Evaluation of Left Ventricular Function in Type-2 Diabetes Mellitus with Microalbuminuria

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ABSTRACT

BACKGROUND
This study intends to assess the left ventricular function in patients with type-2 diabetes mellitus with microalbuminuria and investigate whether any relationship exists between severity of microalbuminuria and duration of diabetes.

METHODS
Type-2 DM patients fulfilling the inclusion and exclusion criteria were subjected to test for Urine Albumin-to-Creatinine Ratio (UACR) using Combilyzer13 strips. Echocardiographic assessment was done using standard criteria in those patients who were positive for microalbuminuria. Statistical analysis was performed using chi-square test, t-test, and correlation test using SPSS software.

RESULTS
102 patients out of 408 selected Type-2 DM patients were positive for microalbuminuria. UACR was positive in 25% of the studied population with male-29% and female-19%. Microalbuminuria was significantly associated with male sex ($p<0.05$). The age range in the study group was 42-68 years (mean 54.44 years), the duration of the disease was from 8-22 years (mean 14.70 years). BMI in the study group was from 18.54 to 38.62 (mean 27.78). The mean values of the lipid profile were Cholesterol-232.34 mg/dL, TG-188.53 mg/dL, HDL 29.39 mg/dL, VLDL 60.38 mg/dL, LDL 159.31 mg/dL which shows an atherogenic lipid profile in the study population. The mean values of FBS and PPBS were 135.90 mg/dL and 221.75 mg/dL respectively. HbA1c had ranges from 5.1 to 9.2 (mean 6.55). LV diastolic and systolic dysfunction was observed in 43.14% and 38.24% of patients respectively. Global LV dysfunction was noted in 8.82% of subjects. Systolic dysfunction showed significant correlation with severity of microalbuminuria and duration of disease with p values <0.01 each. Diastolic dysfunction also showed significant correlation with duration of diabetes ($p<0.01$) and severity of microalbuminuria.

CONCLUSIONS
Left ventricular dysfunction occurs in Type-2 DM with microalbuminuria. It correlates well with both severity of microalbuminuria and duration of diabetes.

KEYWORDS
T2DM, UACR, EF, E/A Ratio, IVRT, DT

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BACKGROUND

Diabetes mellitus is a major public health problem globally. It is one of the top five leading causes of death in most developed countries. It has now emerged as an important public health problem in Asia and particularly South East Asia region. It causes death from coronary artery disease, cerebrovascular disease and end stage renal disease. It perpetuates endless suffering from peripheral artery disease, non-traumatic lower extremity amputation, retinopathy leading to blindness and peripheral neuropathy. Diabetes mellitus is an ice-berg disease. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. It caused 1.5 million deaths in 2012. Higher-than-optimal blood glucose caused an additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Diabetes will be the world's seventh largest killer by 2030.[1]

According to the Lancet study,[2] India is among the top three countries with a high number of diabetic population. The numbers climbed dramatically in India from 11.9 million in 1980 to 64.5 million in 2014. Diabetes is India's fastest growing disease: 72 million cases recorded in 2017, figure expected to nearly double by 2025. India currently represents 49 percent of the world's diabetes burden countries with a high number of diabetic population. Cardiovascular system is one among the worst affected organ system in diabetes mellitus with increased incidence of Angina pectoris, myocardial infarction and congestive cardiac failure. In diabetic population, congestive cardiac failure in the absence of coronary artery disease, hypertension, valvular heart disease or alcoholism is now a well-established clinical entity. Microalbuminuria is a marker of generalised endothelial dysfunction and vasculopathy. It may be a predictor of cardiovascular dysfunction in the same way as for nephropathy. The study intends to assess left ventricular function in patients with Type-2 Diabetes Mellitus with microalbuminuria and to investigate whether any relationship exists between the duration of diabetes and severity of microalbuminuria.

METHODS

This cross-sectional study was conducted in the Department of General Medicine, M.K.C.G. Medical College, Berhampur over a period of 2 years reflecting south Odisha demography. Cases were selected from those attending Medicine OPD as well as those admitted to the Medicine indoor. Diagnostic criteria of ADA 2016 was followed. Cases with clinical diagnosis of Type-2 Diabetes Mellitus were subjected to confirmation of diagnosis according to inclusion criteria. The established cases of Type-2 Diabetes Mellitus who were under treatment and follow up were directly included in the study.

Inclusion Criteria

According to the diagnosis criteria laid down by the expert committee set up under the sponsorship of ADA Standards of Medical Care in Diabetes (2016).[3]

Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no calorie intake for at least 8h.

or

Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

or

HbA1c ≥6.5% the test should be performed in a laboratory using a method that is NGSP certified and standardised to DCCT assay.

or

In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, random blood glucose concentration ≥200 mg/dL (11.1 mmol/L). Random is defined as any time of the day without regard to time since last meal.

Exclusion Criteria

Patients with hypertension, ischemic heart disease, valvular heart disease, chronic renal failure, urinary tract infections, proteinuria, severe anaemia were excluded from the study.

