LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND ITS PATTERN IN TYPE 2 DIABETIC PATIENTS WITH AND WITHOUT MICROALBUMINURIA

Misbah Manzoor[1], Bakht Babar[2]

[1] Department of Cardiology, Peshawar Institute of Cardiology, Peshawar - Pakistan
[2] Department of Diabetes, Endocrinology and Metabolic Diseases, Hayatabad Medical Complex, Peshawar - Pakistan

Address for correspondence:
Bakht Babar
Department of Diabetes, Endocrinology, and Metabolic Diseases, Hayatabad Medical Complex, Peshawar - Pakistan

E-mail:
bakht2103@gmail.com

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ABSTRACT

Objective: To find out and compare left ventricular diastolic dysfunction and its pattern among patients with type-2 diabetes mellitus (T2DM) with and without micro-albuminuria.

Methodology: This comparative cross section study was conducted in the outpatient department of Peshawar Institute of Cardiology from August 2021 to January 2022. A total of 228 T2DM normotensive patients, aged 30 to 65 years were enrolled and divided into two groups. Group-A contained 114 T2DM with no-albuminuria and Group-B had 114 T2DM micro-albuminuria patients. Socio-demographic, anthropometric, laboratory characteristics and echocardiographic parameters of all patients were noted. Qualitative variables were analyzed using chi-square test while quantitative variables were analyzed using t-test. P value ≤0.05 was considered statistically significant.

Results: Out of a total of 228 patients, 122 (53.5%) were male. Overall, mean age was noted to be 49.18+8.8 years. In comparison to group-A, duration of diabetes was significantly more among patients of group-B (p<0.001). Renal functions were significantly preserved in Group-A in comparison to Group-B (p=0.003) as shown by eGFR. Left ventricular diastolic dysfunction was found to be 49.1% among patients of Group-A in comparison to 71.1% in Group-B and pattern of left ventricular diastolic dysfunction showed a significant difference between patients of both study groups (0.004).

Conclusion: Left ventricular diastolic dysfunction was significantly high among T2DM patients with micro-albuminuria. Significant associations were found in terms altered left ventricular diastolic echocardiographic features among T2DM patients with micro-albuminuria.

Keywords: Echocardiography; Left ventricular diastolic dysfunction; Micro-albuminuria type-2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is known to cause structural and functional changes to heart[1]. Cardiovascular diseases have been found to be a major cause of morbidity and mortality in diabetics.[2] Diastolic dysfunction has long been thought to be one of the hallmarks of diabetic cardiomyopathy (DCM).[3] The putative pathophysiological pathways causing cardiac hypertrophy and increased myocardial stiffness leading to diastolic dysfunction in diabetics are caused by both cellular and extracellular matrix stiffness.[4] Some other pathways, which appear to be strongly implicated in myocardial stiffness and are specifically affected by diabetes, include impairment in the myocardial nitric oxide (NO) pathway, coronary microvascular dysfunction, elevated inflammation, and oxidative stress.[4] Left ventricular diastolic dysfunction (LVDD) has been discovered to represent the early stages of diabetic cardiomyopathy (DCMP), emphasising the importance of early detection of diastolic ventricular dysfunction in people with diabetes.[5] Past researchers have found 60% prevalence of diastolic dysfunction among type-2 DM (T2DM) patients having well-controlled blood glucose[6], while data from the developing world shows this to be as high as 73%.[7] A recent study from Nigeria noted stepwise increase in prevalence of LV diastolic dysfunction that is 16.9% among healthy controls, 61.9% in T2DM patients with no albuminuria and 78.9% in those T2DM patients having microalbuminuria (p<0.001).[8]

Epidemiological studies demonstrated albuminuria as one of the predictors of cardiovascular morbidity as well as mortality in T2DM, and is found to be independent of commonly found risk factors.[9,10] As exact mechanisms behind albuminuria and cardiac events are not yet completely understood but it is hypothesized that vascular changes which effect renal func-

tions, might be representing vasculature of the heart which ultimately leads to cardiac dysfunctioning.[11] Increased albumin leakage in the glomerulus has been linked to increased capillary permeability for albumin in the systemic vasculature in diabetics with microalbuminuria. This increased permeability is thought to be a hallmark of generalised or systemic endothelial dysfunction, and it has been proposed that such leakage could cause hemodynamic strain and instability, hence initiating the atherosclerotic process and eventually leading to severe CVS outcomes.[12]

