



Diastolic Heart Failure in Type II Diabetes Mellitus: Association with Clinic-Laboratory Parameters with Special Reference to Nt-Pro Bnp.

Dr. Vishal Bhalerao¹, Dr. Md Ibrahim Siddiqui², Dr. Yogesh Chaudhary³, Dr. Gajanan Gondhali⁴

¹Assistant Professor, Department of General Medicine, MIMSR Medical College, Latur, Maharashtra, India

²Associate Professor, Dept of Pathology, Faculty of Medical Sciences, KBN University, Kalaburagi.

³Specialist, General Medicine i d. 84843 MOH OMAN, NIZWA Hospital.

⁴Professor and Head, Department of General Medicine, MIMSR Medical College, Latur, Maharashtra, India.

Name of the corresponding author: Dr. Yogesh Chaudhary

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KEYWORDS

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ABSTRACT:

A wealth of epidemiological evidence demonstrates that diabetes mellitus is independently associated with the risk of developing heart failure, with the risk increasing by more than twofold in men and by more than fivefold in women. Heart failure is highly prevalent (25 % in chronic heart failure and up to 40 % in acute heart failure) in patients with diabetes mellitus.

Objective: To determine the prevalence of diastolic heart failure in patients with type 2 Diabetes mellitus and its association with different parameters and NTPROBNP.

Methodology: This study was hospital based Cross-sectional observational study conducted in In-patient and outpatient department of Apollo Gleneagles Hospitals Kolkata involving 85 patients between 40-65 years of age both males and females from the general medical inpatient and outpatient pool of Apollo Gleneagles Hospitals Kolkata.

Results: Prevalence of diastolic dysfunction was 63.5% among the patients with type-2 DM. Only 14.8% and 7.4% of the patients had Grade-III and Grade-IV DM respectively. All the parameters of the patients with DM higher than that of the patients without DM and there were mostly significantly higher ($p < 0.01$). Proportion of patients with all clinical parameters was significantly higher among the patients with DM than that of without DM ($p < 0.01$). One way ANOVA showed that there was significant difference in level of NTPRO of the patients with different grades. As per CD the mean NTPRO increased significantly with the increase in grade of DM ($p < 0.01$).

Conclusion: Prevalence of DM in the group of patients with duration of diabetes of ≥ 10 years is more as compared to the patients with duration of diabetes of < 10 yrs. The prevalence of diastolic dysfunction increased with longer duration of diabetes. NT-ProBNP level helps in diagnosing HFPEF cases with equivocal echo findings of diastolic dysfunction. NT-ProBNP level was significantly higher in patients with diastolic heart failure than the value required for diagnosis of HFPEF in the present study.

Introduction:

Type 2 diabetes mellitus (T2DM) is a global epidemic and is expected to affect over 592 million people worldwide by 2035, a dramatic increase from 382 million people with diabetes mellitus in 2013,¹ a prevalence that is likely underestimated.²

T2DM accounts for 90% to 95% of all diabetes mellitus cases,³ for this reason, this review will focus on pharmacological treatments for T2DM and their impact on heart failure (HF) development. Patients with diabetes mellitus have over twice the risk of developing HF than patients without diabetes mellitus.^{4,5} The Framingham



Heart Study suggests that diabetes mellitus independently increases the risk of HF up to 2-fold in men and 5-fold in women compared with age-matched controls, ^{6,7} highlighting a sex discrepancy that is incompletely understood.