A total of 408 cases were selected after considering the inclusion criteria and exclusion criteria. Patients with Type-2 DM fulfilling the inclusion and exclusion criteria were subjected to Urine Albumin-to-Creatinine Ratio (UACR). Immunologic assay for UACR was done using Combina13 strips manufactured by Human Diagnostics Ltd. Echocardiographic assessment was done using standard criteria in those patients who were positive for Microalbuminuria (UACR). Detailed history was taken, meticulous physical examination including fundoscopy was done and relevant investigations were carried out. Echocardiographic assessment of left ventricular function (2D and M mode) was done with commercially available ultrasound system (HDI 1500). Subjects were examined in the supine position using standard parasternal, short-axis, and apical views. All recordings and measurements were obtained by the same observer. Criteria of American society of Echocardiography were used for assessing LV systolic and diastolic dysfunction.

Criteria used for Assessing LV Systolic Dysfunction[4] viz.

- LV Ejection fraction less than 50%.

Criteria used for assessing LV diastolic dysfunction[5] viz.

- E/A ratio
- Deceleration time (DT)
- Isovolumic Relaxation Time (IVRT)
- During Valsalva E/A

The method used for EF estimation was Teichholz Method. Pre-Valsalva E/A and during Valsalva E/A was measured. The Valsalva manoeuvre was done by asking patients to blow sphygmomanometer where >30 mmHg was sustained for 10 sec during which readings were taken.[6]

Stages of Diastolic Dysfunction

Parameters	Normal	Stage I (Impaired Relaxation)	Stage II (Pseudo Normal)	Stage III (Restrictive Filling-Reversible)	Stage IV (Restrictive Filling-Irreversible
E/A Ratio	0.9-1.5	<0.90	0.9-1.5	>1.8	>2.0
E/A with Valsalva	Both E, A dec., ratio unchanged	Both E, A dec., ratio unchanged	E decreases, A increases, ratio reverses	Ratio decreases but still >1	No response
IVRT (ms)	70-90	>90	60-90	<70	<70
DT (ms)	140-240	>240	140-200	<140	<130

The recorded and calculated values of all the parameters in the study group were statistically analysed. Linear regression method was used to find out the correlation among variables. The significance between different groups and means were calculated by students' unpaired t-test and 'p' values were ascertained. Frequencies were calculated by using Chi-square test. X^2 value was observed and 'p' value calculated. The result was accepted to be statistically significant, when p value was <0.05. SPSS software was used to calculate these values and graphs.

RESULTS

408 cases of Type-2 diabetes mellitus were selected after exercising inclusion and exclusion criteria. Urine Albumin-to-Creatinine Ratio (UACR) was found to be positive in 102 cases. UACR was positive in 25% of the studied population with male-29% and female-19%. Microalbuminuria was significantly associated with male sex. (p value <0.05). The age range in the study group was 42-68 years (mean 54.44 years). The duration of the disease was from 8-22 years (mean 14.70 years). BMI in the study group was from 18.54 to 38.62 (mean 27.78). The mean values of the lipid profile were-Cholesterol-232.34 mg/dL, TG-188.53 mg/dL, HDL 29.39 mg/dL, VLDL 60.38 mg/dL, LDL 159.31 mg/dL which shows an atherogenic lipid profile in the study population. The mean values of FBS and PPBS were 135.90 mg/dL and 221.75 mg/dL respectively. HbA1c had ranges from 5.1 to 9.2 (mean 6.55).

The maximum number of cases were from age group 46-55 years and less in age group <45 and >65. In the study group male outnumber the female with M:F=2:1. Majority of study population was having UACR 30-60 mg/g (31%) and least having >120 mg/g (11%). 90.2% of the cases were having LV dysfunction. Diastolic dysfunction was encountered in majority of the cases (43% of total cases). It was more marked in patients with UACR 30-60 mg/g. Systolic and global dysfunction was predominant in patients with UACR 91-120 mg/g.

Age Group (in years)	Male		Female		Total	
	n	%	n	%	n	%
<45	1	1.47	0	0	1	0.99
46-55	32	47.09	23	67.6	55	53.92
56-65	33	48.5	11	32.4	44	43.13
>65	2	2.94	0	0	2	1.96
Total	68	100	34	100	102	100

Table 1. Age & Sex Distribution of Study Group

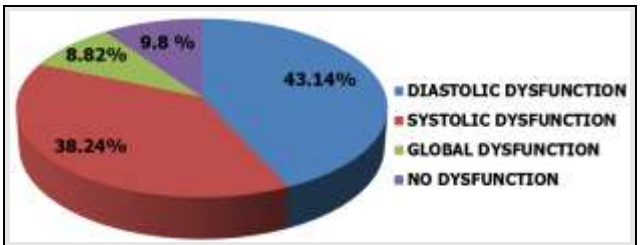

Figure 1. Distribution of Study Group According to LV Function

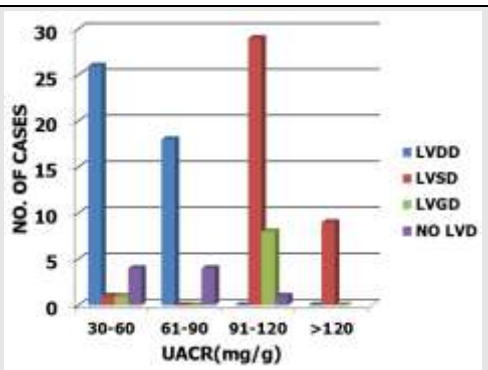

Figure 2. Distribution of LV Function According to Microalbuminuria (UACR)

