Original Article

The Impact of Hyperglycemia on Left Ventricular Function in Type 2 Diabetic Patients

Kunal Thakkar[1], Ritvik Agrawal[2], Pankaj Tanti[3], R P Agrawal[4]

[1,2,3]Senior Resident, [4]Senior Professor, Department of Medicine, SP Medical College and Associated Group of Hospitals, Bikaner, Rajasthan

ABSTRACT

Introduction: There is an increasing recognition that diabetic patients suffer from an additional cardiac insult other than coronary artery disease termed 'diabetic cardiomyopathy' leading to 'ventricular dysfunction'. Some studies also suggested that poor glycemic control adversely affects left ventricular (LV) function. The purpose of this study was to find out the impact of glycemic control on LV function in type II diabetes mellitus patients, which may suggest possible underlying mechanisms and may be of clinical importance in planning preventive and therapeutic strategies.

Methodology: The study was conducted on 100 consecutive type 2 diabetic patients of age group 40 to 65 years, admitted in SP Medical College and Associated Group of Hospitals. Ischemic Heart Disease (IHD) patients were examined clinically and 2D echocardiography was done. LV dysfunction and its severity was graded as mild, moderate and severe for systolic dysfunction and grade I, grade II, grade III, grade IV for diastolic dysfunction. All routine blood investigations, fundus examination, biothesiometry and other necessary examinations were performed. Multifactorial ANOVA test and univariate and multivariate stepwise regression analyses were used to find out association between different variables.

Results: The mean values of glycated hemoglobin (HbA_1C) for moderate and severe LV systolic dysfunction were 9.08% and 9.60% respectively ($p<0.001$). The mean values of HbA_1C for grade I, grade II, grade III and grade IV were 6.72%, 7.36%, 8.70% and 9.68% respectively ($p<0.001$). Correlation of systolic and diastolic dysfunction with different variables shows that all the variables had highly significant differences with systolic function like BMI, duration of diabetes, serum creatinine, triglyceride, HDL, LDL, VLDL and HbA_1C ($p<0.001$). Correlation of diastolic dysfunction with different variables also shows that BMI, LDL and HbA_1C had highly significant correlation with diastolic function ($p<0.001$), while duration of diabetes, serum creatinine, triglyceride, total cholesterol, HDL, VLDL were significantly correlated with diastolic dysfunction ($p<0.05$).

Conclusion: Poor glycemic control in type II diabetic patients is significantly associated with LV systolic and diastolic dysfunction. Various factors like the extent of duration of diabetes and dyslipidemia are also significantly associated with LV systolic and diastolic dysfunction in type II diabetic patients.

INTRODUCTION

Cardiovascular disease is responsible for 80% of deaths among diabetic patients, much of which has been attributed to coronary artery disease (CAD). However, there is an increasing recognition that diabetic patients suffer from an additional cardiac insult termed 'diabetic cardiomyopathy' leading to 'ventricular dysfunction'.[1] This entity was originally described in 1972 on the basis of observations in four diabetic patients who presented with heart failure (HF) without evidence of hypertension, CAD, valvular or congenital heart disease. The increasing recognition of this additional cardiac insult is supported by data from epidemiological, molecular and more refined diagnostic studies.

Diabetic left ventricular (LV) dysfunction is a disorder of the cardiac muscles in people with diabetes. It can lead to inability of the heart to circulate blood through the body effectively, a state known as heart failure, leading to develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalization, a poor quality of life and a shortened life expectancy. Most heart failures in people with diabetes result from coronary artery disease, and

diabetic cardiomyopathy is only said to exist if there is no coronary artery disease to explain the heart muscle disorder.

The Framingham study demonstrated the increased incidence of congestive HF in diabetic males (2.4:1) and females (5:1) independent of age, hypertension, obesity, CAD and hyperlipidemia.[2] Other prospective studies also show that diabetic patients have a significantly increased lifetime risk of developing HF[3], and increased mortality from both Q-wave and non-Q-wave myocardial infarction.[4,5] This suggests that there is an additional insult to diabetic myocardium which predisposes it to more extensive damage and subsequent failure. A study has shown a link between idiopathic cardiomyopathy and diabetes.[6] In contrast with the 4–6% prevalence of diabetes in the community, the over representation of diabetic patients in HF trials such as Studies of Left Ventricular Dysfunction (SOLVD)[7] (26%) Assessment Trial of Lisinopril and Survival (ATLAS)[8] (19%) and Vasodilator-Heart Failure Trial II (V-HeFT II)[9] (20%) attests to the increased prevalence of this condition among diabetic patients.

