Glycosylated Hemoglobin (HbA1c) is a reliable Predictor of left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction (LVDD) in newly diagnosed type 2 diabetic patients of western Uttar Pradesh

Sanjeev Kumar[1], G K Aneja[2], Arvind Trivedi[3], V Atam[4], Abhishek Singh[5], Neetu Verma [6]Ajay Panwar[7], Pradeep Kumar[8]

[1] Senior Resident, Department of Medicine, K GM U, Lucknow,
[2] Professor and Head, Department of Medicine, LLRM, Medical College, Meerut
[3] Professor, Department of Medicine, LLRM, Medical College, Meerut.
[4] Professor, Department of Medicine, K G M U, Lucknow .
[5] Assistant Professor Department of Medicine, , K G M U, Lucknow.
[6] MBBS Student, GSVM Medical College Kanpur, UP
[7] Senior Resident, Department of Neurology, K GM U, Lucknow .
[8] Professor, Department of Physiology, K GM U, Lucknow.

Abstract- Cardiovascular diseases like congestive heart failure, coronary artery disease, myocardial infarction account for highest mortality in diabetic patient. Left ventricular hypertrophy which is an ominous prognostic sign and independent risk factor for cardiac events is often present along with left ventricular diastolic dysfunction (LVDD) in type 2 diabetes mellitus patients. the aim of the present study is to verify whether HbA1c detect pre-clinical diastolic dysfunction in type-2 diabetic patients. Total 100 patients of newly diagnosed type 2 diabetes mellitus were selected for this cross sectional study. Patients of age between 30 to 60 yrs were selected for the study. HbA1C was estimated by Boronate affinity chromatography. Left ventricular hypertrophy was detected by measuring left ventricular mass index (LVMI) using Transthoracic Echocardiography, according to recommendation of American Society of Echocardiography (ASE). HbA1c is seems to be reliable predictor of LVDD. Our Study demonstrated a very significant positive correlation between level of glycosylated hemoglobin(HbA1C) and frequency of LVH and LVDD in the newly diagnosed cases of type 2 diabetes mellitus. Similar correlation was also observed with FPG.

Index Terms- Glycocylated Hemoglobin Left ventricular dysfunction

I. INTRODUCTION

Diabetes mellitus is a worldwide health problem, afflicting millions in both developed and developing countries[1]. Moreover, there is emerging evidence that a diabetes-related syndrome called Syndrome-X (characterized by truncal obesity, insulin resistance, diabetes, high blood pressure and premature coronary artery disease) [2] is the most important cause for the rapidly increasing urban menace of coronary artery disease afflicting urban middle and upper classes. Cardiovascular diseases like congestive heart failure, coronary artery disease, myocardial infarction account for highest mortality in diabetic patient[3, 4]. Left ventricular hypertrophy which is an ominous prognostic sign and independent risk factor for cardiac events is often present along with left ventricular diastolic dysfunction (LVDD) in type 2 diabetes mellitus patients[5] .The possible contribution of hyperinsulinemia and hyperglycemia to left ventricular mass have been suggested in normotensive diabetic patient[6]. Echocardiography provides a reliable non invasive tool for detection of LVDD and left ventricular mass and has been proven more sensitive method for detection of left ventricular hypertrophy[7] than other techniques. Left ventricular mass in diabetic patients may also increases with the HbA1C level[8, 9]. So a poor glycemic control is also associated with more chances of having left ventricular hypertrophy[10]. Hence, the aim of the present study is to verify whether HbA1c detect pre-clinical diastolic dysfunction in type-2 diabetic patients.

II. METHODS

Study population

This was a cross sectional study conducted at the L.L.R.M. Medical College, Meerut during 2012–2013 **.**All patients with type 2 diabetes mellitus who are attending Medicine OPD, Endocrinology OPD, were included in the study who fulfilled the following inclusion criteria.(Age > 30 years & < 60 years , Patient who gave written informed consent, Mentally and physically fit up to a minimum level required to participate in study and patients with newly diagnosed type 2 diabetes mellitus (with in 1 month) according to WHO criteria and ADA recommendations for diabetes mellitus[11])

The Exclusion criteria were: those who were unable to provide informed consent, any substance abuse, mental illness or

medical condition that in opinion of investigator would make it difficult to participate in intervention and Patient of known hypertension with or without treatment, ischemic heart disease, cardiomyopathy, valvular heart disease, heart failure, chronic pulmonary illness, severe anaemia, hemoglobinopathies.

