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Original Article

Left ventricular systolic and diastolic dysfunction in asymptomatic, normotensive type 2 diabetes mellitus

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ABSTRACT

Diastolic dysfunction has been described as an early sign of diabetic heart muscle disease preceding the systolic damage. The present study was taken up with an objective to evaluate systolic and diastolic dysfunction in asymptomatic normotensive type 2 diabetes mellitus patients. Left ventricular function was evaluated by m-mode, 2-D echo and colour Doppler studies was done in 50 cases and compared with 50 age- and sex- matched controls. All the investigations were within normal limits except mean Fasting blood glucose of 142 ± 9.94 and post-prandial blood sugar of 226 ± 18.61. In systolic function the mean ejection fraction (EF) was 63.12 ± 6.19 and mean fractional shortening was 35.42 ± 5.03. The EF was < 50% in 3 (6%) patients, but was asymptomatic. The mean E/A ratio was 0.95 ± 0.10 and 26 (52%) had E/A ratio of < 1 as compared to 24 (48%) > 1%. The mean isovolumetric relaxation time was 87.94 ± 20.36, and mean DT of E was 180.68 ± 34.64. Left ventricular diastolic dysfunction (LVDD) is much more common than previously reported in subjects with well controlled type 2 diabetes mellitus that are free of clinically detectable heart disease.

Key Words: Left ventricular diastolic dysfunction; Left ventricular systolic dysfunction; Ejection fraction; E/A ratio; isovolumetric relaxation time; DT of E

INTRODUCTION

Diabetes mellitus is a disease known to mankind for the past 2500 years. The term Diabetes mellitus which in Greek, means "to run through" or "Siphon", was first coined by Arataeus of Cappadocia in 2nd century AD as a generic description for conditions causing increased urine output [1-3].

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion and/or insulin action, which is modulated by genetic, HLA and environmental factors resulting in micro and macroangiopathy. It often runs in families. It is associated with decrease in insulin production or utilization, resulting in body's inability to utilize nutrients appropriately. Various genetic and environmental factors influence the etiology and prognosis of diabetes. Important differences in the types and frequency of Diabetes mellitus and its complications have been reported between countries as well as ethnic and cultural groups. Diabetes mellitus was formerly considered a disease of affluent. It has now become apparent that increase in Diabetes mellitus is due to demographic changes, cultural transition and population ageing, urbanization, increased consumption of refined foods, westernization, sedentary habits and over nutrition [4,5].

Diabetes mellitus has become a leading cause of premature death, disability and high health care costs. It is a silent killer disease. The World Health Organisation estimates that the disease burden of Diabetes mellitus world over would be more than 500 million in 21st century. Indians are genetically more susceptible to Diabetes mellitus compared to other races. Indians settled abroad also show increased prevalence to Diabetes mellitus indicating that environmental factors also play a role in incidence of diabetes. India will have the largest number of diabetic subjects in the world by 2025 and one out of 5 diabetic subjects in the world will be an Indian. India is going to be the "Diabetic capital of the world" [4,5].WHO has estimated that

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the number is likely to be 5.72 crore by 2025. The rapid increase in population, increased longevity and high ethnic susceptibility to diabetes, coupled with rapid urbanization and changes from traditional lifestyles will most likely trigger a diabetes mellitus epidemic [4,5].

Subclinical abnormalities of left ventricular function are recognized in both Type 1 and Type 2 diabetes mellitus. Studies using Doppler echocardiography have confirmed the findings of abnormal diastolic function as an early indicator of cardiac involvement in asymptomatic patients with Type 1 or Type 2 diabetes mellitus [6].

Diabetic subjects have been reported to develop congestive heart failure in the absence of coronary heart diseases, hypertension or any known structural heart disease [7]. The term 'diabetic cardiomyopathy' has been introduced for this condition. It has been suggested that microangiopathic lesions of the myocardium, altered composition and fibrosis of myocardial interstitium and accumulation of lipids in myocardial cells are involved in pathogenesis of diabetic cardiomyopathy [8,9].