A prospective, open-label, follow up study to investigate whether good glycemic control had favorable effects on subclinical LV dysfunction and coronary flow reserve (CFR) was conducted in 2014.[10] It was concluded that diabetics with poor and good glycemic control were comparable with respect to echocardiographic parameters reflecting subclinical LV dysfunction, and good glycemic control did not affect these parameters, however good glycemic control improved CFR. Owing to lack of such studies in Indian population; this study aimed to find out effects of hyperglycemia on left ventricular function in type II diabetes mellitus patients.

METHODS

The study was conducted on 100 consecutive type 2 diabetic patients in age group of 40 to 65 years admitted in SP Medical College and Associated Group of Hospitals. 18 patients, who were subsequently found to be either hypothyroid and/or having ECG signs of IHD were excluded. Remaining 82 patients were examined clinically and 2D echocardiography was done.

Patients with past history of hypertension, IHD and with other major co-morbidities were excluded.

All the patients were examined systematically. Baseline investigations were done which included complete blood count, blood urea, serum creatinine, HbA_1C, serum lipid profile, liver function tests, ECG, chest X- ray, serum electrolytes, biothesiometry. Detailed history regarding their present illness, total duration of diabetes and other significant past, family and personal history were recorded.

Statistical analysis was performed with SPSS software (version 10.0; SPSS Inc., Chicago, IL, U.S.A.). Differences between groups were tested for significance using $\chi 2$ test. Analyses of univariate and multiple stepwise linear regression were performed to define the most important correlates of LV dysfunction. Multifactorial ANOVA test was used to study the independent effects of different variables on left ventricular systolic and diastolic function.

RESULTS

All patients (100%) were having diabetes for >10 years. Mean duration of diabetes for moderate and severe LV systolic dysfunction was 15.0 and 16.7 years respectively. Mean duration of diabetes for grade I, grade II, grade III and grade IV diastolic dysfunction was 7.73, 7.11, 9.94 and 12.0 years respectively.

In this study, out of 82 patients, 11 patients were having systolic dysfunction and all of had BMI⩾ 30 kg/m2. Mean BMI was 33.87 and 36.86 kg/m^2 for moderate and severe LV dysfunction, respectively.

Difference between obese and non-obese individuals in relation to LV systolic dysfunction was statistically highly significant ($p<0.001$) (Table 1).

Among patients with diastolic dysfunction, mean BMI was 25.9, 25.77, 32.9 and 35.3 kg/m^2 for patients with grade I, grade II, grade III and grade IV respectively. Difference between obese and non-obese individuals in relation to LV diastolic dysfunction was also statistically highly significant ($p<0.001$) (Table 2).

In our study, out of 11 patients LV systolic dysfunction four had moderate and seven had severe LV systolic dysfunction. All patients were having HbA_1C >8%. Mean HbA_1C for moderate and severe LV systolic dysfunction was 9.08% and 9.60% respectively. It shows that HbA_1C >8% is definitely a strong risk factor for LV systolic dysfunction and increasing level of HbA_1C beyond that is also definitely associated with increasing severity of LV systolic dysfunction. The difference between level of HbA_1C in relation to LV systolic dysfunction was statistically highly significant ($p<0.001$) (Table 3).

Table 1: Distribution of cases according to systolic dysfunction in relation to BMI

BMI (kg/m^2)	Systolic Dysfunction									
	Normal		Mild		Moderate		Severe		Total	
	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%
<18.5	0	-	0	-	0	-	0	-	0	-
18.5-24.99	17	23.9	0	-	0	-	0	-	17	20.7
25-29.99	45	63.4	0	-	0	-	0	-	45	54.9
≥30	9	12.7	0	-	4	100	7	100	20	24.4
Total	71	100	0	-	4	100	7	100	82	100
Mean	27.13		-		33.87		36.86			
SD	3.58		-		3.54		1.84			
p	<0.001									

(n) = Number

Table 2: Distribution of cases according to diastolic dysfunction in relation to BMI

BMI (kg/m^2)	Diastolic Dysfunction											
	Normal		Grade I		Grade II		Grade III		Grade IV		Total	
	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%
<18.5	0	-	0	-	0	-	0	-	0	-	0	-
18.5-24.99	8	26.7	6	40	3	21.4	0	-	0	-	17	20.7
25-29.99	18	60	8	53.3	10	71.4	8	47.1	1	16.7	45	54.9
≥30	4	3.3	1	6.7	1	7.1	9	52.9	5	83.3	20	24.4
Total	30	100	15	100	14	100	17	100	6	100	82	100
Mean	26.65		25.9		26.77		32.09		35.3			
SD	3.23		2.75		3.05		4.52		4.34			
p	<0.001											

