

Correlation of Left Ventricular Dysfunction with Severity of Microalbuminuria in Type 2 Diabetes Mellitus.

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Abstract:

Background: To study the left ventricular(LV) function in Type 2 Diabetes mellitus patients having no other known risk factors of myocardial dysfunction and to find out its correlation with severity of microalbuminuria.

Methods: In this prospective observational study Type 2 DM patients fulfilling the inclusion and exclusion criteria were subjected to Micral test . Those patients who were positive for microalbuminuria (n=62) underwent Echocardiographic assessment of left ventricular systolic and diastolic function .The severity of left ventricular dysfunction was statistically correlated with the severity of microalbuminuria .

Results: Total number of patients in the study group were 62.(male 39 and female -23).The age range in the study group was 46-66 years (mean-53.7 years).The mean duration of the disease was 14.5 years(9-18 years).Mean BMI among the subjects was 27.17(21.05 to 36.89). The mean values of lipid profile were Total cholesterol 217 mg/dl, TG 188mg/dl, HDL-29.4 mg/dl, VLDL- 60 mg/dl and LDL- 159 mg/dl. Subjects with microalbuminuria in the range of 20mg/dl, 50mg/dl ,100mg/dl and 150 mg/dl were 18%,31%, 40% and 11% respectively.Majority of cases with LV dysfunction were above 50 years of age (81% of cases were >51 years).LV diastolic dysfunction was noted in 46% of cases and systolic dysfunction in 19% cases. 11% of patients had global LV dysfunction. The mean values of Ejection Fraction(EF) were from 61.12±5.11 to 43.00±2.16, mean value of cardiac output (CO) were from 4.11±0.27 to 3.11±0.4. Mean values of Isovolumic relaxation time (IVRT) were from 108±9.9 to 116.43±7. and deceleration time(DT) from 232 ± 11.58 to 241 ± 12. The ejection fraction, fractional shortening and cardiac output were decreasing with increasing severity of microalbuminuria from 20mg/dl to 150 mg/dl with statistically significant values (P < 0.001, P < 0.001 and P <0.001 respectively) . similarly E - point septal separation, Isovolumic relaxation time, Deceleration time and A/E ratio linearly increasing with severity microalbuminuria with P values <0.01, < 0.001, < 0.001, and < 0.001 respectively.

Conclusions:Left ventricular dysfunction occurs in Type 2 DM and the severity of dysfunction well correlates with severity of microalbuminuria.

Keywords: Cardiomyopathy, Diastolic dysfunction, Systolic dysfunction, Microalbuminuria, Nephropathy.

I. Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by hyperglycemia as a result of either absolute or relative insulin deficiency arising from insulin resistance or progressive deterioration of beta cell function. Diabetes mellitus has become a global epidemic with increasing prevalence worldwide especially for populations in Asia and among young people. The prevalence of DM is estimated to increase from 382 million in the year 2013 to 592 million by the year 2035.¹ This is mostly attributable to rise in the incidence of Type 2 DM which represents about 90-95% of all diabetes mellitus cases.

Cardiovascular diseases is the leading cause of death among individuals with diabetes mellitus .Individuals with Type 2 DM have a three to four fold increased risk of cardiovascular disease related mortality when compared with healthy counterparts.² Patients with Type 2 DM might have as high a risk of myocardial infarct as persons without Type 2 DM but with prior history of Myocardial infarction.³ Though the pathophysiology of atherosclerosis is mostly similar in people with diabetes and without diabetes mellitus, unique characteristics related to insulin resistance and hyperglycemia substantially increases the risk of cardiovascular disease and heart failure in Type 2 Diabetes mellitus.¹

Studies have found that diabetes mellitus produces functional, biochemical and morphological myocardial abnormalities independent of coronary atherosclerosis and hypertension. These abnormalities may result in impaired left ventricular diastolic function, contributing importantly to heart failure with normal systolic function.⁴ This points to a mechanism other than macrovascular damage as the pathogenesis process and probably the microvascular damage in myocardial vasculature in a similar manner as occurs in retina, kidney and peripheral nerves . Diabetic nephropathy is an important Chronic microvascular complication of diabetes mellitus and one of the hallmark of diabetic nephropathy is the development of proteinuria which usually follows progressive deterioration of renal function.⁵Development of diabetic nephropathy is a major risk

factor for cardiovascular disease⁶ and the phenomenon of microalbuminuria in Type 2 DM is predictive of future development of nephropathy and End stage renal disease. Microalbuminuria is an early marker of glomerular injury and is extensively used as a sensitive test for the detection of kidney dysfunction in diabetic patients prior to development of overt proteinuria. Various studies have indicated that microalbuminuria is a marker of widespread microvascular damage like nephropathy, neuropathy and retinopathy.⁷⁻¹⁰ we have tried to find out the correlation of microalbuminuria with other complication like cardiovascular dysfunction.