This study was taken up with an objective to identify the systolic and diastolic dysfunction in normotensive asymptomatic type 2 diabetes mellitus patient to recognize the early involvement of heart.

MATERIALS AND METHODS

All patients with history of type 2 diabetes who were attending to Krishnarajendra (KR) and combined hospital, Government Medical College, Mysore were considered for the study during the period from April 2004 to March 2006. Informed consent was taken prior to their enrolment. Simple Random Sampling method was used to select the subjects and they were divided into two groups. Group I consisted of 50 cases with Type 2 Diabetes mellitus and Group II consisted of 50 healthy persons who were age and sex matched to serve as controls. All patients were evaluated for the left ventricular systolic and diastolic dysfunction. The study group included both outpatients as well as in-patients. Patients with history of hypertension, coronary artery disease and with any other acquired or congenital heart disease causing systolic and diastolic dysfunction were excluded from the study. Subjects with thyroid disorder, overt renal disease, cor-pulmonale, heart failure secondary to any cause or any other disease/disorders interfering with the cardiac function were also excluded from the study. The relevant information was recorded in a pre-tested proforma. After taking detailed history, thorough clinical examination was done according to the proforma and the following investigations were done –FBS, PPBS, Blood urea, Serum creatinine, Serum cholesterol, Glycated hemoglobin, ECG in all 12 leads, fundus examination, TMT, Echocardiography.

2D echocardiography, M-mode and colour Doppler examination were done by Agilent Image Point (Hewlett Packard) machine with 2.5 to 5 mHz probes. All recordings were done with patients in supine and left lateral position. The transducer was placed in the left parasternal, apical and subcostal areas of chest and the parasternal long axis and short axis were taken to record various dimensions and measurements. At least three recordings with their mean were taken. For the systolic and diastolic function of the left ventricle echocardiographic measurements were done in four chamber view. To assess the left ventricular systolic function, Fractional shortening (FS) and Ejection fraction (EF) were considered. Fractional shortening is the percent change in left ventricular cavity dimensions. Normal values of FS are 28 to 42%. In the present study FS < 25% was taken as significant systolic dysfunction. Ejection fraction represents ratio of stroke value to end-diastolic volume. Normal values are 62-85%. In the present study, EF < 50% was taken as significant.

Diastolic function of left ventricle is best assessed by evaluating the mitral in flow velocity curves (MIVC) by Echo-Doppler techniques. In this study the following parameters were used to assess LV diastolic dysfunction.

1. Mitral 'E' velocity (Peak velocity of early mitral flow)
2. Mitral 'A' velocity (Peak velocity of late (atrial) mitral flow)
3. Mitral E/A ratio (Normal 1-2)
4. Isovolumic relaxation time (IVRT) (Normal 60-100 msec)
5. Deceleration time of mitral 'E' curve (DT of E) (Normal 150-200 msec)

Mitral flow velocities were measured by pulsed wave Doppler with sample volume placed between the leaflet tips.

Statistical analysis was done by using percentages, mean values, standard deviation, standard error, χ^2 test (Chi-square test) (with Yates correction), t-test (unpaired) and proportion tests. The level of significance used was 0.05 level for the corresponding degree of freedom to draw the inference. p-value < 0.05 was considered statistically significant and p > 0.05 was considered as not statistically significant.

RESULTS

In the present study, LV systolic function was assessed by using ejection fraction and fractional shortening as important parameters through m-mode and 2D echocardiography, left ventricular ejection fraction and fractional shortening was calculated and analyzed. Figures 1-2 depicts the age and sex distribution between the cases and controls respectively. Figure 3 shows the duration of diabetes and Figure 4 shows the blood pressure control compared between the two groups.