(n) = Number

Table 3: Distribution of cases according to systolic dysfunction in relation to HbA_1C

HbA_1C (gm%)	Systolic Dysfunction									
	Normal		Mild		Moderate		Severe		Total	
	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%
<7	29	40.8	0	-	0	-	0	-	29	35.4
7-8	25	35.2	0	-	0	-	0	-	25	30.5
>8	17	23.9	0	-	4	100	7	100	28	34.1
Total	71	100	0	-	4	100	7	100	82	100
Mean	7.39		-		9.08		9.6			
SD	1.01		-		0.31		0.37			
p	<0.001									

(n) = Number

Mean HbA_1C for grade I, grade II, grade III and grade IV diastolic dysfunction were given in table 4. The difference between levels of HbA_1C in relation to LV diastolic dysfunction was also statistically highly significant (p<0.001)(Table 4).

On applying ANOVA test, all the parameters had highly significant correlation with systolic dysfunction and diastolic dysfunction like BMI, duration of diabetes, serum

Table 4: Distribution of cases according to diastolic dysfunction in relation to HbA_1C

HbA_1C (gm%)	Diastolic Dysfunction											
	Normal		Grade I		Grade II		Grade III		Grade IV		Total	
	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%
<7	15	50	9	60	5	35.7	0	-	0	-	29	35.4
7-8	10	33.3	6	40	7	50	2	11.8	0	-	25	30.5
>8	5	16.7	0	-	2	14.3	15	88.2	6	100	28	34.1
Total	30	100	15	100	14	100	17	100	6	100	82	100
Mean	7.38		6.72		7.36		8.7		9.68			
SD	1.1		0.49		0.72		0.54		0.23			
p	<0.001											

(n) = Number

creatinine, HDL, VLDL, LDL, triglyceride, total cholesterol and HbA_1C ($p<0.001$).

Mean HDL for moderate and severe systolic dysfunction was 35.5 and 29.0 mg/dl, respectively. Mean HDL for grade I, grade II, grade III and grade IV diastolic dysfunction were 43.2, 45.3, 39.0 and 34.3 mg/dl respectively. The difference between LV systolic and diastolic dysfunction in relation to serum HDL level was statistically significant ($p<0.05$). Similarly mean LDL for moderate and severe LV systolic dysfunction were 146.5 and 169.1 mg/dl, respectively. While mean LDL for grade I, grade II, grade III and grade IV diastolic dysfunction were 97.0, 99.7, 125.0 and 151.5 mg/dl, respectively. Difference between serum LDL level in relation to LV systolic and diastolic dysfunction was statistically highly significant ($p<0.001$) (Figure 1 and 2).

DISCUSSION

In this study, out of 82 patients, 11 patients were having systolic dysfunction and all of them belonged to BMI $\geqslant$ 30 kg/m^2 out of which 7 patients were having severe and 4 patients were having moderate LV systolic dysfunction (Table1). Kistorp et al[11], reported that BMI has a very strong impact on asymptomatic LV systolic and diastolic function in diabetics. Kuznetsova et al [12] observed that BMI was associated with diastolic dysfunction in 539 out of 2150 patients from the general community in Europe. However, the prevalence of diastolic dysfunction was much lower (25%), the mean BMI was significantly smaller than that in our study (26%) and with virtually no patients with BMI $\geqslant$35 kg/m^2(Table 2).

It has been reported by From et al[13] that a history of type 2 diabetes mellitus lasting $\geqslant$ 4 years was independently associated with the presence of LV dysfunction, both systolic and diastolic, with the subsequent development of overt HF and with increased mortality. Our observations regarding extent of duration of studies and associated with LV dysfunction.