The increased incidence of HF in diabetic patients persists even after adjusting for other risk factors such as age, hypertension, hypercholesterolemia, and coronary artery disease. Thus, the term diabetic cardiomyopathy was coined over 40 years ago and was initially used to describe ventricular dysfunction in the absence of coronary artery disease and hypertension in diabetic patients.⁸ However, its use has been broadened to describe the increased vulnerability of the myocardium to dysfunction that characterizes individuals with diabetes mellitus. While 10% to 15% of the general population have diabetes, a recent study suggested that 44% of patients hospitalized for HF have diabetes mellitus.⁹

A wealth of epidemiological evidence demonstrates that diabetes mellitus is independently associated with the risk of developing heart failure, with the risk increasing by more than twofold in men and by more than fivefold in women. Heart failure is highly prevalent (25 % in chronic heart failure and up to 40 % in acute heart failure) in patients with diabetes mellitus. Its prevalence is four-times higher than that of the general population, suggesting a pathogenetic role of diabetes in heart failure. This pathogenetic role is also suggested by the fact that patients with diabetes and without heart failure have an increased risk of developing heart failure compared with a matched population (29 versus 18 %, respectively).¹⁰

Objective: To determine the prevalence of diastolic heart failure in patients with type 2 Diabetes mellitus and its association with different parameters and NTPROBNP

MATERIAL AND METHODS

STUDY SITE -This study was conducted in In-patient and outpatient department of Apollo Gleneagles Hospitals Kolkata.

STUDY POPULATION- Age between 40-65 years of age both males and females from the general medical inpatient and outpatient pool of Apollo Gleneagles Hospitals Kolkata.

STUDY DESIGN- Hospital based Cross-sectional observational study.

SAMPLE SIZE- 85 subjects were enrolled in the study.

STUDY PERIOD AND DURATION- Study was carried out in the period September 2015 to November 2016, in duration of 15 months.

INCLUSION CRITERIA:

- Both male and female patients aged between 40-65 years.
- Patients satisfying criteria for diabetes mellitus

EXCLUSION CRITERIA:

- Patients with Age less than 40 years and above 65 years
- Patients with coronary artery disease
- Patients with already diagnosed with heart failure and on diuretics plus other medications.
- Hypertensive patients on antihypertensive agents and/or angiotensin-converting enzyme (ACE) inhibitors and subjects with poor transthoracic echo window.
- Patients with LV systolic dysfunction apart from heart failure.

Methods of data collection

This study was done on 85 patients with Diabetes mellitus (as per diagnostic criteria), who will be in-patient and outpatient department of Apollo Gleneagles Hospitals Kolkata, over a period of fifteen months. All subjects were determined to be having type 2 Diabetes Mellitus as per diagnostic criteria. Biochemical investigations in the form of blood fasting blood sugar, post-prandial blood sugar, HbA1C, NT-Pro BNP and standard 12 lead electrocardiogram and a transthoracic echocardiogram in a “M” mode will also be carried out.

Statistical methods:

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations. A $p < 0.05$ was taken to be statistically significant.



Results

Table-1: Distribution of Diastolic Dysfunction of the patients

Diastolic Dysfunction	Number	%
Present	54	63.5%
Absent	31	36.5%
Total	85	100.0%

We included 85 patients of Type 2 diabetes in our study. Of these 85 cases, majority were from less than 55 years age group i.e. 43 and remaining 42 from above 55 years age group.

Out of 85 patients with type-2 DM 54(63.5%) of the patients were having diastolic dysfunction. Thus, the prevalence of diastolic dysfunction was 63.5% among the patients with type-2 DM.

Table-2: Distribution of grades of Diastolic Dysfunction of the patients

Grades of Diastolic Dysfunction	Number	%
I	18	33.3%
II	24	44.4%
III	8	14.8%
IV	4	7.4%
Total	54	100.0%

Out of 54 patients with DM 54(63.5%) most of the patients were having Grader-II DM (44.4%) followed by Grade-I DM (33.3%). In overall proportion of patients with Grade-I & II DM (77.7%) was significantly higher ($Z=8.92;p<0.0001$). Only 14.8% and 7.4% of the patients had Grade-III and Grade-IV DM respectively.

