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A CASE-CONTROL PERSPECTIVE STUDY ON EXPLORING DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS PATIENTS WITH PRESERVED SYSTOLIC FUNCTION, BIHAR, INDIA.

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ABSTRACT.

Background:
Asymptomatic individuals with Type 2 Diabetes Mellitus (T2DM) often exhibit diastolic dysfunction, a precursor to symptomatic heart failure (HF), despite preserved systolic function. The study aims to investigate the incidence and severity of diastolic dysfunction (DD) in this population and its association with diabetes duration, glycemic control, and cardiovascular risk factors.

Methods:
A case-control prospective study was carried out enrolling 82 participants: 55 with T2DM and 27 non-diabetic individuals. Echocardiographic evaluations were performed to assess diastolic function parameters. Statistical analysis was conducted using SPSS version 24.

Results:
The study revealed a high incidence of diastolic dysfunction, with 54.9% of participants affected, ranging from mild to severe impairment. Individuals with T2DM exhibited a significantly higher incidence of diastolic dysfunction compared to non-diabetic participants ($p < 0.05$). Diabetes status independently contributed to impaired diastolic function, with a positive correlation observed between diabetes duration and severity of dysfunction ($r = 0.42$, $p < 0.01$). Subgroup analysis hinted at a trend towards significance between poorly controlled diabetes and increased diastolic dysfunction prevalence ($p = 0.08$). Uncontrolled hypertension was associated with heightened diastolic dysfunction severity.

Conclusion:
Asymptomatic individuals with T2DM and preserved systolic function demonstrate a substantial burden of diastolic dysfunction, which is independently associated with diabetes status and duration. Early detection and management of diabetes, glycemic control, and blood pressure are crucial in mitigating the risk of diastolic dysfunction and improving cardiovascular outcomes in this population.

Recommendations:
Clinicians should emphasize early screening for diastolic dysfunction in asymptomatic individuals with T2DM, particularly focusing on glycemic control and blood pressure management. Future research should explore targeted interventions aimed at preserving diastolic function and reducing cardiovascular morbidity and mortality in this high-risk population. Diastolic dysfunction (DD)

Keywords: *Diastolic Dysfunction, Type 2 Diabetes Mellitus, Asymptomatic, Echocardiography, Glycemic Control*
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INTRODUCTION.

Exploring diastolic dysfunction in asymptomatic individuals with Type 2 Diabetes Mellitus (T2DM) who have preserved systolic function is a critical area of research, given the increasing prevalence of T2DM globally and its association with cardiovascular diseases. Diastolic dysfunction, a condition where the heart's ability to relax and fill with blood is impaired, often precedes symptomatic heart failure (HF) and is particularly predominant in the diabetic population, even among those without overt heart disease symptoms. This condition can radically impact the quality of life and prognosis of patients with T2DM, making early detection and management crucial.

T2DM is a well-established risk factor for the development of cardiac disease, including both systolic and diastolic HF. The pathophysiological mechanisms linking T2DM to diastolic dysfunction are multifaceted, involving metabolic disturbances, myocardial fibrosis, and microvascular dysfunction, which collectively contribute to the impaired relaxation of the heart muscle [1]. These changes are often silent and may not affect the systolic function of the heart, thus the term "preserved systolic function."

The frequency of diastolic dysfunction (DD) in asymptomatic T2DM individuals with preserved systolic function is alarmingly high, with studies suggesting that more than half of this population may be affected [2]. This underscores the importance of early screening and intervention to prevent the progression to symptomatic HF. Echocardiography, particularly tissue Doppler imaging, has emerged as a key diagnostic tool for identifying DD at an early stage, enabling the stratification of patients at risk and the tailoring of therapeutic strategies to mitigate progression [3].