The mean glycated hemoglobin of Group I was 7.4800 ± 0.6465 and t-test value 1.601. The mean glycated hemoglobin of Group II was 5.46 ± 0.7879 with p value of < 0.01, which is statistically significant. About 60% (30 cases) of the patients had poor control as shown in Table-1.The mean BMI of Group I was 26.080 ± 1.74 and t-values show 11.188 and p-value (2 tailed) shows statistically significance 0.002. The mean BMI of Group II was 22.056 ± 1.84. Mean BMI in diabetic group is more than that of controls as evident from Table-2. Tables 3-6 shows the serum glucose levels, lipid profile, serum urea and serum creatinine levels compared between the two groups. ECG had been taken in all the patients and was within normal limits. TMT was done in 21 diabetic patients who presented with history of chest pain which is not typical of angina. However, all 21 diabetic patients in the study group were negative for inducible ischemia. Tables 7-11 shows the comparison of the echocardiographic parameters while Figure -5 shows the ejection fraction % compared between the two groups.

DISCUSSION

Epidemiological data indicate a greater risk of cardiovascular morbidity and mortality particularly heart failure, in diabetic patients compared to non-diabetic patients. Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease and left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy. Several studies have shown the evidence of left ventricular systolic and diastolic dysfunction in asymptomatic, normotensive, type 2 diabetic patients. However, the exact causes and mechanisms remain unclear. Previous studies suggest that impairment of diastolic function of left ventricle, i.e. its filling abnormalities are far more common than systolic dysfunction [10].

The mitral E shows mean of 67.32 ± 6.22, mitral A shows mean of 70.72 ± 7.42. E/A ratio shows mean of 0.95 ± 0.10 with p-value of 0.001 which is statistically significant. 26 patients had E/A ratio of < 1 constituting 52% of study group. 24 patients had E/A ratio > 1. E/A < 1 is very sensitive and specific indicator of LV diastolic dysfunction. In the present study more than half of the patients had LV diastolic abnormalities in spite of relatively normal LV systolic function and absence of cardiac symptoms. The present study is comparable to that of some previous researchers who showed the mean E/A ratio of 0.72 ± 0.13, 0.9 ± 0.2 and 0.95 ± 0.29, respectively [11-13]. Few studies reported that diabetics who had normal ejection fraction had evidence of diastolic dysfunction in the form of decreased E/A ratio [14,15]. They too found that LV fractional shortening was normal in all subjects who had decreased E/A ratio among diabetics.

In the present study, the late atrial filling wave (A) was significantly increased, probably due to elevated LV filling pressure secondary to impaired relaxation among diabetic individuals. The diastolic abnormalities in diabetic patients most likely to indicate reduced LV compliance secondary to small vessel disease, infiltrative myocardial process, metabolic derangement or a combination of the three.

The prolongation of IVRT more than 100 msec is a significant indicator of early LV diastolic dysfunction. In the present study, 26 patients had IVRT of > 100. All these patients also had E/A ratio of < 1. IVRT was within normal range in 21 patients and it was < 60 msec in 3 patients who also had coexisting LV systolic dysfunction with ejection fraction of < 50%. Similar results were seen in previous studies where diabetic patients had greater isovolumetric relaxation time [15,16].

Prolongation of DT of E more than 200 msec is a significant indicator of early LV diastolic dysfunction. In the present study, DT of E was > 200 msec in 23 (46%) patients. All these patients had E/A < 1 and IVRT > 100 msec suggestive of early diastolic dysfunction. 25 patients (50%) had DT of E between 150 msec to 200 msec. Two patients had DT of E < 150 msec suggestive of severe LV diastolic dysfunction. Both these patients had coexisting LV systolic dysfunction also. In the present study, echocardiographic evidence of LV diastolic dysfunction among asymptomatic type 2 diabetes mellitus patient was recognized in more than 50% of patients and systolic dysfunction was seen in 6% of patients.

Conventional echocardiography is a simple test to detect early LVDD in type 2 diabetes mellitus patients. Alteration of E/A ratio < 1 is a sensitive and specific indicator of early diastolic dysfunction.LV systolic dysfunction was also seen in a small number of asymptomatic normotensive

Type 2 DM which may point towards high prevalence of silent cardiac muscle disease in asymptomatic Type 2 DM. LV diastolic dysfunction is a marker of evolving heart disease among diabetics.