Investigations:
Fasting and Post prandial Plasma glucose (FPG and PPPG) – HbA1C
Electrocardiography (ECG)
Plane Chest X-ray

2D Echocardiography: M-mode and pulsed Doppler Transthoracic Echocardiography according to recommendation of American Society of Echocardiography[12]

Venous blood was collected after 8 hours of fasting, into two test tubes; with P vial for plasma glucose and with Ethylene Diamine Tetra Acetic Acid (EDTA) for HbA1c.

HbA1C was estimated by Boronate affinity chromatography (HPLC) which separates total glycosylated haemoglobin by binding to solid–phase dihydroxyborate using Nycocard immunoassay kit (USA).

Table showing diagnostic criteria for IFG, IGT & diabetes mellitus

	FBS (mg/dl)	2 hr Glucose (mg/dl)	HbA1C (%)
Normal	< 100	< 140	< 6
IFG	≥100 & < 126	< 140	6 – 6.4
IGT	< 126	≥ 140	6- 6.4
DIABETES	≥ 126	≥ 200	≥ 6.5

LEFT VENTRICULAR HYPERTROPHY-

Left ventricular hypertrophy was detected by measuring left ventricular mass index (LVMI) using Transthoracic Echocardiography, according to recommendation of American Society of Echocardiography (ASE).
The following M Mode parameters were measured -
• Left ventricular end diastolic diameter (LVIDed)
• Left ventricular end systolic diameter (LVIDes)
• Ventricular septum thickness (IVSTed)
• Posterior wall thickness in diastole (PWTed)

Left ventricular mass (LVM): calculated by ASE formula i.e. LVM = $0.8[1.04\{(LVIDed+PWTed+IVSTed)^3-(LVIDed)^3\}]+0.6$ gm
Left ventricular mass index (LVMI)- LVM / BSA

LVH is considered if LVMI >45 g/m2.7 in female and >49 g/m2.7 in male.

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION:

This was evaluated by **Pulsed Doppler echocardiography**. Pulsed-wave Doppler (PWD)-derived transmitral inflow velocities were obtained in the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips. Measurements included the transmitral early diastolic rapid filling (**E-wave**) and atrial contraction late filling (**A-wave**) velocities to calculate E/A ratio, isovolumteric relaxation time (IVRT) and deceleration time (DT). For tissue Doppler imaging (**TDI**), the mitral annulus velocity was obtained with a 2 mm sample volume lateral side and septal side of the mitral annulus. Diastolic dysfunction was labeled according to the standard guidelines. Left ventricular overall ejection fraction (systolic function) was calculated by modified Simpson‘s method; and, LVEF ≥ 50% was considered as normal. All echocardiographic measurements were averaged over three consecutive cardiac cycles, measured by a single investigator blinded to all other variables. LV diastolic dysfunction was considered to be present if any of the following findings were seen, as previously described:
• E/A ratio < 1 or > 2