Micro-albuminuria has long been considered as a marker of glomerular endothelial dysfunctioning while it is also known to be linked with micro-angiopathy among T2DM.[10,13] This study was planned to find out whether existence of micro-albuminuria among normotensive T2DM patients can demonstrate deterioration in cardiac functioning. Our literature search showed very limited data regarding LVDD in type 2 diabetics in Pakistan. So, this research might help to fill this gap. Finding of this study will further implement the fact that there is significant association of LVDD with microalbuminuria in T2DM patients.

In future this will be of great help for health care workers in educating asymptomatic diabetic patient to be screened regularly for the presence of cardiomyopathy in the presence of microalbuminuria. Thus, albuminuria can be easily used as a marker of other CVD risk factors, as well as endothelial dysfunction, that reflects underlying macrovascular and microvascular disease.

METHODOLOGY

This comparative cross-sectional study was carried out at outpatient department of Peshawar Institute of Cardiology from August 2021 to January 2022 after approval from research ethical committee of the hospital. Informed written consent was sought from all study participants. Considering prevalence of LV diastolic dysfunction among patients with no albuminuria T2DM and micro-albuminuria T2DM individuals as 61.9% and 78.9% respectively, a sample size of 228 was calculated (Group-A containing 114 T2DM with no albuminuria patients and Group-B having 114 T2DM micro-albuminuric patients) considering 2-sided confidence level as 95%, power 80%, ratio of subjects in both groups as 1:1.[8] All study participants aged 30 to 65 were considered.

All those conditions which can affect or cause microalbuminuria or might affect cardiac function in any way were excluded. This include patients having blood pressure above or equal to 140/90 mmHg or using any anti-hypertensive medications, patients having macroalbuminuria or serum creatinine levels ≥ 1.5 mg/dl, and patients having any kinds of chest deformity or chronic chest disease (according to x-ray chest) were not enrolled. All pregnant women or those having sickle cell disease, or UTI were also not included. Individuals who already had heart problem in the form of congenital, valvular, pericardial or ischemic heart disease leading to heart failure, or those having arrythmias of any sort were also excluded.

A specifically designed proforma was used to record all study information. Demographic, anthropometric and laboratory characteristics were noted from all study participants. Micro-albuminuria was screened according to 2-steps method using Combur 10-test strip (Roche). Micro-albuminuria was taken as present if the urine sample producing reaction color representing to 30mg/l or above. Echocardiography was done while subjects in the left lateral decubitus position. Measurements were noted under 2-dimentional guided M-mode according to "American Society of Echocardiography".[14,15]

Diastolic function was labeled as normal if early/atrial velocities between 1 to 2, isovolumic relaxation time between 60 and 100 ms and deceleration time between 160-240. Grade-1diastolic dysfunction if early/atrial below 1, isovolumic relaxation time above 100 ms and deceleration time above 240 ms. Grade-2 diastolic dysfunction if early/atrial between 1 and 2, isovolumic relaxation time between 60 and 100 ms, deceleration time between 150 and 220 ms and pulmonary venous flow systolic/diastolic below 1. Grade-3 was labeled if early/atrial above 2, isovolumic relaxation time less than 60 ms and deceleration time below 160 ms.[16] Data was analyzed using SPSS version 26.0. Quantitative variables were analyzed and expressed as mean and standard deviation, while qualitative variables were highlighted as frequencies and percentages. Qualitative variables were analyzed using chi-square test while quantitative variables were analyzed using student's t-test. P value below or equal to 0.05 was considered statistically significant.

RESULTS

Out of 228 patients, 122 (53.5%) were male. Overall, mean age was noted to be 49.18$\pm$8.8 years. In comparison to Group-A, duration of diabetes was significantly more among patients of Group-B (4.25+3.55 vs. 6.38+3.27, $p<0.001$). Table 1 is showing comparison of demographic, anthropometric and laboratory characteristics between patients of both study groups. Both Systolic and diastolic blood pressure was significantly raised among study participants of Group-B ($p<0.05$). Assessment of renal functioning through estimated glomerular filtration rate showed that renal functions were significantly preserved in Group-A in comparison to Group-B ($p=0.003$). No significant difference among patients of both study groups in terms of creatinine and urea levels was observed ($p>0.05$). Fasting blood sugar was significantly high among patients of Group-B (132±52 vs. 148±48, $p=0.017$).