However this study has its limitations. Diagnosis of diastolic dysfunction by conventional Doppler was limited value in the setting up of elevated end diastolic pressure and apparently normal transmitral flow velocity. This could have been overcome by performing Doppler study during Valsalva maneuver or by tissue Doppler imaging which could have given much better results than conventional Doppler. The coronary artery disease was excluded by patients' history, ECG and TMT (selected patients). However, the invasive procedure like angiography and non-invasive procedure like scintigraphy was not done in the present study.

To conclude, LV diastolic dysfunction in asymptomatic normotensive patients with type 2 DM without evidence of coronary heart disease is significantly higher than previously suspected. Conventional echocardiography is a simple economical test for detecting LV dysfunction in type 2 normotensive, asymptomatic, diabetes mellitus patients.

Table 1: Showing diabetic status as determined by glycated hemoglobin (ADA 2006)

Control	Group I	Group II
Normal (4-6%)	-	50 (100%)
Good (< 7%)	4 (8%)	-
Fair (< 7-8%)	16 (32%)	-
Poor (> 9% and above)	30 (60%)	-
Total	50 (100%)	50 (100%)

Table 2: Comparison of body mass index (WHO criteria) between two groups

BMI (kg/m^2)	Group I	Group II
< 18.5 (Under weight)	-	-
18.5-24.9 (Normal)	14 (28%)	47 (94%)
25-29.9 (Over weight)	34 (68%)	3 (6%)
30-39.9 (Obese)	2 (4%)	-
≥ 40 (Morbid)	-	-
Total	50 (100%)	50 (100%)

Table 3: Comparison of blood sugar (FBS and PPBS) between two groups

	Group I	Group II
FBS	142.4 ± 9.94	102.62 ± 6.09
PPBS	226 ± 18.61	151.68 ± 9.13

Table 4: Comparison of Blood urea between two groups

	Group	Mean	Standard Deviation	Standard Error Mean
Blood urea	Group I	31.82	5.0858	0.7192
	Group II	31.70	5.0800	0.7184

Table 5: Comparison of Serum creatinine between two groups

	Group	Mean	Standard Deviation	Standard Error Mean
Serum creatinine	Group I	0.8820	0.1410	1.994
	Group II	0.8660	0.1423	2.012

Table 6: Comparison of Lipid profile between two groups

	Group	Mean	Standard Deviation	Standard Error Mean
Total cholesterol	Group I	192.30	15.4104	2.1794
	Group II	175.88	14.7560	2.0868
Total glycerides	Group I	122.04	15.7958	2.2339
	Group II	119.68	9.3665	1.3246
HDL	Group I	38.98	3.2039	0.4531
	Group II	40.54	2.2876	0.3235

	t-test for equality of means			
	t	df	Significance (2-tailed)	Mean difference
Total cholesterol	5.442	98	0.000	16.42
Triglyceride	0.909	98	0.366	2.36
HDL	-2.802	98	0.006	-1.56

Table 7: Comparison of Ejection Fraction (%) between two groups

	Ejection fraction < 50%	Ejection fraction > 50%
Group I	3 (6%)	47 (94%)
Group II	-	50 (100%)

Table 8: Comparison of Fractional shortening (%) between two groups

		Group I	Group II	p-value
Factional shortening	< 25%	7 (14%)	-	0.041^{NS}
	> 25%	43 (86%)	50 (100%)	
Total		50 (100%)	50 (100%)	

	Group	Mean	Standard Deviation	Minimum	Maximum
Fractional shortening	Group I	35.42	5.0390	21	46
	Group II	37.02	4.2402	28	48

Table 9: Comparison of Diastolic parameters between two groups

	Group	Mean	Standard Deviation	Standard Error Mean
Mitral E	Group I	67.32	6.22	0.8799
	Group II	74.84	4.95	0.7001
Mitral A	Group I	70.72	7.42	1.0502
	Group II	62.88	6.52	0.9226