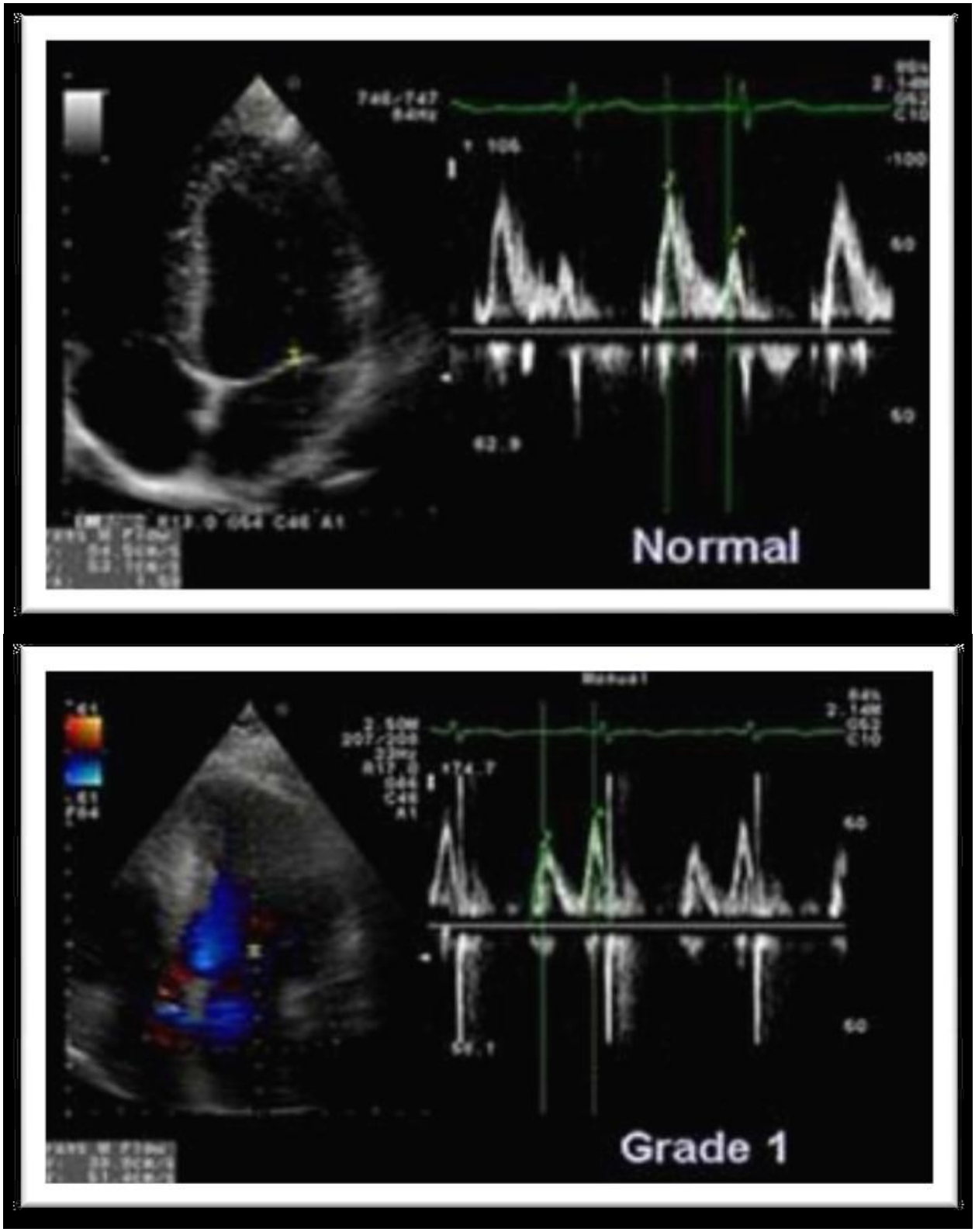
• DT < 150 or > 220 ms,

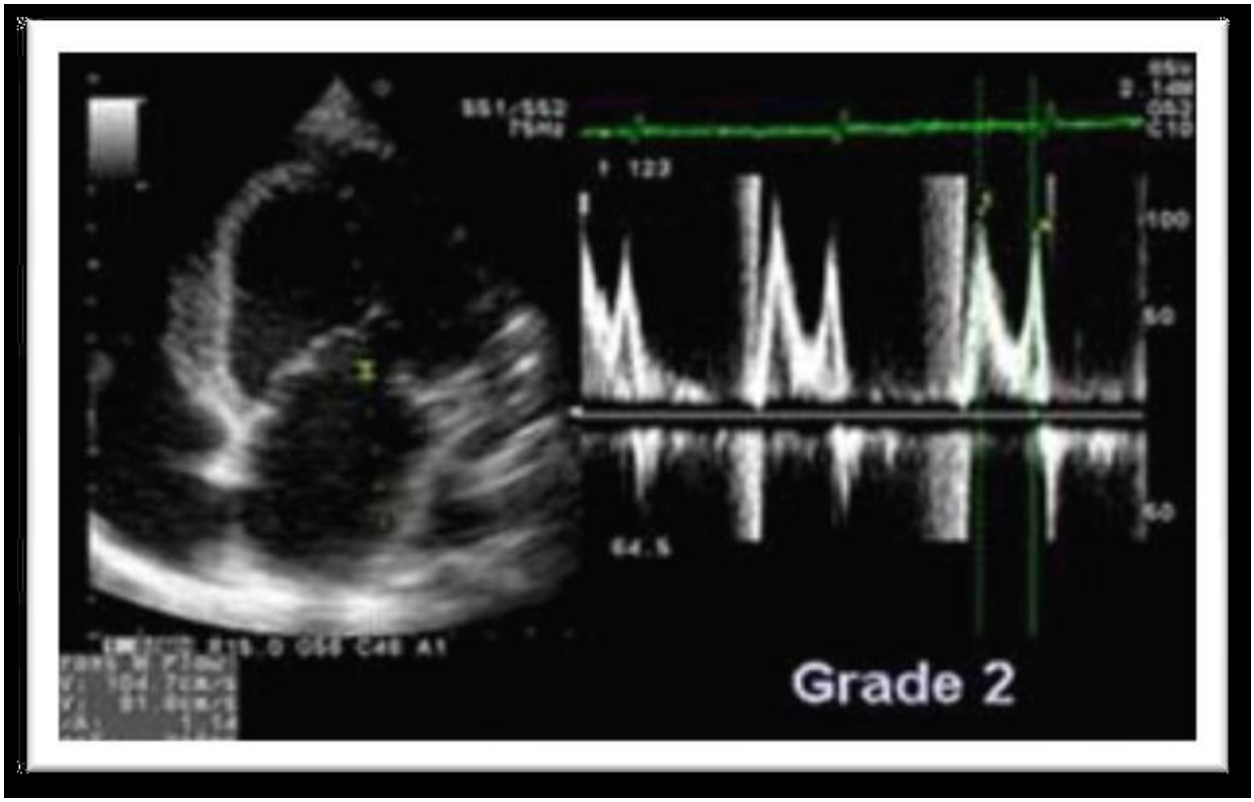
• IVRT < 60 or > 100 ms, or

• E/e‘ratio > 15

Evaluation of different degrees of diastolic dysfunction using data obtained from the transmitral flow pattern (top) and analysis of tissue Doppler at the mitral annulus level (bottom). Legend: DD-diastolic dysfunction; DDT-diastolic deceleration time; E-transmitral flow velocity during early ventricular filling; A-transmitral flow velocity during atrial contraction; e'-Tissue Dopper velocity at the mitral annulus level during early ventricular filling.

2D-ECHO PHOTOGRAPHS SHOWING LVDD





Statistical analysis: Data were analysed for mean, percentage, standard deviation, Student_t' test, Fisher's exact test, by using SPSS-16 (Statistical Package for the Social Sciences) for Windows (SPSS, Chicago, IL). The t'-test and Fisher's exact tests were applied to study quantitative and qualitative data, respectively with P'value < 0.05 was considered statistically significant.

III. OBSERVATIONS AND RESULTS

Table 2: Age and Sex wise distribution of cases

Age (yrs)	Male		Female		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
30-40	04	04	04	04	08	08
41-50	16	16	20	20	36	36
51-60	40	40	16	16	56	56
Total	60	60	40	40	100	100

Total 100 patients of newly diagnosed type 2 diabetes mellitus were selected for this cross sectional study. Out of which 60 (60%) were males and 40 (40%) females. Patients of age between 30 to 60 yrs were selected for the study. Maximum patient belongs to age group 50-60 yrs (56 patients) and minimum in age group 30-40 yrs (08 patients).

