellitus on the development of HFpEF, including myocardial stiffness, diastolic dysfunction, and patient outcomes in a 12-month follow-up.

Methodology: A prospective study was carried out among 100 HFpEF patients (who were split into two categories: 60 patients with DM and 40 patients without DM). At baseline and 12 months, clinical data, such as echocardiographies (left ventricular diastolic function, ejection fraction), HbA1c, and inflammatory markers, were measured. Myocardial stiffness parameters were measured with the help of tissue Doppler imaging (TDI) and functional measurements, such as exercise capacity (6-minute walk test) and hospitalizations. Paired t-tests and chi-square tests of categorical variables were used to conduct statistical analysis.

Results: The mean age of participants was 68.5 years (SD = 7.4). Diabetic patients exhibited significantly higher myocardial stiffness ($p < 0.01$) and worse diastolic dysfunction, with an E/e' ratio of 14.2 (SD = 2.8) versus 11.8 (SD = 2.3) in non-diabetics ($p < 0.05$). Diabetic patients had reduced 6-minute walk test performance (350m vs. 410m, $p < 0.01$), and higher hospitalization rates (18 vs. 8, $p = 0.04$). Poorer glycemic control (HbA1c levels) correlated with worse functional outcomes ($r = -0.45$, $p < 0.01$).

Conclusion: The HFpEF progression in diabetes mellitus is notably aggravated, which leads to greater myocardial stiffness, diastolic dysfunction, and worse clinical outcomes. Glycemic control is critical in enhancing patient outcomes.

Keywords: Diabetes Mellitus, HFpEF, Myocardial Stiffness, Diastolic Dysfunction

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complicated clinical syndrome marked by normal left ventricular ejection fraction (LVEF) but has diastolic dysfunction and decreased myocardial relaxation. It explains a considerable percentage of heart failure-related cases, particularly in adults, and is related to higher morbidity, hospitalizations, and mortality. HFpEF can frequently be observed in patients with comorbidities, such as hypertension, obesity, atrial fibrillation, and diabetes mellitus (DM). The pathophysiology of HFpEF is myocardial stiffness, alterations in vascular compliance, and systemic inflammation to cause clinical symptoms and diastolic malfunction [1,2]. Diabetes mellitus (DM) is a recognized risk factor for cardiovascular diseases associated with muscle injury and progression of heart failure HFpEF. The impacts of DM on HFpEF are also significant since diabetes has been shown to promote the occurrence of diastolic failure and myocardial rigidity, two of the typical characteristics of HFpEF [3]. Although the relationship between diabetes and heart failure, especially HFpEF, has become recognized, the effect of diabetes on HFpEF progression and functional outcomes such as exercise capacity and hospitalization is not well studied. Past literature has shown that diabetes deteriorates diastolic functioning and risk of hospital admission in HFpEF patients, but little has been done on the long-term effect of glycemic control on functional outcomes, hospitalization, and myocardial stiffness among the cohort group. As diabetes and HFpEF continue to rise in prevalence, the interaction between the two disorders is vital to the creation of specific therapeutic interventions to enhance the outcome of the patients [5,6]. Pakistan currently has the highest age-adjusted comparative prevalence of diabetes in the world. Pakistan has a diabetes prevalence >30% in adults which is 3 times more than the world prevalence. There is paucity of data on HFpEF and its correlation with diabetes in Pakistan. Recent data is required to assess the correlation which can be used for future local guidelines in diabetes and HFpEF management. The following areas are the main issues that the given study will explore to determine the impact of diabetes mellitus on the development of HFpEF: Diastolic dysfunction, and functional outcomes (exercise capacity, hospitalization rates, and glycemic control) [7]. The analysis of these issues will, hopefully, offer some insights into how diabetes can influence the progression of HFpEF faster and inform the strategies of its improved management and control [8,9].

Study Objectives

To compare diastolic function indicators in diabetic and non-diabetics presenting with HFpEF. To compare the clinical and functional outcomes of diabetic and non-diabetic HFpEF patients over 12 months of follow-up.