	Group	Mean	Standard Deviation	Minimum	Maximum
E/A	Group I	0.9578	0.1020	0.83	1.31
	Group II	1.2045	0.1680	1.00	1.63

		Group I	Group II
E/A ratio	< 1.0	26 (52%)	-
	> 1.0	24 (48%)	50 (100%)
Total		50 (100%)	50 (100%)

Table 10: Comparison of Isovolumetric Relaxation Time (IVRT) between two groups

	Group	Mean	Standard Deviation
IVRT (msec)	Group I	87.94	20.3675
	Group II	77.84	4.1471

		Group I	Group II
IVRT (msec)	< 60 msec	3 (6%)	-
	60-100 msec	21 (42%)	50 (100%)
	100+ msec	26 (52%)	-
Total	50 (100%)	50 (100%)	50 (100%)

Table 11: Comparison of Deceleration Time of E (DT of E) between two groups

	Group	Mean	Standard Deviation	Minimum	Maximum
DT (msec)	Group I	180.68	34.6460	200	232
	Group II	156.18	17.1627	154	225

		Group I	Group II
DT of E (msec)	< 150 msec	2 (4%)	-
	150-200 msec	25 (50%)	50 (100%)
	> 200 msec	23 (46%)	-
Total		50 (100%)	50 (100%)

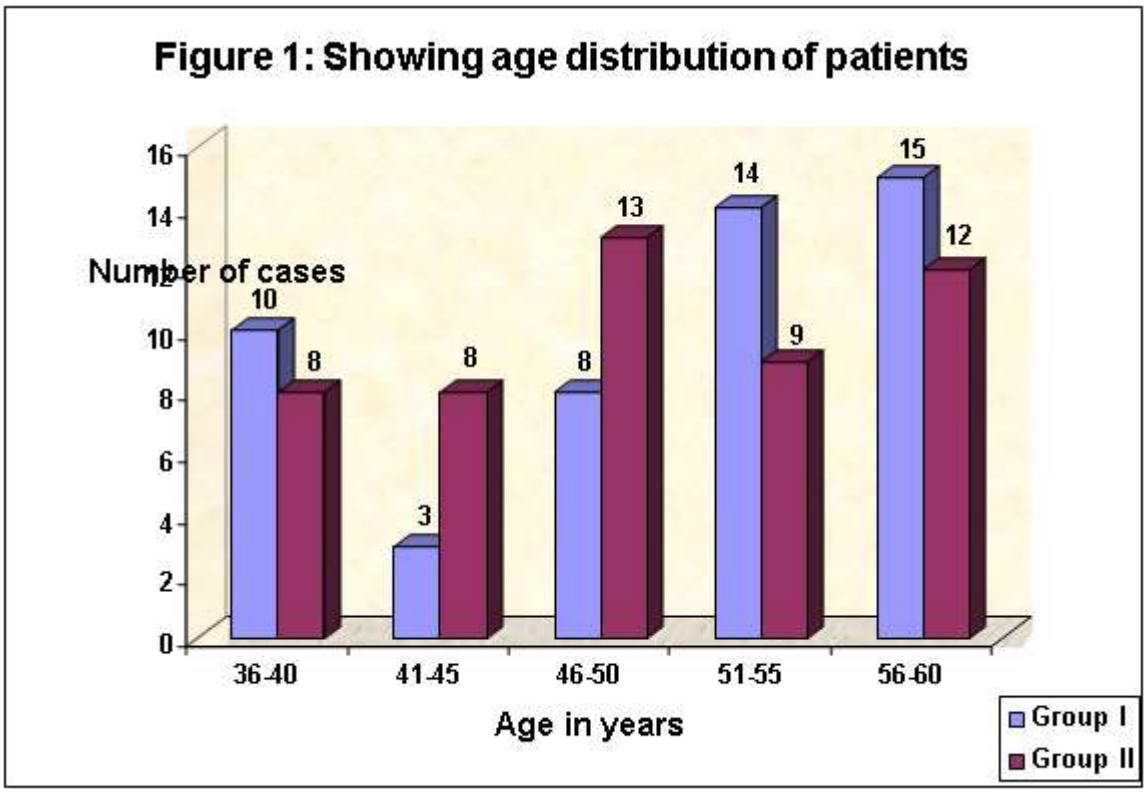
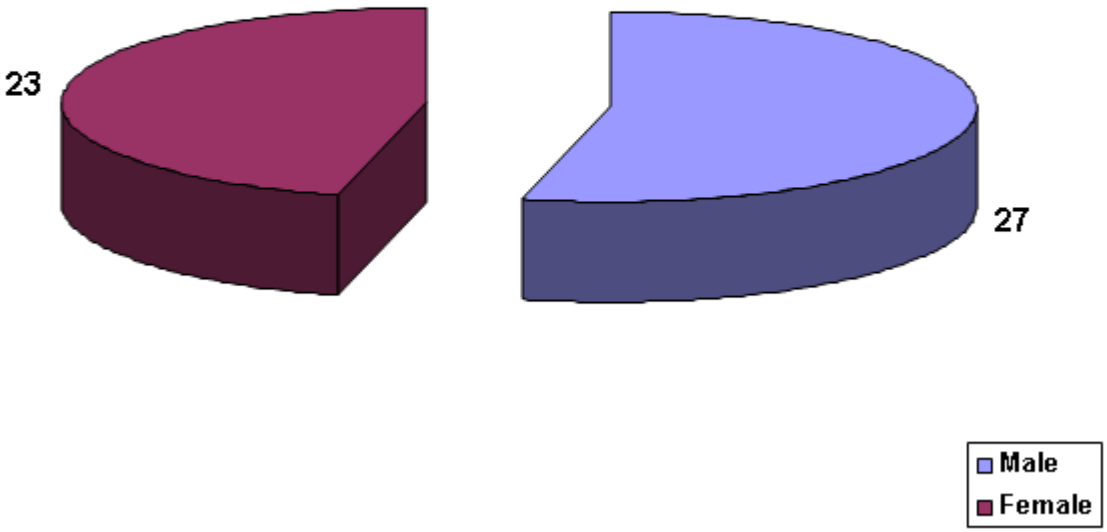