Figure 1: Bar diagram showing age and sex wise distribution of cases

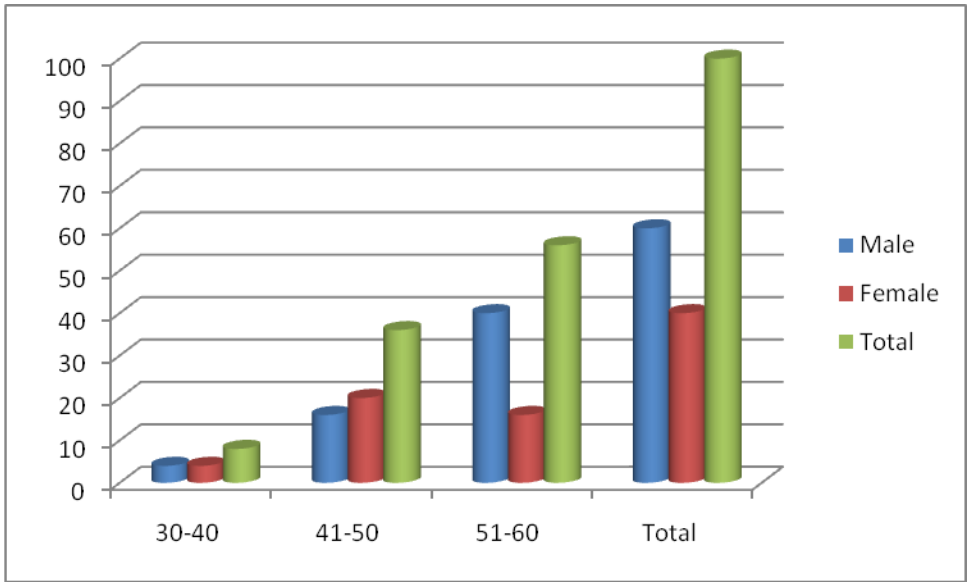


Table 3: Frequency of Left Ventricular hypertrophy in Subjects and gender wise distribution of cases

Mild LVH	**Moderate LVH**	**Severe LVH**	**Overall cases of LVH**	**Mild LVH**
Male	27	0	0	**27**
Female	09	0	0	**09**
Total	**36**	**0**	**0**	**36**

Table 3 shows that, out of 100 patients of newly diagnosed normotensive type 2 DM ; 36 % patients were found to have left ventricular hypertrophy. Only mild left ventricular hypertrophy was present in all cases as detected by 2D echocardiography by measuring left ventricular mass index Out of 36 cases 27 were male and 09 were females.

Figure 2: Frequency of Left Ventricular hypertrophy in subjects and gender wise distribution of cases

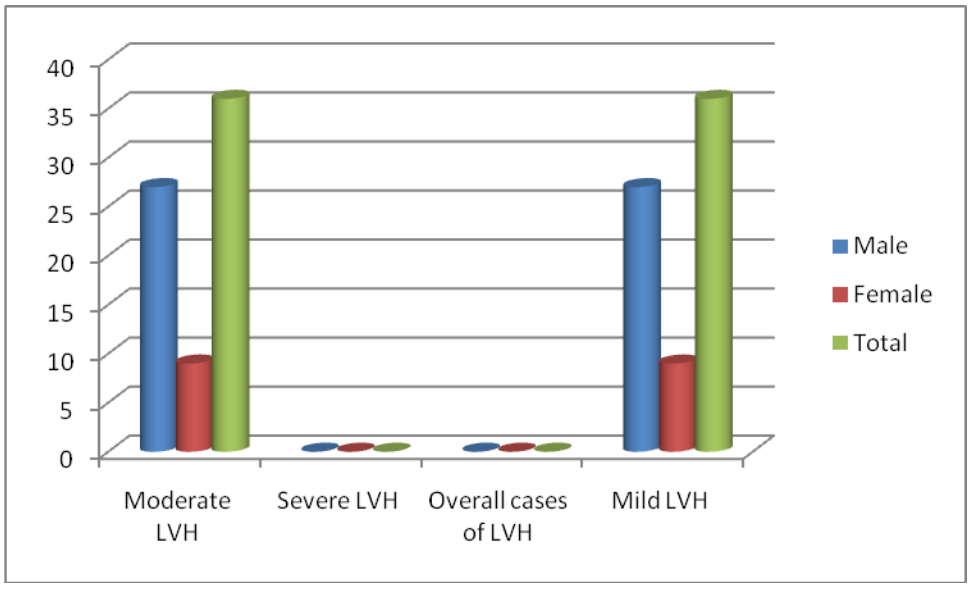
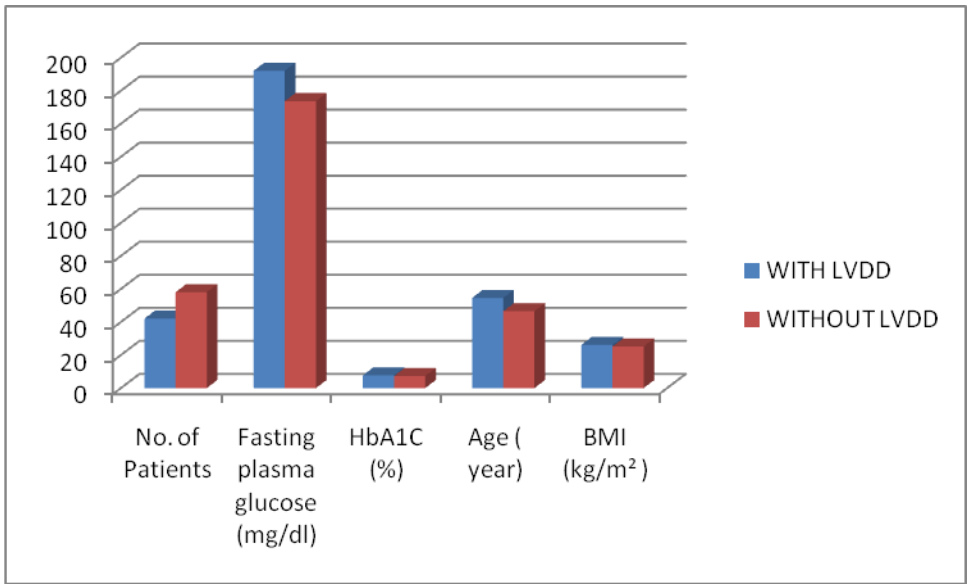