In the study, it was observed that, dyslipidemia is a very strong risk factor for LV systolic and diastolic dysfunction. In a study by Wang et al[14] covering 114 consecutive diabetic patients, a significant positive

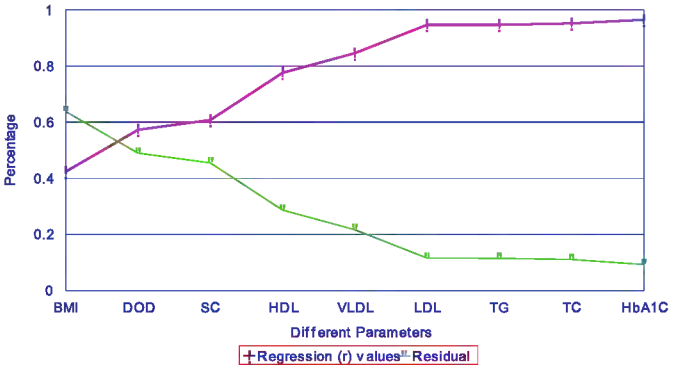

Figure 1: Different parameters in relation to systolic dysfunction

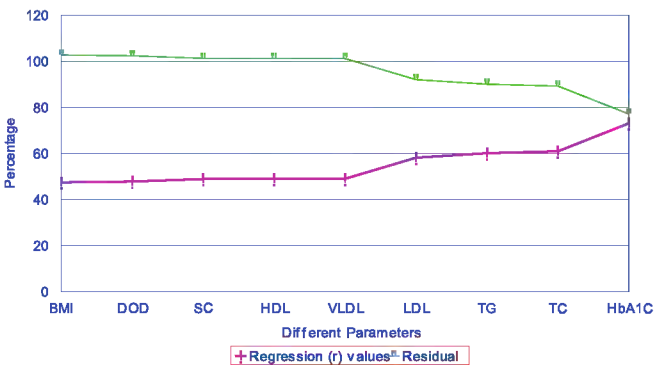

Figure 2: Different parameters in relation to diastolic dysfunction

correlation between serum high-density lipoprotein (HDL) cholesterol and left ventricular ejection fraction (LVEF) ($r=0.49$, $p<0.0001$) was found. Patients in the lower tertile of serum HDL cholesterol had a significantly lower mean LVEF than those in the upper tertile. Stepwise multiple linear regression analysis revealed that LVEF significantly correlated with HDL cholesterol ($p<0.0001$). Moreover, this correlation remained significant even in patients with normal coronary angiograms, suggesting HDL cholesterol might influence left ventricular systolic performance through extra-atherosclerotic mechanisms. In another study by Vinereanu et al[15] seventy subjects had echocardiography at rest and during dobutamine stress. Resting longitudinal systolic function correlated inversely with low-density lipoprotein–cholesterol (correlation coefficient $r=-0.53$), glycated hemoglobin ($r=-0.48$), age ($r=-0.41$) and diastolic blood pressure ($r=-0.38$) ($p<0.05$). They also concluded that patients with type II diabetes and no clinical heart disease have impaired subendocardial function of the left ventricle at rest and peak stress, which is related to glycated hemoglobin and serum low-density-lipoprotein cholesterol.

Various studies by Poirier et al[16], Fang et al[17], Hansen et al[18] and Astorri et al[19] have confirmed the findings of our studies using traditional echocardiographic assessment of global diastolic function that early diastolic filling of the left ventricle is reduced in diabetes mellitus patients. However, study by Poirier et al[16], global diastolic dysfunction failed to correlate with HbA_1C. A study by D Vinereanu et al[15] showed from both univariate and multivariate analyses that HbA_1C correlates inversely with longitudinal systolic velocities, and thus may be an important determinant of it. This hypothesis had also been tested by other investigators[18] but they were unable to demonstrate a relationship probably because they studied patients with better average glycemic control and a narrower range of results in their study (mean HbA_1C 7.4–7.9% compared with 9.2 %). They concluded that patients with type 2 diabetes have subclinical subendocardial dysfunction both at rest and peak stress, which correlates with the overall glycemic control of diabetes (HbA_1C), lipid profile (LDL–cholesterol), diastolic blood pressure and age. The research may be extended with large sample size by performing coronary angiography,radionuclide scanning, contrast echocardiography etc.

CONCLUSION

Poor glycemic control in type II diabetic patients is significantly associated with LV systolic and diastolic dysfunction. Various factors like the extent of duration of diabetes and dyslipidemia are also significantly associated with LV systolic and diastolic dysfunction in type II diabetic patients.

Limitations : There were a few limitations to the study. This was a single centre study. It was cross-sectional in design and therefore, a cause and effect relationship determination was not possible.

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Corresponding Author

Dr R P Agrawal, Senior Professor Department of Medicine, S P Medical College and Associated Group of Hospitals, Bikaner.

email: drrpagrawal@yahoo.co.in