Figure 2: Showing sex distribution of patients



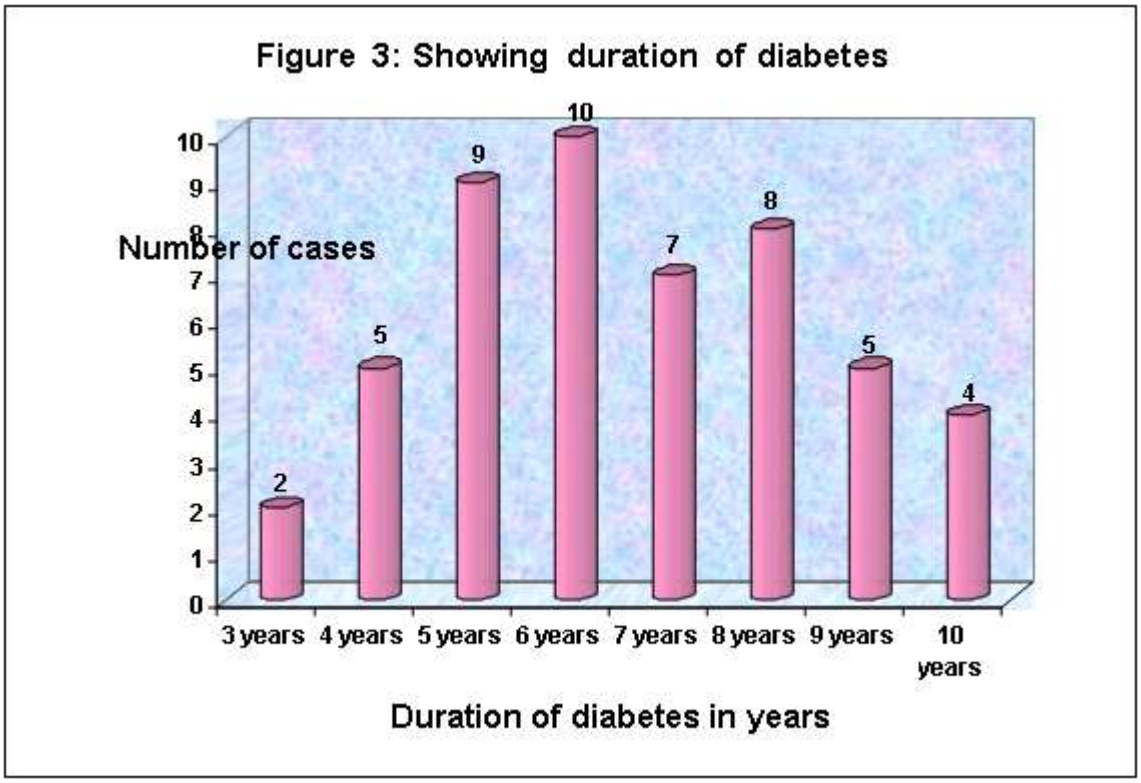


Figure 4: Showing blood pressure in diabetic patients and control

