A STUDY TO CORRELATE HBA1C LEVELS AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NEWLY DIAGNOSED TYPE II DIABETES MELLITUS

Vasanthi Perumal[1], Namitha Narayanan[2], Jayanthi Rangarajan[3], Elangumanan Palanisamy[4], Mohamed Kalifa[5], Uma Maheshwari Perincheri[6], Pravin Selvam Selvaraj[7], Santhi Chinnathambi[8]

[1]*Associate Professor, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[2]*Assistant Professor, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[3]*Professor, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[4]*Junior Resident, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[5]*Assistant Professor, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[6]*Junior Resident, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[7]*Junior Resident, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*
[8]*Junior Resident, Department of Internal Medicine, Govt. Stanley Medical College & Hospital, Chennai.*

ABSTRACT

AIM
To assess the correlation of HBA1C levels with left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetic patient. This prospective study was done at Department of General Medicine, OPD, Medical Wards, Stanley Medical College and Hospital, Chennai.

RESULT
The mean HBA1C levels were meaningfully more in Left Ventricular Diastolic Dysfunction (LVDD) positive group compared to the LVDD negative group by 1.33%. This significant difference of 15% increase in mean HBA1C levels in LVDD positive group compared to the LVDD negative group is true and has not occurred by chance.

CONCLUSION
One-fifth to one-third of diabetic patients will develop LVDD. Patients with HBA1C (8 to 10) have double the chances to develop LVDD than with HbA1c 6.5 to 8. Patients with HBA1C more than 10 have five times the chances to develop LVDD than with HbA1C 6.5 to 8. Patients with HBA1C more than 10 have three times the chances to develop LVDD than with HBA1C 8 to 10. One-fourth to one-half of diabetic patients will develop LVDD grade 1. Patients with HBA1C 8 to 10 have double the chances to develop LVDD grade 1 than with HBA1C 6.5 to 8. Patients with HBA1C more than 10 have four times the chances to develop LVDD grade 1 than with HBA1C 6.5 to 8. Patients with HBA1C more than 10 have two times the chances to develop LVDD than with HBA1C 8 to 10.

KEYWORDS
Type 2 Diabetes, Left Ventricular Diastolic Dysfunction, HbA1C.

INTRODUCTION
Diabetes mellitus is one of the most common diseases in the world and is acquiring epidemic proportions. Its prevalence is growing in both developed and developing countries. Globally and nationally, diabetes and its complications has become the most important contemporary and challenging health problem. Compared to other races, Indians are genetically more susceptible. Diabetes is one such important metabolic disease, which affects nearly every organ system in the body. The main cause of morbidity and mortality in diabetic patients is due to cardiac complications. It has been estimated that by the year 2025, 300 million individuals would be affected with diabetes all over the world. In India, it is estimated that presently 19.4 million individuals are affected by this deadly disease, which is likely to go up to 57.2 million by the year 2025.

Although, the prevalence of both Type 1 and Type 2 DM is increasing worldwide, the prevalence of Type 2 DM is on the rise much more rapidly, which is due to increasing obesity and reduced activity levels.[1]

Diabetic individuals have been reported to develop congestive heart failure in the absence of coronary heart disease, hypertension or any structural heart disease.[2] The term "Diabetic Cardiomyopathy" has been introduced for this condition. The existence of a diabetic cardiomyopathy was first proposed by Rubler in 1972.[3][4]

Diabetic Cardiomyopathy
In India Tripathy reported in 1973, the existence of cardiac enlargement and failure in diabetes without obvious coronary artery disease, hypertension or structural heart disease suggesting a specific entity - Diabetic cardiomyopathy.

Pathogenesis
The proposed mechanisms responsible for development of diabetic cardiomyopathy are:

J. Evolution Med. Dent. Sci./ eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 5/ Issue 51/ June 27, 2016

Page 3312

Hyperglycaemia

It affects contractility of heart by two main mechanisms,
1. Production of advanced glycation end products.[5]
2. Production of free radicals.

Myocardial fibrosis results from elevated collagen deposition in myocardium; this is a result of over–production of reactive oxygen species from the above mechanisms.

Free Fatty Acids

Increased free fatty acids are associated with activation of proliferation activated receptor alpha (PPAR alpha), which promote mitochondrial uncoupling of oxidative phosphorylation and reduces myocardial high energy reserves.[6] These mechanisms are responsible for cardiac dysfunction.