Table-3: Comparison of different parameters of the patients under study with diastolic dysfunction

Parameters (mean±s.d.)	Patients with Diastolic Dysfunction	Patients without Diastolic Dysfunction	t-test (t_{83})	p-value
Age (in years)	56.46±4.60	51.03±5.64	4.81	<0.0001*
BMI (kg/m ²)	25.93±2.87	25.75±2.62	3.88	<0.0001*
Level of HbA1c (in %)	7.70±1.07	6.53±0.61	5.53	<0.0001*
Duration of DM (in years)	7.64±2.30	6.12±2.33	2.90	0.005*
Pulse Rate per minute	91.29±7.18	90.61±9.03	0.38	0.70 NS
SBP (mmHg)	137.62±8.01	136.70±7.36	0.52	0.60 NS
DBP (mmHg)	86.85±5.08	86.58±3.90	0.25	0.79 NS
Level of urine ACR	55.48±26.27	33.77±15.60	4.18	<0.0001*
NTPRO	5084.72±2109.51	181.22±19.12	10.61	<0.0001*

All the parameters of the patients with DM higher than that of the patients without DM and there were mostly significantly higher ($p<0.01$).

Table-4: Assessment of signs and symptoms of diastolic dysfunction

Clinical characteristics	Patients with Diastolic Dysfunction (n=54)	Patients without Diastolic Dysfunction (n=31)	Z-test	p-value
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Orthopnea	36(66.7%)	7(22.6%)	6.27	<0.0001*
PND	33(61.1%)	8(25.8%)	5.03	<0.0001*
Edema	31(57.4%)	7(22.6%)	5.02	<0.0001*
JVP	37(68.5%)	8(25.8%)	6.04	<0.0001*
Crepitation	35(64.8%)	11(35.5%)	4.14	<0.0001*
S3	34(63.0%)	9(29.0%)	4.82	<0.0001*
S4	35(64.8%)	12(38.7%)	3.69	<0.0001*
Hepatomegaly	15(27.8%)	4(12.9%)	2.61	<0.0001*
Pleural Effusion	9(16.7%)	2(6.5%)	2.25	<0.0001*
BVM	28(51.9%)	10(32.3%)	2.80	<0.0001*
Bigunides	34(63.0%)	11(35.5%)	3.88	<0.0001*
Sulphonylureas	27(50.0%)	7(22.6%)	4.02	<0.0001*
DPP4 Inhibitor	38(68.5%)	12(38.7%)	4.22	<0.0001*
Alpha Glucosidase Inhibitor	17(31.5%)	5(16.1%)	2.55	0.043*
Thiazolenediones	12(22.2%)	6(19.4%)	0.48	0.52 NS
SGLT2 Inhibitor	11(20.4%)	2(6.5%)	2.88	0.028*
Insulin	29(53.7%)	10(32.3%)	3.05	<0.0001*

Proportion of patients with all clinical parameters was significantly higher among the patients with DM than that of without DM ($p < 0.01$).

Table-14: Comparison of different parameters of the patients under study with different grade of diastolic dysfunction

Parameters (mean±s.d.)	Patients with Diastolic Dysfunction (Grade-I) (n=18)	Patients with Diastolic Dysfunction (Grade-II) (n=24)	Patients with Diastolic Dysfunction (Grade-III) (n=8)	Patients with Diastolic Dysfunction (Grade-IV) (n=4)	F _{3,50} -value	p-value
NTPRO	3404.56±1596.90	5468.71±1657.71	6121.38±1459.29	8268.25±1906.34	13.03	<0.0001*

One way ANOVA showed that there was significant difference in level of NTPRO of the patients with different grades. As per CD the mean NTPRO increased significantly with the increase in grade of DM ($p < 0.01$).

Discussion

This is a single centered hospital based cross sectional study undertaken among inpatients and outpatients of Apollo Gleneagles hospital Kolkata. This study was carried out in a time period of 15 months. Heart failure is one of the common reasons for admission in hospital.

Previously it was thought that heart failure is because of decreased pumping action of ventricles that is EF but over the time it was shown that patients present to hospital with heart failure but EF was normal. Then the concept came into action that is Diastolic heart failure.