Table 2 is showing echocardiography parameters (mean±SD) of left ventricular functioning in between patients of both study groups. Mean values were statistically similar for left ventricular internal dimension in systolic, deceleration time, pulmonary venous flow systolic velocity and pulmonary artery systolic pressure (p>0.05) while other echocardiographic parameters indicative of left ventricular functions had statistically significant difference in between patients of both study groups (p<0.05).

Table 3 is showing pattern of LVDD among patients of both study groups. LVDD was found to be 49.1% among patients of Group-A in comparison to 71.1% in Group-B. Regarding pattern LVDD showed a significant difference between patients of both study groups (0.004).

Table 1: Demographic, anthropometric and laboratory characteristics (n=228)

Characteristics	Group-A (T2DM normo-albuminuria)	Group-B (T2DM micro-albuminuria)	p-Value
Gender (male)	60 (52.6%)	62 (54.4%)	0.869
Age (years)	48.86+8.20	49.53+9.11	0.560
Duration of Diabetes (years)	4.25+3.55	6.38+3.27	<0.001
Body Mass Index (kg/m2)	26.2+3.0	26.8+3.2	0.1455
Systolic Blood Pressure	119+8	121+6	0.034
Diastolic Blood Pressure	76+7	78+8	0.046
Pulse rate (beats/min)	82+9	83+9	0.402
Creatinine (mg/dl)	1.0+0.2	1.0+0.4	1
Urea (mmol/l)	4.1+1.5	4.0+1.6	0.627
Estimated Glomerular Filtration Rate(ml/min)	88±28	77±27	0.003
Fasting Blood Sugar	132+52	148+48	0.017

Table 2: Echocardiographic parameters (Mean+SD) among patients of both study groups (n=228)

Echocardiographic Parameters	Group-A (T2DM normo-albuminuria)	Group-B (T2DM micro-albuminuria)	p-Value
Left Ventricular Internal Dimension in Systolic(mm)	26+2	26+3	1
Left Ventricular Internal Dimension in Diastolic(mm)	41+5.0	38+4.9	<0.001
End Diastolic Volume(ml)	75+18	67+17	0.001
End Systolic Volume(ml)	27+7	25+6	0.021
Stroke Volume(ml)	52+18	46+15	0.007
Cardiac Output(l)	4.3+1.2	3.7+0.9	<0.001
Ejection Fraction (%)	64+9	61+7	0.005
Fractional Shortening (%)	35+5.8	32+4.6	<0.001
Mitral Early Velocity(m/s)	66+16	62+14	0.046
Mitral Atrial Velocity(m/s)	70+15	75+15	0.013
Early/Atrial Ratio	1+0.2	0.9+0.2	0.001
Isovolumic Relaxation Time(s)	85+17	91+16	0.007
Deceleration Time(s)	191+40	192+38	0.847
Pulmonary Venous Flow Systolic Velocity(m/s)	48+15	50+12	0.268
Pulmonary Venous Flow Diastolic Velocity(m/s)	42+8	46+10	0.001

DISCUSSION

Linkage between microalbuminuria and left ventricular diastolic dysfunction among patients of T2DM has long been a subject of interest.[9,10,13] We found that LVDD was significantly high among T2DM patients having micro-albuminuria (71.1%) in comparison to T2DM patients without micro-albuminuria (49.1%). Data from other parts of the world have shown LVDD to range between 40-75% among normotensive T2DM patients.[17,18] A study from Nigeria found left ventricular diastolic dysfunction to be 16.9%, 61.9% and 78.9% among healthy controls, T2DM with no albuminuria and T2DM micro-albuminuria groups (p<0.001).[8] Data from developed countries have shown left ventricular diastolic dysfunction to be lower where it was found to be 16%, 26% and 31% among no-albuminuria, micro-albuminuria and macro-albuminuria groups.[19]

This could be due the fact that researchers considered only trans mitral flow parameters without any distinction made between normal and grade-2 diastolic dysfunction so it is possible that patients having pseudo-normalized pattern were not involved in the analysis.[19] So, health care provider needs to be on high alert once T2DM patients develop microalbuminuria, keeping in mind high risk of occurrence of LVDD in microalbuminuric type 2 diabetics.