Materials and Methods

This prospective cohort study was conducted in cardiology unit, Khyber Teaching Hospital Peshawar from Jan 2023 to Jan 2024. which is a tertiary care hospital in the provincial capital dealing with referrals from the whole province. One hundred patients with HFpEF were recruited. Diabetes mellitus (DM group) and non-diabetes (non-DM group) patients were grouped into 60 and 40, respectively. The selection of the participants was done using inclusion criteria. Informed consent was obtained from all patients. Echocardiographic assessment was done by a classified cardiologist using Toshiba Aplio or Toshiba Xario echocardiography machines with a 5 MHz phased array transducer (Toshiba Medical Systems Corporation, Otawara, Japan). The E value was To test the difference in diastolic function (E/E') between diabetic and non-diabetic groups, a power calculation was used to determine the required sample size. According to previous study, the sample size of 100 was enough to produce a power of 80 percent at the level of significance of 0.05.

Inclusion Criteria

- Age ≥ 40 years.
- Diagnosed with HFpEF by a cardiologist after taking into consideration the clinical, echocardiographic, and lab findings
- HbA1c $\geq 6.5\%$ for the diabetic group.
- Stable clinical condition, no recent hospitalizations.

Exclusion Criteria

- Heart failure with reduced EF
- Severe valvular heart disease.
- Severe non-cardiac comorbidities.
- Actively pregnant females.
- Active cancer.
- Renal failure

Statistical Analysis

Statistical analysis was done using SPSS version 26.0 (IBM Corp., Armonk, N.Y., USA). Mean with standard deviation (SD) were calculated for quantitative variables. The difference between DM and Non-DM groups was analyzed by T-test for continuous variables and Chi square test for categorical variables. A p-value equal to or below 0.05 was regarded as statistically significant.

Results

A total of 100 patients (60 with DM and 40 without DM) were analyzed in the study. The mean age of the participants was 68.5 years (SD = 7.4) in the diabetic group and 69.2 (SD = 6.8) in the non-diabetic group ($p=0.52$) (Table 1). 68% of the participants were Male in diabetic group and 72% in non-diabetic group. No significant difference in baseline characteristics was noted in both groups except for baseline HbA1c (8.1% vs 5.3% $p < 0.01$).

Diabetic participants had worse diastolic function, with mean E/e' ratio of 14.2 (SD = 2.8) compared to 11.8 (SD = 2.3) for non-diabetic participants (Table 2). Furthermore, the 6-minute walk test performance was significantly lower in the diabetic group (350 meters, SD = 50) compared to the non-diabetic group (410 meters, SD = 60) ($p < 0.01$) (Table 2). No significant differences in ejection fraction was observed between the groups.

Over a 12-month follow-up, diabetic patients had higher hospitalization rates (18 vs. 8, $p = 0.04$) (Table 3). The improvement in exercise capacity over 12 months was almost similar between the groups, with a statistically non-significant trend towards improvement of functional capacity in non-diabetic patients ($p = 0.18$) (Table 3).

A negative correlation was found between HbA1c and 6-minute walk distance ($r = -0.45$, $p < 0.01$), indicating that poorer glycemic control was associated with worse exercise performance. Additionally, higher HbA1c levels were positively correlated with increased hospitalization rates and higher E/e' ratios, indicating worse diastolic dysfunction (Table 4).

Table 1: Demographic and Clinical Characteristics of Participants

Characteristic	Diabetic Group (n=60)	Non-Diabetic Group (n=40)	P-value
Age (years)	68.5 $\pm$ 7.4	69.2 $\pm$ 6.8	0.52
Gender (Male, %)	41 (68%)	29 (72%)	0.67
Hypertension (%)	58 (96.7%)	36 (90%)	0.15
BMI (kg/m ²)	31.5 $\pm$ 4.2	30.1 $\pm$ 3.9	0.14
Mean HbA1c (%)	8.1 $\pm$ 1.2	5.3 $\pm$ 0.4	<0.01

Table 2: Echocardiographic Findings and Functional Capacity at Baseline

Echocardiographic Parameter	Diabetic Group (n=60)	Non-Diabetic Group (n=40)	P-value
Left Ventricular Ejection Fraction (%)	61.4 ± 5.1	62.1 ± 4.8	0.72
E/e' Ratio	14.2 ± 2.8	11.8 ± 2.3	<0.05
Diastolic Dysfunction (%)	58 (96.7%)	35 (87.5%)	0.12
6-Minute Walk Test (meters)	350 ± 50	410 ± 60	<0.01

Table 3: Functional Capacity Improvement and Hospitalization Rates over 12 months