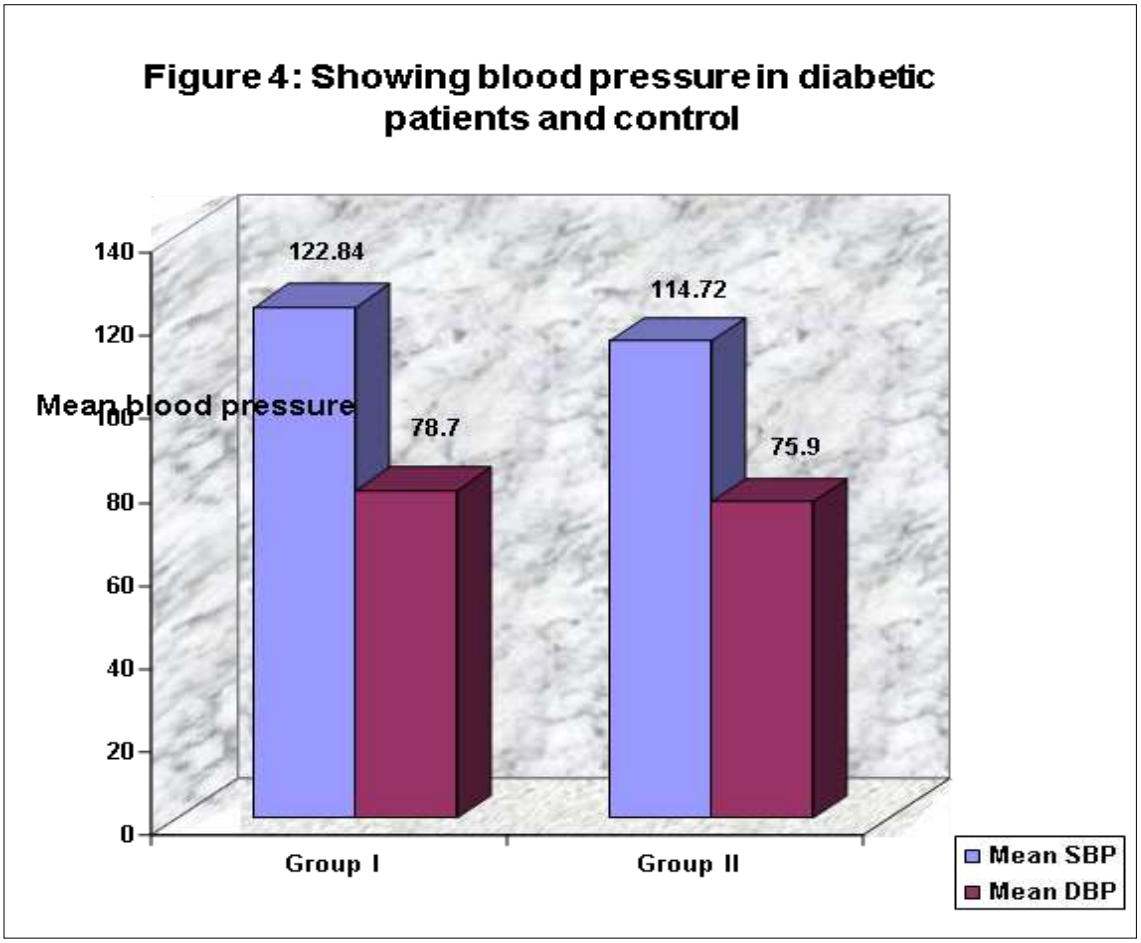
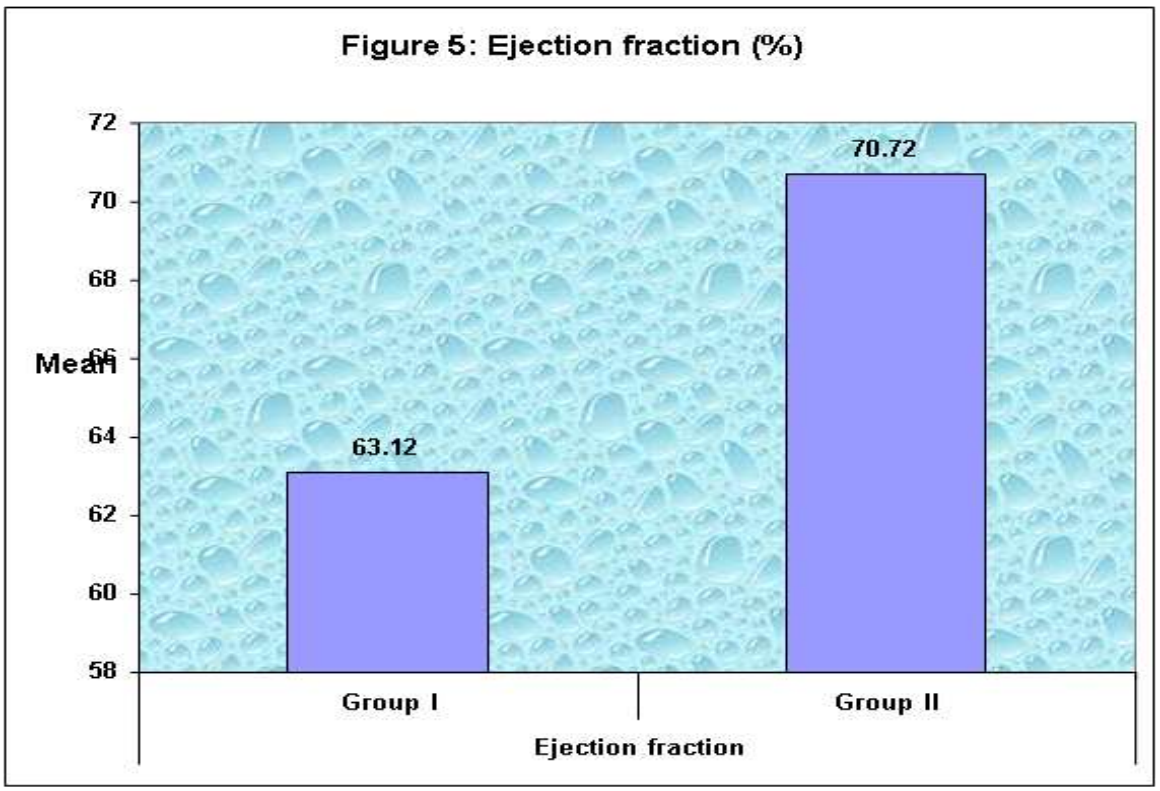


Figure 5: Ejection fraction (%)



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