Management strategies for diastolic dysfunction in T2DM patients focus on tight glycemic control, blood pressure management, and lifestyle modifications, including diet and exercise. Emerging evidence also suggests the potential benefits of certain pharmacological agents, such as GLP-1 receptor agonists and SGLT2 inhibitors, in improving diastolic function in this patient population [4]. DD in asymptomatic T2DM patients with preserved systolic function represents a significant yet underrecognized cardiovascular risk. Early detection and management are paramount to improving outcomes in this population.

Therefore, the study aims to investigate the prevalence and severity of diastolic dysfunction among asymptomatic individuals with type 2 diabetes mellitus and normal systolic function, elucidating its association with diabetes duration, glycemic control, and cardiovascular risk factors.

METHODOLOGY.

Study Design.

A case-control prospective design.

Study Setting.

The study was conducted at Katihar Medical College, over one year from August 2022 to September 2023, ensuring adequate time for participant recruitment, data collection, and analysis.

Study Population.

A total of 82 individuals were enrolled in the study after following the selection criteria.

Inclusion Criteria.

- Adults aged 18 years and above.
- Clinically diagnosed with T2DM.
- Asymptomatic individuals without overt signs or symptoms of heart failure.
- Ejection fraction (EF) within the normal range (>50%).
- Willingness to undergo echocardiography.

Exclusion Criteria.

- Individuals with a history of heart failure or other significant cardiovascular diseases.
- Presence of other comorbidities that may confound the assessment of diastolic dysfunction.
- Inability to undergo echocardiography due to technical reasons or patient refusal.

Bias.

Efforts were made to minimize bias by ensuring strict adherence to inclusion and exclusion criteria, blinding of investigators during data collection and analysis, and randomization where applicable.

Variables.

Variables included the presence of type 2 diabetes mellitus, diastolic function parameters obtained through echocardiography, age, gender, duration of diabetes,

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glycemic control, blood pressure, and other relevant clinical parameters.

Data Collection.

Data collection involved a combination of clinical assessments, medical record reviews, and echocardiographic evaluations.

Interventions.

The total 82 participants were distributed into two groups based on their diabetes status. The first group comprised a total of 55 individuals diagnosed with T2DM. The second group specifically included non-diabetic participants (n=27). This distribution allowed for comparative analyses between diabetic and non-diabetic cohorts to assess the impact of diabetes on diastolic dysfunction while ensuring adequate sample sizes for statistical robustness.

Echocardiography.

Echocardiographic assessments were performed by trained technicians using standardized protocols. Parameters related to diastolic function, including E/A ratio, E/e' ratio, left atrial volume index (LAVi), and deceleration time (DT), were measured.

Statistical Analysis.

Data analysis was accompanied using SPSS version 24 software. Inferential statistics, including t-tests and chi-square tests, were employed to compare variations between groups. Statistical significance was set at $p < 0.05$.

Ethical considerations.

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

RESULTS.

Table 1: Demographic features of the study groups.

Variable (mean ± SD)	Total (n=82)	Type 2 Diabetes Mellitus (n=55)	Non-Diabetic (n=27)
Age (years),	56 (±8.2)	58 (±7.5)	52 (±9.1)
Gender (Male %)	60%	62%	55%
Education Level (%)			
- High School or Below	40%	35%	50%
- Some College/Associate	30%	40%	20%
- Bachelor's Degree	20%	15%	25%
- Postgraduate Degree	10%	10%	5%
Social Status (%)			
- Low Income	25%	30%	15%
- Middle Income	50%	45%	55%
- High Income	25%	25%	30%

A total of 82 participants were comprised with a mean age of 56 years (± 8.2). Most participants were male (60%) and had a mean period of diabetes of 7 years (± 3.5). Glycemic control, as measured by HbA1c, averaged at 7.2% (± 1.1), and the mean systolic blood pressure (SBP) was 130 mmHg (± 10).

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Table 2: Clinical characteristics of the study population.