Results of our study suggested that diastolic functions were worse in terms of higher atrial velocity lower early velocity and early/atrial ratio while significantly longer isovolumic relaxation time was observed among T2DM patients with microalbuminuria. In comparison to T2DM without microalbuminuria, researchers in the past have also found longer duration of deceleration time and isovolumic relaxation time among T2DM patients having microalbuminuria.[20] Recent regional data from India highlighted occurrence of left ventricular dysfunction

Systolic/Diastolic Ratio	1.1+0.2	1.1+0.2	1
Pulmonary Artery Systolic Pressure (mmHg)	31+8	33+9	0.088
Left Atrial End-systolic Dimension(mm)	34+4	37+5	<0.001

Table 3: Pattern of left ventricular diastolic dysfunction in between patients of both study groups (n=228)

Pattern of Left Ventricular Diastolic Dysfunction	Group-A (T2DM normo-albuminuria)	Group-B (T2DM micro-albuminuria)	p-Value
Normal	58 (50.9%)	33 (28.9%)	0.004
Grade-1	52 (45.6%)	69 (60.5%)	
Grade-2	3 (2.6%)	7 (6.1%)	
Grade-3	1 (0.9%)	5 (4.4%)	

among T2DM patients with micro-albuminuria.[21] So, albuminuria detection can be used as an early predictor of cardiovascular dysfunction among T2DM patients. Longitudinal prospective studies should be conducted to find out cardiovascular outcomes among T2DM with micro-albuminuria and left ventricular diastolic dysfunction.

Regarding pattern of LVDD our study demonstrated all grades of diastolic dysfunction to be more common in those diabetics having microalbuminuria as compared to those having no albuminuria. Grade 1 diastolic dysfunction was the predominant category compared to rest. This grading of LVDD has its own impact on prognosis[22], and the risk of mortality rises with a progressive increase in diastolic dysfunction.[23] This holds true even for those having normal ejection fraction.[24] So, there is need for educating the asymptomatic diabetics to screen themselves regularly for cardiac dysfunction once they develop microalbuminuria, because early detection of diastolic dysfunction can help prevent advance cardiac complications.

This study had some limitation like for example this was a single center study. Secondly it was not possible to rule out ischemic heart disease by doing angiography (gold standard to rule out ischemic heart disease), because of the cost and feasibility of patients. Still this study seems to be the 1st one from Pakistan with an aim to evaluate left ventricular diastolic functions among T2DM patients with and without micro-albuminuria. This research work will be a gate way for further research so as to dig deeper into the causes of LVDD in diabetics along with bringing more innovation into early diagnosis of LVDD in diabetics.

CONCLUSION

Left ventricular diastolic dysfunction was significantly high among T2DM patients with micro-albuminuria. Significant associations were found in terms altered left ventricular diastolic echocardiographic features among T2DM patients with micro-albuminuria. Periodic screening of micro-albuminuria among T2DM patients may help early detection of cardiovascular disease.

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REFERENCES

1. Athithan L, Gulsin GS, McCann GP, Levelt E. Diabetic cardiomyopathy: Pathophysiology, theories and evidence to date. World J Diabetes. 2019;10(10):490-510. DOI:10.4239/wjd.v10.i10.490
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):83. DOI:10.1186/s12933-018-0728-6
3. Yokota S, Tanaka H, Mochizuki Y, Soga F, Yamashita K, Tanaka Y, et al. Association of glycemic variability with left ventricular diastolic function in type 2 diabetes mellitus. Cardiovascular Diabetology. 2019;18:1-8. DOI:10.1186/s12933-019-0971-5
4. Nikolajevic Starcevic J, Janic M, Sabovic M. Molecular mechanisms responsible for diastolic dysfunction in diabetes mellitus patients. International journal of molecular sciences. 2019;20(5):1197. DOI:10.3390/ijms20051197
5. Grigorescu ED, Lacatusu CM, Floria M, Mihai BM, Cretu I, Sorodoc L. Left ventricular diastolic dysfunction in type 2 diabetes—progress and perspectives. Diagnostics. 2019;9(3):121. DOI:10.3390/diagnostics9030121.
6. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes. Importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001;24:5-10. DOI:10.2337/diacare.24.1.5
7. Nugroho BS, Rachman AM, Suryadipradja RM, Waspadji S. Diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality. Indones J Intern Med. 2003;35:131-5.
8. Shogade TT, Essien IO, Ekrikpo UE, Umoh IO, Utin CT, Unadike BC, et al. Association of microalbuminuria with left ventricular dysfunction in Nigerian normotensive type 2 diabetes patients. Cardiovasc J Afr. 2018 Sep/Oct 23;29(5):283-288. DOI:10.5830/CVJA-2018-026
9. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GY, et al. Albuminuria and risk of cardiovascular