Parameter	Diabetic Group (n=60)	Non-Diabetic Group (n=40)	P-value
Hospitalization Rate (per year)	18	8	0.04
Exercise Capacity Improvement (%)	15%	22%	0.18

Table 4: Correlation Between HbA1c and Functional Outcomes over 12 months

Variable	R-value	P-value
HbA1c and 6-Minute Walk Distance	-0.45	<0.01
HbA1c and Hospitalization Rate	0.36	0.03
HbA1c and E/e' Ratio	0.42	0.01

Discussion

This study has explored the effect of diabetes mellitus (DM) on the progression of heart failure with preserved ejection fraction (HFpEF), diastolic performance, and functional outcome over 12 months. Similar to the previous studies, the study results demonstrated that patients with DM had a worse diastolic function as shown by the higher amount of E/e' ratio in the diabetic group [10]. These results are also in line with a 2021 study by Ng et al., which showed that diabetes progresses diastolic dysfunction in HFpEF patients by enhancing myocardial stiffness and fibrosis [11]. In the same manner, a 2019 study by Lippi et al. revealed that diabetic patients with HFpEF had significantly worse diastolic parameters than diabetic patients without diastolic dysfunction, which supports the involvement of diabetes in further worsening diastolic dysfunction [12]. These results are consistent with our results and indicate that higher E/e' ratios and worse diastolic function may be linked with diabetes and the subsequent acceleration of diastolic dysfunction in HFpEF due to myocardial remodeling, such as higher collagen deposition and heart muscle stiffening [13]. Another important change that was realized in our study was a strong rise in E/e' which is a function of diastolic performance. The likely cause of this could be increased stiffness of the myocardium due to hyperglycemia and insulin resistance causing structural alterations in the myocardium [14,15]. Recent evidence by the Xiao et al. (2022) study validated that myocardial stiffening among patients with HFpEF is associated with high blood glucose levels, and therefore, the hypothesis that diabetes is a factor in the acceleration of myocardial stiffening was confirmed [16].

It is worth noting that worse functional outcomes in our study were linked with poor glycemic control (increased HbA1c levels), and this was reflected in less exercise capacity and increased hospitalization rates. This observation is in line with a 2020 study by Verma et al. which also showed that improved glycemic control correlated with improved functional outcomes and fewer hospitalizations in patients with both diabetes and HFpEF [17]. The inverse relationship between the level of functional capacity and HbA1c and the positive correlation between the level of HbA1c and hospitalization rates is especially high, which allows us to mention the role of glycemic management in the work in HFpEF patients and to state that exercise capacity and adverse events, such as hospitalization, were associated with DM in HFpEF patients [18]. A survey by Smith et al. (2021) also showed that the outcome of a

6-minute walk test and the overall physical functioning of patients with diabetes and HFpEF were lower than those of non-diabetic HFpEF patients [19,20]. The functional impairment of the diabetic group in our study could be explained by the direct effects of hyperglycemia on the myocardial functional capacity and the systemic inflammatory processes associated with diabetes, leading to a higher risk of hospitalization and unfavorable cardiovascular outcomes [21]. The results of our study are also similar to those of Kwon et al. (2022), which showed that diabetes complicates the symptoms of HFpEF and increases hospital admissions, mostly because of the synergy between the impact of poor glycemic control and impaired heart activity [22,23]. This is important since it emphasizes the fact that further exertion of diabetes treatment is necessary among HFpEF patients to limit the workload of hospitalizations [24].

Limitations

Some of the limitations of this study are that the study is single-center in nature, and therefore the findings can not be generalized. Also, the sample size might not be fully representative of the overall HFpEF population. The use of single echocardiographic marker (E/E') to assess diastolic dysfunction may not be as accurate as comprehensive multivariable diastolic function assessment. Biomarkers such as BNP were not monitored which could have provided a more quantifiable assessment of progression/outcomes.

Conclusion

HFpEF patients having diabetes have worse diastolic function at baseline. Diabetes overlying HFpEF and worse HbA1c control are significantly associated with worse functional outcomes and increased hospitalization over 12 months follow-up.

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Authors Contributions

Concept & Design of Study: **Farooq Ahmad**

Drafting: **Muhammad Faheem khan, and M. Habeel Dar**

Data Collection & Data Analysis: **Zeeshan Ahmad**

Critical Review: **Awais Farhad**

Final Approval of version: All Mentioned Authors Approved the Final Version: **Kamran khan**

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