Diabetes is a common risk factor for diastolic heart failure. The prevalence of patients with concomitant heart failure (HF) and diabetes mellitus (DM) is growing exponentially with the aging of the general population. Approximately 40% of patients hospitalized with HF and reduced ejection fraction (EF) have Diabetes Mellitus Type 2 with an important epidemiologic, clinical, and economic impact. Diabetes was an independent predictor of CV morbidity and mortality in patients with HF, regardless of EF. The relative risk of CV death or HF hospitalization conferred by diabetes was significantly



greater in patients with preserved when compared with those with low EF HF.¹¹

The prevalence of diastolic dysfunction increases with age and it is more common in females. The age group of patients in our study is 40-65 yrs. There was significant association between age and diastolic dysfunction of patients ($p < 0.0001$). The risk of having diastolic dysfunction was 6.85 times more among the patients with age group of > 55 yrs as compared the patients with age of < 55 yrs and risk was significant. In this study 54 patients were having diastolic dysfunction, amongst which 36 patients were age of < 55 yrs and 18 were above the age group of > 55 yrs. Mean age group of patients with DM is 56.46 ± 4.60 yrs and those without DM mean age group is 51.03 ± 5.64 yrs ($p < 0.0001$). These findings were consistent with the finding from study by Patil et al.¹² They have strongly concluded that prevalence of diastolic dysfunction increases with age.

Obesity is a risk factor for heart failure. Patients in this study above the BMI of ≥ 25 were total 46. Amongst 46 patients, 36 had diastolic dysfunction and those with BMI of < 25 were total 39, amongst which 18 showed DM. Chi-square test showed that there was significant association between obesity and DM of patients ($p = 0.002$). Risk of having DM was more among the patients with BMI of > 25 as compared with BMI of < 25 and risk was significant (OR-4.20), ($p = 0.002$). Mean BMI for patients with DM 25.93 ± 2.87 kg/m² and those without DM mean BMI is 25.7 ± 2.62 kg/m². These findings are consistent with the study done by Patil VC et al.¹² They strongly concluded that obesity is a strong risk factor for diastolic heart failure. Subjects with high waist circumference and high waist to hip ratio had statistically significant diastolic dysfunction.¹²

Duration of diabetes is an important factor in heart failure prevalence. In this study it was found that patients with duration of diabetes > 10 yrs were total 10 patients, amongst which 9 patients had DM and patients with duration of < 10 yrs were total 75 patients amongst which 45 showed DM. Risk of having DM was 6 times more among the patients with duration of > 10 yrs as compared to the patients with duration of < 10 yrs but risk was not significant ($p = 0.06$). So the prevalence of DM in the group of patients with duration of diabetes of > 10 yrs is more as compared to the patients with duration of diabetes of < 10 yrs. These findings are consistent with

findings from study of Patil V C¹² they concluded that prevalence of DM is more in the group of patients with duration of diabetes is more. The prevalence of diastolic dysfunction increased with longer duration of diabetes. There was a linear progression of diastolic dysfunction with the increase age group.

Proteinuria is an isolated risk factor for diastolic heart failure. Proteinuria is now widely accepted as an independent risk factor for cardiovascular morbidity and mortality.¹³

In this study there are total 85 patients, amongst which 66 patients had microalbuminuria. Among 66 patients with microalbuminuria, 49 patients had DM and 17 patients didn't have DM. 19 Patients showed normal ACR amongst only 4 patients had DM and 14 patients didn't have DM. Chi-square showed that there was significant association between status of urine ACR and DM of patients ($p < 0.0001$). Mean level of urine ACR for patients with DM (55.48 ± 26.27) and mean level of urine ACR for patients without DM is (33.77 ± 15.60) $p < 0.0001$. Albuminuria, including microalbuminuria, is one of the earliest clinical signs of DKD and is a marker of renal progression and an increased risk of cardiovascular morbidity.¹⁴