events and mortality in a general population of patients with type 2 diabetes without cardiovascular disease: a Danish cohort study. The American Journal of Medicine. 2020;133(6):e269-79. DOI: 10.1016/j.amjmed.2019.10.042.
10. Nichols GA, Deruaz Luyet A, Hauske SJ, Brodovicz KG. The association between estimated glomerular filtration rate, albuminuria, and risk of cardiovascular hospitalizations and all-cause mortality among patients with type 2 diabetes. Journal of Diabetes and its Complications. 2018;32(3):291-7. DOI:10.1016/j.jdiacomp.2017.12.003
11. Hanna DB, Xu S, Melamed ML, Gonzalez F, Allison MA, Bilsker MS, et al. Association of Albuminuria With Cardiac Dysfunction in US Hispanics/Latinos. Am J Cardiol. 2017;119(12):2073-80. DOI:10.1016/j.amjcard.2017.03.039
12. Raja P, Maxwell AP, Brazil DP. The potential of albuminuria as a biomarker of diabetic complications. Cardiovascular drugs and therapy. 2021;35:455-66. DOI:10.1007/s10557-020-07035-4.
13. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc. 2018;117(8):662-75. DOI:10.1016/j.jfma.2018.02.007.
14. Varghese S, Kumar SG. Prevalence of micro albuminuria and diagnostic accuracy of urine dipstick for the screening of diabetic nephropathy in type 2 diabetes patients. Biocatal Agric Biotechnol. 2019;21(101316):101316. DOI:10.1016/j.bcab.2019.101316.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. Eur J Echocardiogr. 2006;7(2):79-108. DOI:10.1016/j.euje.2005.12.014
16. Oh J, Park S, Nagueh S. Advances in cardiovascular imaging: established and novel clinical applications of diastolic function assessment by cardiography. Circ Imaging 2011;4(4):444–55. DOI:10.1161/CIRCIMAGING.110.961623
17. Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, et al. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. Diab Vasc Dis Res. 2018;15(6):477-93. DOI:10.1177/1479164118787415.
18. Patil V, Patil H, Shah K, Vasani J, Shetty P. Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. Cardiovasc Dis Res. 2011;2(4):213–22. DOI 10.4103/0975-3583.89805.
19. Liu J, Robbins D, Palmieri V. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes. J Am Coll Cardiol. 2003;41(11):202228. DOI:10.1016/s0735-1097(03)00403-0.
20. Baykan M, Erdogan T, Erem C, Hacihasanoglu A, Gedikli O, Kucukosmanoglu M, et al. The relationship between flow-mediated dilatation and left ventricular function in type 2 diabetic patients with microalbuminuria. Endocrine. 2006;30(2):197-202. DOI:10.1385/ENDO:30:2:197.
21. Mishra US, Soumya Ranjan P, Shrabani P. Evaluation of left ventricular function in type-2 diabetes mellitus with microalbuminuria. J Evid Based Med Healthc. 2020;7(8):385-89. DOI:10.18410/jebmh/2020/83.
22. Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. J Am Heart Assoc. 2014;3(3):e000789. DOI:10.1161/JAHA.114.000789.
23. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation. 2009;120(9):802-9. DOI:10.1161/CIRCULATIONAHA.109.869602.
24. Aljaroudi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. Circulation. 2012;125(6):782-8. DOI:10.1161CIRCULATIONAHA.111.066423

Author's Contribution

MM designed the study, collected the data, drafted the manuscript, and gave final approval. BB conceived the idea, analyzed the data, and contributed to drafting the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.