Table-4: Comparative Parameters of the Patients with LV Diastolic dysfunction

PARAMETERS	WITH LVDD	WITHOUT LVDD	P VALUE ('t' test)
No. of Patients	42	58	n/a
Fasting plasma glucose (mg/dl)	192.05 ±29.82	173.67 ± 27.71	0.0020
HbA1C (%)	7.69 ±1.01	7.26 ± 0.74	0.0157
Age (year)	54.56 ± 6.49	46.48 ±7.15	0.0012
BMI (kg/m²)	26.09±2.84	25.15±2.36	0.0743

Figure-3: Comparative Parameters of the Patients with LV Diastolic dysfunction



Mean FPG of subjects with LVDD was 192.05 ±29.82/dl and that of population without LVDD was 173.67 ± 27.71mg/dl .This shows that FPG is positively associated with the incidence of LVDD in population as mean of FPG of population with LVDD was higher as compare to population without LVDD and correlation was found very significant (p=0.0020) .

The mean HbA1C of subjects with LVDD was 7.69 ± 1.01as compare to subjects without LVDD 7.26 ± 0.74 the Correlation was found significant using unpaired t test (p value 0.0157**).**This signifies that higher the value of HbA1C at the time of diagnosis , higher will be the incidence of LVDD .Mean age of subjects with LVDD was 54.56 ± 6.49yrs and that of population without LVDD was 46.48 ± 7.15yrs. Age is positively associated with the incidence of diabetic LVDD in population as mean of age of population with LVDD was higher as compare to population without LVDD and correlation was found very significant (p=0.0012) mean body mass index of subjects with LVDD was 26.09±2.84 kg/m² and that of population without LVDD was 25.15±2.36kg/m² .BMI is not positively associated with the incidence of diabetic LVDD in population as mean of BMI of population and correlation was not significant (p=0.0743) .

IV. Discussion

Diabetes Mellitus is a metabolic disease, associated with a number of complications including nephropathy, neuropathy, ischemic heart disease, cerebrovascular disease and peripheral vascular diseases. Type 2 DM is likely to remain undiagnosed for years. The gap between the onset of the disease and clinical diagnosis of diabetes leads to the development of these chronic complications, which are the leading causes of premature mortality among diabetic patients. In this study, which is one of the first studies in this regards in western U.P., we assessed the correlation of left ventricular diastolic dysfunction (LVDD) with various parameters like glycosylated haemoglobin (HbA1C), plasma Glucose, Age and body mass index (BMI). In our study, incidence of left ventricular hypertrophy in Type 2 diabetics without known hypertension, cardiac, cerebrovascular or peripheral vascular disease, has demonstrated that LVH (defined according to the ASE guidelines) was common, occurring among 36 % of the patients[13], which is similar to study done by **Somratne et al[14].** suggesting that type 2 diabetes per se is associated with LVH. Left ventricular hypertrophy which is an ominous prognostic sign and independent risk factor for cardiac events is often present in type 2 diabetes mellitus patients .The possible contribution of hyperinsulinemia and hyperglycemia to left ventricular mass have been suggested in normotensive diabetic patient but. **Dawson et al** [15]in UK found a very high prevalence of 74 % which may be because he included already diagnosed cases of type 2 DM[16]. In this study a positive correlation was found between prevalence of LVH and level of HbA1C and Age but association with BMI was not significant. Incidence of LVH was found higher in males as compare to

females. Study demonstrates high incidence of diastolic dysfunction in normotensive and asymptomatic type 2 diabetics even at the time of diagnosis and this finding has a positive correlation with HbA1C and age at the time of diagnosis of diabetes. No significant HbA1C and age at the time of diagnosis of diabetes.