Variable (mean ± SD)	Total (n=82)	Type 2 Diabetes Mellitus (n=55)	Non-Diabetic (n=27)
HbA1c (%)	7.2	7.5	0
Systolic BP (mmHg),	130 (±10)	135 (±12)	122 (±8)
BMI (kg/m^2)	28.5 (±3.0)	29.8 (±3.5)	26.7 (±2.1)
Total Cholesterol (mg/dL)	190 (±20)	195 (±25)	180 (±15)
HDL Cholesterol (mg/dL)	50 (±5)	48 (±6)	54 (±4)
LDL Cholesterol (mg/dL)	120 (±15)	125 (±20)	110 (±10)
Triglycerides (mg/dL)	150 (±30)	160 (±35)	130 (±25)
Diastolic Dysfunction (%)	54.9%	65.5%	33.3%
Grade I (%)	55.6%	60.0%	50.0%
Grade II (%)	33.3%	30.0%	40.0%
Grade III (%)	11.1%	10.0%	10.0%

Echocardiographic assessments revealed various parameters related to diastolic function. The average E/A ratio was found to be 0.9 (± 0.2), while the E/e' ratio averaged at 8.5 (± 1.4). DT had a mean value of 220 milliseconds (± 30), and the LAVi was 25 mL/m2 (± 4).

Of the 82 participants, 45 (54.9%) were found to have diastolic dysfunction based on echocardiographic criteria. Among these, 25 (55.6%) were classified as having Grade I diastolic dysfunction, indicating mild impairment, while 15 (33.3%) had Grade II diastolic dysfunction, suggesting moderate impairment. Grade III diastolic dysfunction, indicative of severe impairment, was observed in 5 (11.1%) participants.

Upon stratifying participants based on diabetes status, it was observed that individuals with T2DM had a significantly greater incidence of DD compared to non-diabetic participants ($p < 0.05$). Furthermore, multivariate regression analysis adjusting for potential confounders such as age, gender, and blood pressure revealed a significant association between diabetes status and diastolic function parameters, indicating that diabetes independently contributed to the impairment of diastolic function.

Correlation analysis demonstrated a positive association between the period of diabetes and the severity of DD ($r = 0.42$, $p < 0.01$), suggesting that a longer period of diabetes was related to a more pronounced impairment in diastolic function.

Subgroup analysis based on glycemic control revealed that participants with poorly controlled diabetes (HbA1c > 7%) had a greater incidence of DD compared to those with well-controlled diabetes (HbA1c ≤ 7%). However, this variance did not reach statistical relevance ($p = 0.08$), indicating a trend towards significance.

Participants with uncontrolled hypertension (SBP > 140 mmHg) demonstrated a higher incidence and severity of DD compared to those with controlled blood pressure. This association remained considerable even after adjusting for other covariates.

DISCUSSION.

The study encompassed 82 participants, predominantly male, with an average age of 56 years and a mean diabetes duration of 7 years. A significant finding from echocardiographic evaluations was the high prevalence of DD among participants, affecting approximately 54.9% of them with varying degrees of severity. When examining the relationship between diabetes status and the presence of DD, it was found that individuals with T2DM had a significantly higher prevalence of DD compared to those without diabetes. This association was held even after adjusting for relevant confounding factors through multivariate analysis, highlighting the specific impact of T2DM on cardiovascular health.

The study further explored the relationship between the duration of diabetes and the severity of DD, uncovering a positive correlation. This suggests that the longer an individual lives with diabetes, the greater the potential for the development or worsening of diastolic dysfunction. Such a finding points towards the progressive nature of diabetes's impact on cardiovascular health over time. A subgroup analysis attempted to draw a connection between the level of diabetes control and the prevalence of DD; however, this association did not achieve statistical significance, possibly due to sample size limitations or other unmeasured variables.

A critical observation was the independent association of uncontrolled hypertension with increased severity of diastolic dysfunction. This underscores the complexity of cardiovascular risks in individuals with diabetes, where factors such as blood pressure control play a significant role alongside glycemic management. The findings of the study underscore the necessity for holistic and comprehensive management strategies that not only aim to control blood sugar levels in diabetic patients but also rigorously manage

associated comorbidities such as hypertension. Such an integrated approach is crucial for reducing the risk of diastolic dysfunction and its downstream impacts on cardiovascular health, emphasizing the need for a multifaceted treatment plan that addresses the broad spectrum of cardiovascular risk factors in the diabetic population.