The diagnosis of diastolic heart failure is made on the basis of following points: 1) Presence of signs and symptoms of congestive heart failure. 2) Presence of normal or mildly abnormal LV systolic function. 3) Evidence of LV diastolic dysfunction. The last criteria can be fulfilled by three ways (as already mentioned), one of them is the NT-PROBNP > 220 pg/ml. Nowadays NT-PROBNP has gained more importance in the diagnosis of HFPEF. In this study Mean \pm s.d. of NT-PROBNP the group of patients with diastolic dysfunction was 5084.72 ± 2109.51 and mean value for patients without DM was 181.22 ± 19.12 ; $p < 0.001$. Median value of NT-PROBNP for patients with DM was 5120 and patients without DM was 184. t-test showed that the median level of NT-PROBNP of patients with DM was significantly higher than that of patients without DM ($t_{83} = 10.60$; $p < 0.0001$). In this study it has also seen that the NT-PROBNP value according to the grades of DM. In grade 1 the NT-PROBNP value was (mean \pm s.d.) 3404.56 ± 1596.90 . In grade 2 the value of NT-PROBNP was 5468.71 ± 1657.71 . In grade 3 NT-PROBNP was 6121.38 ± 1459.29 . In grade 4 it was



8268.25+_1906.34. So it has been seen that as the grade of DM increases the NTPROBNP value also increases. One way ANOVA showed that there was significant difference in level of NTPROBNP of the patients with different grades. As per CD the mean NTPROBNP increased significantly with the increase in grade of DM ($p < 0.01$). This was also supported by study by Tschope et al¹⁵ in which they have shown that NTPROBNP levels were four-fold higher in patients with diastolic abnormalities compared group. They also showed NTPROBNP level increased significantly according to the severity of diastolic dysfunction. The diastolic heart failure in this study was found in 54 patients out of 85 patients. All 54 patients with DM had NTPROBNP value above 220, signs and symptoms of heart failure and diastolic dysfunction on Echocardiography.

Conclusion

- HFPEF is a new entity but its very common and accounts for about 50% of the all cases of heart failure. HFPEF has not been studied as extensively as HFREF. Diabetes was an independent predictor of CV morbidity and mortality in patients with HF, regardless of EF. In the present study diastolic heart failure was more common in diabetes and prevalence of diastolic heart failure was 63.5%. There was significant association between age and diastolic dysfunction of patients ($p < 0.0001$). The risk of having diastolic dysfunction was 6.85 times more among the patients with age group of ≥ 55 years as compared the patients with age of < 55 yrs and risk was significant. Chi-square test showed that there was significant association between gender and diastolic dysfunction. The risk of having DM was 2.91 times more among female patients as compared to male patients and the risk was not significant. In this study diastolic dysfunction was more common in females.
- Prevalence of DM in the group of patients with duration of diabetes of ≥ 10 years is more as compared to the patients with duration of diabetes of < 10 yrs.
- The prevalence of diastolic dysfunction increased with longer duration of diabetes.
- NT-ProBNP level helps in diagnosing HFPEF cases with equivocal echo findings of diastolic dysfunction. NT-ProBNP level was significantly higher in patients with diastolic heart failure than the value required for diagnosis of HFPEF in the present study. Median value of NT-PROBNP for patients with DM was

5120 and patients without DM was 184. t-test showed that the median level of NTPROBNP of patients with DM was significantly higher than that of patients without DM. One way ANOVA showed that there was significant difference in level of NTPROBNP of the patients with different grades. NT-proBNP levels had the best negative predictive value of all methods (94%) and correlated strongly with indices of LV filling pressure. As per CD the mean NTPROBNP increased significantly with the increase in grade of DM ($p < 0.01$). Hence level of NTPROBNP could be used to assess the severity and monitor the response to therapy in patients with diastolic heart failure.

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