UACR(mg/g)	Duration (yr.)	
	Mean	Standard Deviation
30-60	12	2
61-90	14	1
91-120	16	1
>120	19	2

Table 2. Severity of Microalbuminuria and Duration of Diabetes

Parameters of LV Dysfunction	UACR (mg/g)				p
	30-60	61-90	91-120	>120	
EF (%)	59±4	54±2	46±4	43±7	0.000
Pre Valsalva E/A	0.99±0.18	1.48±0.35	1.03±0.16	1.28±0.04	0.020
During Valsalva E/A	0.85±0.11	1.24±0.51	1.03±0.16	1.28±0.04	0.001
IVRT (ms)	84±14	74±7	108±18	77±6	0.028
DT (ms)	210±43	165±25	233±27	179±9	0.047

Table 3. Parameters Of LV Dysfunction and Severity 0f Microalbuminuria

The mean value of ejection fraction (EF) decreased with increasing severity of microalbuminuria. The correlation of severity of microalbuminuria with EF was statistically very much significant (p<0.001). The association of severity of microalbuminuria with diastolic dysfunction was also statistically very much significant (p<0.001). Diastolic dysfunction was evident in patients with UACR 30-90 mg/g. Duration of diabetes was significantly correlated to both LV systolic and diastolic function with p value <0.001 each. There was definite correlation between microalbuminuria and duration of diabetes (r=0.82, p<0.001). Mean values of

all components of lipid profile were higher in LV dysfunction. Statistically cholesterol and triglyceride were found to be significantly associated with LV dysfunction (p value for both chol. and TG <0.05). BMI was higher in LV dysfunction. Higher BMI was found to be significantly related to LV dysfunction (p<0.05).

DISCUSSION

The distribution of left ventricular function in the study group, indicates left ventricular dysfunction in significantly higher number of cases (90.2%). This may be explained by the fact that microalbuminuria in our study group may contribute to increased left ventricular dysfunction. In the study by Rao MS et al.[7] (1996), diastolic dysfunction and systolic dysfunction were observed in 56% and 23% cases respectively. Nilul Panchal et al.[8] in their study observed LV systolic dysfunction in 36% of diabetic patients and diastolic dysfunction in 76% of diabetic patients. In our study, left ventricular diastolic dysfunction was more common than systolic dysfunction (diastolic dysfunction in 43.14% cases, systolic dysfunction in 38.24% cases) which is consistent with the previous studies.[9-10]

Left ventricular dysfunction was observed with only isolated diastolic dysfunction at UACR 30-60 mg/g to global dysfunction at UACR 91-120 mg/g. Rutter M. K. et al.[11] in their case control study involving 58 age and sex matched cases concluded that left ventricular dysfunction was more common and more severe in those cases with microalbuminuria. Guglielmi MD et al[12] also had similar observation in their study and concluded that microalbuminuria was associated with significant changes in left ventricular morphology and more severe impairment of cardiac function. Hanna DB et al[13] in their study found that higher urine albumin-to-creatinine ratio (UACR) was associated with cardiac dysfunction in the general population.

The association of microalbuminuria with left ventricular dysfunction can be well explained by the fact that microalbuminuria is a marker of extensive endothelial dysfunction and generalized vasculopathy.[14-15] It reflects renal and systemic transvascular albumin leakage that is perhaps due to low vessel wall content of heparan sulphate. It has been seen not only in glomerular basement membrane but also in coronary arteries. This generalized increase of vascular permeability can cause leakiness of collagen, cholesterol and advanced glycated end products that have been reported in the myocardium of human hearts. These tissue alterations can increase end diastolic myocardial stiffness as well as alter normal systolic functions. The change in permeability causing insudation of lipoproteins into the intima can cause atherosclerosis of small arterioles of heart.

Microalbuminuria was associated with significant changes in left ventricular morphology and more severe impairment of cardiac function. Elevated UACR, even at high-normal levels, was significantly associated with left ventricular dysfunction. A strong correlation between severity of microalbuminuria and left ventricular dysfunction has been well established by various studies.[16,17] With increasing severity of microalbuminuria left ventricular function have been reported to deteriorate. A longer duration of prediabetes and diabetes in adults may be associated independently with the development of subclinical atherosclerosis and left ventricular systolic and diastolic dysfunction later in life according to a study conducted by Reis JP et al.[18] Kim JJ et al.[19] also had similar observations in their study.

CONCLUSIONS

Left ventricular dysfunction in Type-2 DM with microalbuminuria correlates well with duration of diabetes and severity of microalbuminuria. Albuminuria, even at low levels, is associated with LV diastolic dysfunction. This emphasizes the value of UACR in risk stratification and preventive strategies. Therefore periodic screening for microalbuminuria could help in early identification of cardiovascular disease.

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