II. Material and Methods

The study was carried out over a period of 2 years as a prospective observational study. Cases were selected both from out-patient Dept. as well as indoor patients. Cases of Type 2 DM were diagnosed according to the diagnostic criteria of ADA(2000). Both newly diagnosed and old cases of Type 2 DM on treatment and follow up were considered. Those patients with Hypertension, Ischemic heart disease, Valvular heart disease, Chronic renal failure, anemia and overt proteinuria were excluded from the study. After exercising the exclusion criteria 251 cases both male and female were selected for detection of microalbuminuria by Micral test. Micral test is a semiquantitative immunologic dipstick test manufactured by Boehringer Mannheim Ltd. It gives immediate and reliable semi quantitative estimate of microalbuminuria in urine. It is able to detect low concentration of urine albumin with sensitivity and specificity of 96.7% and 71% respectively. The test consists of immersing the test strip into freshly voided urine sample for 5 seconds and matching the colour of the test strip with colour code provided over the test strip container. The albumin content of urine considered around 20mg/dl, 50 mg/dl and 100mg/dl as per its match with the respective colour codes.

Those patients who came out to be positive for microalbuminuria were taken for final study. Detailed history was taken, a thorough physical examination including fundus examination was done and relevant investigations were carried out. Echo-cardiographic assesment of left ventricular function (2D and M Mode) was done with commercially available ultrasound system(HDI 1500). All recordings and observations were carried out by the same observer according to the recommendations of American society of Echocardiography. Particular attention was given to record the LV size and systolic function and the LV Diastolic function by Doppler recording of the LV filling velocities. Criteria of American society of Echocardiography were used for assessing LV systolic dysfunction. The parameters considered were LV ejection fraction less than 50%, Percentage Fractional Shortening less than 36%, E-Point septal separation more than 7 mm and cardiac output less than 3 lit/min. Mayo clinic criteria were used for detecting LV Diastolic dysfunction. The echocardiographic parameters used were A velocity higher than E velocity on PW mitral Doppler, A/E ratio greater than 1, Deceleration time more than 240 m sec, IVRT more than 110 m sec on dual M-mode echo of aortic and mitral valve recorded simultaneously.

The recorded and calculated values of all parameters were statistically analyzed using Microsoft Excel software. Linear regression method was used to find out correlation among variables. Significance between different groups and means were calculated by Students unpaired T –test. Chisquare test was used to calculate frequencies of parameters.

III. Result

After careful consideration of inclusion and exclusion criteria a total of 251 patients were considered for detection of microalbuminuria by Micral test out of which 62 patients (25%) showed positive result and were taken up for final study with a male to female ratio of 1.6:1. There was no significant sex difference in the prevalence of microalbuminuria. The age range in the study group (n=62) was 46-66 years (mean age 53.7 years). The duration of the disease in the study population was from 9-18 years (mean 14.5 years). The BMI in the study group ranges from 21.05 to 36.89(mean 27.17). The mean values of lipid profile were LDL 159mg/dl, TG-188mg/dl, HDL-29.4mg/dl which shows an atherogenic lipid profile in the study group. Majority of the study population were having moderate range microalbuminuria (50mg/L and 100 mg/L combinedly accounting for 71% of the cases. Only 18% were below 20mg/L and 11% were above 150 mg/L. 76% of the study population were having LV dysfunction and diastolic dysfunction was observed in majority of cases(46% of the total cases). Number of patients with LV systolic or diastolic dysfunction were maximum at albuminuria range of 50mg/dl (40% of total population.)