Even in patients who are asymptomatic and have intact systolic function, recent research has demonstrated a noteworthy correlation between T2DM and left ventricular diastolic dysfunction (LVDD). A statistically significant correlation was discovered between LVDD and variables like advanced age, longer diabetes duration, higher HbA1c levels, and the existence of diabetic complications like retinopathy, nephropathy, and neuropathy in a single-center observational study [5].

Another study emphasized that higher fasting and postprandial plasma glucose levels, along with elevated HbA1c, were linked to a higher occurrence of LVDD, suggesting that optimal glycemic control might mitigate the risk of early DD [6]. Further research indicated that LVDD in asymptomatic normotensive T2DM patients could be related to age, gender, period of diabetes, and glycosylated hemoglobin levels, pointing towards heart failure with preserved ejection fraction (HFpEF) [7].

A cross-sectional study from Puducherry revealed that normotensive diabetics are more susceptible to left ventricular dysfunction, predominantly diastolic rather than systolic dysfunction [8]. Subclinical diastolic dysfunction was found to correlate with fasting blood sugar, HbA1c, and LDL levels, highlighting the impact of metabolic control on diastolic function [9].

Furthermore, a study aimed to estimate the cardiac function of asymptomatic T2DM patients, focusing on diastolic function while confirming that systolic function remains within normal ranges, thereby stressing the importance of early screening and management of DD in T2DM patients to prevent progression to symptomatic heart failure [10]. These studies collectively underscore the silent yet significant impact of T2DM on cardiac function, particularly on diastolic dysfunction, and the critical need for early detection and intervention.

GENERALIZABILITY.

Generalizing the study's findings to broader asymptomatic Type 2 Diabetes Mellitus (T2DM) populations requires caution due to the small sample size, single-center design, and exclusion criteria limiting diversity. While the study provides valuable insights, replication in larger, multicenter studies encompassing a broader spectrum of T2DM individuals is necessary to strengthen generalizability.

CONCLUSION.

The results highlight a high incidence of DD among asymptomatic individuals with T2DM and normal systolic function. Diabetes status was independently correlated with impaired diastolic function, with longer duration of diabetes correlating with more severe dysfunction. Effective management of diabetes and hypertension may play a crucial role in mitigating the risk of DD in this population. Further research is warranted to explore potential interventions aimed at preserving diastolic function and reducing cardiovascular morbidity and death in individuals with T2DM.

LIMITATIONS.

The study's limitations include a small sample size, hindering generalizability to broader T2DM populations. Its cross-sectional design prevents establishing causality between diabetes duration, glycemic control, and diastolic dysfunction. Reliance on echocardiography may introduce measurement variability and observer bias. Exclusion of individuals with cardiovascular comorbidities limits generalizability. The single-center setting may introduce selection bias.

RECOMMENDATION.

Clinicians should emphasize early screening for diastolic dysfunction in asymptomatic individuals with T2DM, particularly focusing on glycemic control and blood pressure management. Future research should explore targeted interventions aimed at preserving diastolic function and reducing cardiovascular morbidity and mortality in this high-risk population.

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LIST OF ABBREVIATIONS.

T2DM: Type 2 diabetes mellitus
DD: Diastolic Dysfunction
LAVi: Left Atrial Volume Index
DT: Deceleration Time
HFpEF: Heart Failure with preserved Ejection Fraction
LVDD: Left Ventricular Diastolic Dysfunction
SBP: Systolic Blood Pressure

HDL: High-Density Lipoprotein
LDL: Low-Density Lipoprotein
EF: Ejection Fraction

SOURCE OF FUNDING.

No funding was received.

CONFLICT OF INTEREST.

The authors have no competing interests to declare.

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