V. Conclusion

HbA1c is seems to be reliable predictor of LVDD. Our Study demonstrated a very significant positive correlation between level of glycosylated hemoglobin(HbA1C) and frequency of LVH and LVDD in the newly diagnosed cases of type 2 diabetes mellitus. Similar correlation was also observed with FPG.

References

[1] N. Kochupillai, Diabetes Mellitus – A National health problem with major socioeconomic implications; INT. J. DIAB. DEV. COUNTRIES (1998), VOL. 18: 69-70.

[2] Isomaa BAlmgren PTuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24683- 689

[3] Vokonas PSKannel WB Diabetes mellitus and coronary heart disease in the elderly. Clin Geriatr Med 1996;1269- 78

[4] Saunders J, Mathewkutty S, Drazner MH, McGuire DK: Cardiomyopathy in type 2 diabetes: update on pathophysiological mechanisms. Herz 2008, 33:184-90, Review.

[5] Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care. 2001;24:1614 –1619.

[6] Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA. Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well controlled type 2 diabetes mellitus. Am J Cardiol. 2001;87:320 –323.

[7] Isaaz K, Thompson A, Ethevenot G, Cloez JL, Brembilla B, Pernot C: Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall. Am J Cardiol 1989, 64(1):66-75

[8] 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.

[9] Nicolino A, Longobardi G, Furgi G, Rossi M, Zoccolillo N, Ferrara N, Rengo F: Left ventricular diastolic filling in diabetes mellitus with and without hypertension. Am J Hypertens 1995, 8:382-389.

[10] Eckel RH, Wassef M, Chait A, et al.: Prevention Conference VI: Diabetes and cardiovascular disease: Writing Group II: Pathogenesis of atherosclerosis in diabetes. Circulation 2002, 105:e138-43

[11] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33():S62–S69

[12] Saadeh B. Jureidini, ,Cynthia J. Marino, Brian Waterman, P.Syamasundar Rao, Transthoracic Doppler Echocardiography of Normally Originating Coronary Arteries in Children Journal of the American Society of Echocardiography Volume 11, Issue 5, May 1998, Pages 409–420

[13] Holzmann M, Olsson A, Johansson J, Jensen-Urstad M. LV diastolic function is related to glucose in a middle-aged population. J Intern Med, 2002, 251, 415-20

[14] Somaratne JB, Whalley GA, Poppe KK, ter Bals MM, Wadams G, Pearl A, Bagg W, Doughty RN. Screening for left ventricular hypertrophy in patients with type 2 diabetes mellitus in the community, Cardiovasc Diabetol. 2011;10:29.

[15] Dawson A, Morris AD, Struthers AD. The epidemiology of left ventricular hypertrophy in type 2 diabetes mellitus, Diabetologia. 2005; 48(10):1971-9.

[16] Sukamal Santra, Asish Kumar Basu, Pradip Ray Chowdhury Ramtanu Banerjee ,Pankaj Singhania, Sudhakar Singh , Utpal Kumar Datta. Comparison of left ventricular mass in normotensive type 2 diabetes mellitus patients with that in the nondiabetic population, J Cardiovascular Dis 2011; 2(1): 50-56.

Authors

First Author – Sanjeev Kumar, Senior Resident, Department of Medicine, K GM U, Lucknow
Second Author – G K Aneja, Professor and Head, Department of Medicine, LLRM, Medical College, Meerut
Third Author – Arvind Trivedi, Professor, Department of Medicine, LLRM, Medical College, Meerut.
Fourth Author – V Atam, Professor, Department of Medicine, K G M U, Lucknow .
Fifth Author – Abhishek Singh, Assistant Professor Department of Medicine, , K G M U, Lucknow.
Sixth Author – Neetu Verma, MBBS Student, GSVM Medical College Kanpur, UP
Seventh Author – Ajay Panwar , Senior Resident, Department of Neurology, K GM U, Lucknow
Eight Author – Pradeep Kumar, Professor, Department of Physiology, K GM U, Lucknow.