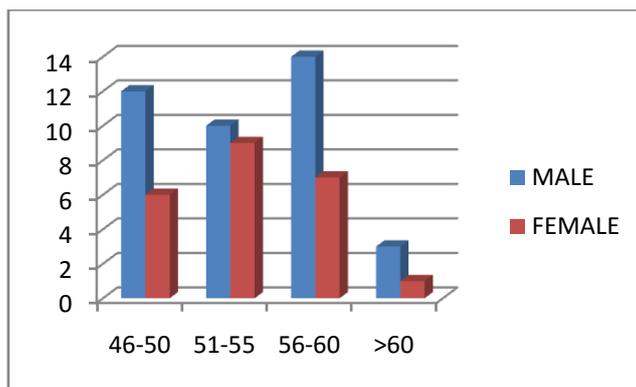


Fig.1 .Age and sex distribution of study group (n=62)

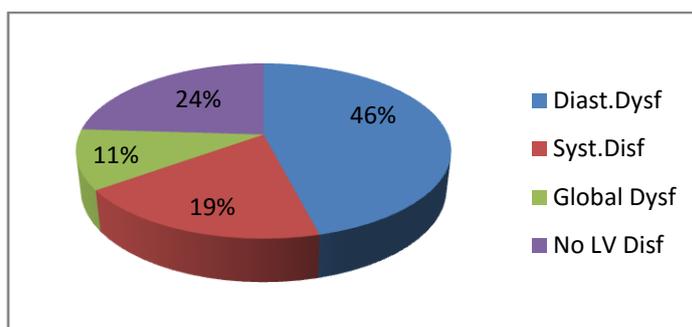


Fig 2. LV Dysfunction among study population

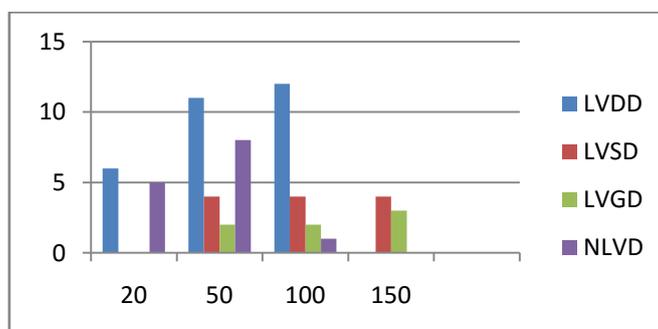


Fig 3. Distribution of LV dysfunction according to severity of albuminuria (LVDD: LV diastolic dysfunction,

LVSD: LV systolic dysfunction, LVGD: LV Global dysfunction, NLVD: No LV Dysfunction)

Table1. Distribution of parameters of LV systolic and diastolic dysfunction with increasing severity of microalbuminuria

Parameters of LV dysf.	Severity of microalbuminuria				"p"
	20mg/dl	50mg/dl	100mg/dl	150mg/dl	
EF±SD	61.12±5.11	55.7±8.86	53.00±8.43	43.00±2.16	<0.001
FS±SD	41.39±2.36	39.8±6.64	38.2±4.03	33.91±1.2	<0.001
EPSS±SD	5.95±1.21	7.59±2.47	7.21±1.92	9.5±2.06	<0.01
CO±SD	4.11±0.27	3.81±0.56	3.66±0.67	3.11±0.49	<0.001
IVRT±SD	108±9.9	112.3±9.64	114.34±8.18	116.43±7.0	<0.01
DT ± SD	232 ± 11.58	242 ± 7.25	250 ± 7.4	241± 12.24	<0.01
A/E ± SD	0.94±0.16	1.04±0.16	1.05±0.15	0.89±0.17	<0.01

As shown in the Table- 1 the mean values of EF decreasing from 61.12±5.11 to 43.00±2.16 with increasing severity of microalbuminuria. and mean cardiac output decreasing from 4.11±0.27 to 3.11±0.49 with increasing level of microalbuminuria from 20 mg/dl to 150 mg/dl. The correlation of decreasing ejection fraction, fractional shortening and cardiac output with severity of microalbuminuria was found to be statistically very much significant ("P"<0.001).

Similarly parameters of left ventricular diastolic function were also found to be deteriorating with increasing severity of microalbuminuria as shown in the table. Mean values of Isovolumic relaxation time

(IVRT) increasing from 108 ± 9.9 to $116.43 \pm 7.$, deceleration time(DT) from 232 ± 11.58 to 241 ± 12.24 with increasing level of microalbuminuria from 20 mg/dl to 150 mg/dl. Change in parameters of left ventricular function with increase in severity of microalbuminuria was statistically significant with “p” values for IVRT, DT and A/E ratio being <0.01 , <0.01 and <0.01 respectively.

IV. Discussion

Microalbuminuria is considered as a marker of widespread microangiopathy. so in diabetic subjects with microalbuminuria ,microvascular complications in different organs are anticipated and are established by various workers. The heart in diabetic patients suffer both macrovascular and microvascular complications in the form of coronary atherosclerosis as well as cardiomyopathy. Here in this study we have tried to establish the correlation of increasing severity of microalbuminuria with left ventricular systolic as well as diastolic dysfunction.

In our study out of 251 patients 62 patients (25%) came out to be positive for microalbuminuria. This is in accordance with observation of many other workers including Gupta et al-26%¹¹, Alzaid AA et al-7.6% to 42% in different population¹², Lamba et al-33.93%⁹, Raman et al-25%¹⁰ and Allqwi et al 27% .¹³

Left ventricular function in Type 2 DM patients has been investigated by various researchers and all have reported LV dysfunction of variable extent. Rao MS et al in their study comprising of 30 adult Type 2 DM subjects observed the left ventricular diastolic and systolic dysfunction in 56% and 23% cases respectively.¹⁴ Zabalgotia M (2001) in their study of 86 normotensive Type 2 DM cases observed LV diastolic dysfunction in 47% cases.¹⁵ Porier P et al and Redfield MM et al have also noted left ventricular diastolic dysfunction in 32% and 52% cases respectively in their study.¹⁶ In our study LV diastolic dysfunction was observed more frequently than systolic dysfunction (46% and 19% respectively) which is consistent with observations of other workers like Rao MS et al.

In our study Left ventricular function is deteriorating from only isolated diastolic dysfunction at 20 mg/dl range to global dysfunction at 150 mg/dl rage. Isolated systolic dysfunction cases were maximum in 100 mg/L range. This observation correlates with the findings of Liu JE et al¹⁷ in the Strong Heart Study, which evaluated the left ventricular systolic and diastolic function in 1576 Type 2 DM patients comprising 685 non albuminuric ,519 microalbuminuric and 372 macroalbuminuric cases. They have observed a step-wise deterioration of left ventricular diastolic and systolic function from non-albuminuric group to macroalbuminuric group and have concluded that microalbuminuria is independently associated with worse systolic and diastolic function. Rutter M.K. et al.¹⁸ 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 al¹⁹ 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. These observations supported by the observation in Table –1 of our study which show that ejection fraction, fractional shortening and cardiac output are decreasing with increasing severity of microalbuminuria with statistically significant values ($P < 0.001$, $P < 0.001$ and $P < 0.001$ respectively) . similarly E - point septal separation, Isovolumic relaxation time, Deceleration time A/E ratio linearly increasing with severity of microalbuminuria with P values <0.01 , <0.001 , <0.001 , and <0.001 respectively)

This association of microalbuminuria with left ventricular dysfunction can well be explained by the fact that microalbuminuria is a marker of extensive endothelial dysfunction and generalised vasculopathy. It reflects renal and systemic transvascular albumin leakage that is perhaps due to low vessel wall content of heparan sulfate that has been shown 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 alteration 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. In addition, loss of heparan sulfate proteoglycan from the plasma membrane of endothelial cells, which is having anti-thrombotic property leads to formation of microthrombi and occlusion of small vessels of heart. Small vessel disease can lead to subendocardial ischemia causing systolic and diastolic myocardial dysfunction. Liu JE et al.¹⁷ in their study also have given a similar conclusion.

V. Conclusion

Diabetes mellitus is sometimes regarded as a vascular disease with both macro and microvasculature in different organs being the target of injury. Microalbuminuria which is considered as a marker of incipient nephropathy also correlates well with complications in other organs like heart .Further , various studies including our study have proved that severity of microalbuminuria very much correlates with the severity of myocardial (left ventricular) dysfunction. so microalbuminuria can be considered as a surrogate of left ventricular function.

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