Protein Kinase C

The levels of protein kinase C are elevated in diabetic patients. It reduces the levels of nitric oxide and increases the production of free radicals. These sequential changes lead to dysfunction of the endothelium.[7]

Renin Angiotensin and Aldosterone Mechanism

In concomitant hyperglycaemia, the RAAS mechanism gets dysregulated and both aldosterone and glucose stimulate growth of myofibroblast leading to myocardial fibrosis.[8]

Vascular Endothelial Growth Factor (VEGF)

In diabetics the vascular endothelial growth factors levels are reduced, which is responsible for angiogenesis and collateral formation in cardiac ischaemia.[9]

Autonomic Neuropathy

In cardiac autonomic neuropathy, the loss of parasympathetic activity results in relative predominance over sympathetic activity in the sympathovagal balance. The sympathetic over-activity stimulates renin angiotensin–aldosterone–adrenergic system which increases the heart rate, stroke volume and peripheral resistance. The sympathetic over-activity with myocardial sympathetic denervation leads to impairment of coronary vasodilator reserve, impaired ventricular diastolic filling and diastolic dysfunction.

Risk Factors

- Chronic high blood sugar level.
- Obesity.
- Hypertension.
- Dyslipidaemia.
- Smoking.
- Alcoholism.
- Sedentary lifestyle.

Clinical Features

Diabetic cardiomyopathy is a progressive state initially with myocardial diastolic dysfunction, later on systolic dysfunction supervenes with classical features of CCF. Patient has no symptoms in early stage, later progresses to fatigue, weakness, effort intolerance, shortness of breath with cough, swelling of the feet. Cardiomegaly, atrial and ventricular gallop, pulmonary congestion is frequent.

STAGING OF DIABETIC CARDIOMYOPATHY

Stage 1

It includes diastolic heart failure with preserved ejection fraction with hypertrophy without hypertension.

Stage 2

Diastolic and systolic heart failure with dilatation and reduced ejection fraction without hypertension.

Stage 3

Systolic and diastolic heart failure with microvascular disease and hypertension without CAD.

Stage 4

Heart failure associated with ischaemia/infarction.

DIAGNOSIS

Evaluation of Left Ventricular Function

There are two chief methods of evaluating the LV function.

Non-Invasive Methods Include

a. Echocardiography and Cardiac Doppler.
b. Systolic Time Intervals (STI).
c. Apex Cardiography (ACG).
d. Gadolinium-enhanced cardiac MRI.

Invasive Method

Cardiac catheterization.

Doppler Echocardiography

This is an inexpensive tool to detect the functional and structural cardiac anomaly.

Trans-mitral Doppler is a very useful method in diagnosis of left ventricular diastolic dysfunction. The variables commonly measured are early ventricular filling (E), late ventricular filling wave (A) and E/A ratio, Isovolumetric Relaxation Time (IVRT), Deceleration Time (DT), velocity at the mitral annulus level during early ventricular filling (e'). LV diastolic dysfunction was considered to any one of the following findings.

E/A ratio <1 or >2

DT <150 OR >220 ms

IVRT <60 OR >100 ms

E/e' ratio >15 (Ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e').

ECHOCARDIOGRAPHIC GRADING OF DIASTOLIC DYSFUNCTION.[10]

Grade I

Abnormal relaxation pattern.

Reversal of E/A ratio

IVRT > 100 ms

DT > 240 ms

E caused by accumulation of blood in the atria during previous systole.

A caused by atrial contraction.

Grade II

Pseudonormal filling pattern.

Elevated atrial filling pressure.

E/A ratio return to range of 0.8 to 1.5.

IVRT <90 ms.

DT < 160 ms.

J. Evolution Med. Dent. Sci./ eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 5/ Issue 51/ June 27, 2016

Page 3313

Grade III
Reversible restrictive pattern.
Reversal of diastolic abnormalities on Valsalva manoeuvre.
E/A ratio >2.
IVRT <80 ms.
DT<160 ms.

Grade IV
Fixed restrictive pattern.
Most severe form of diastolic dysfunction.
No reversibility of diastolic abnormalities on Valsalva manoeuvre.
E/A ratio >2.

Gadolinium Enhanced MRI
It is used to assess the myocardial flow reserve and myocardial perfusion and fibrosis. Cardiac MRI diagnosed myocardial scar without evidence of myocardial infarction. It is a non-invasive technique to assess the left ventricular function and size.

Invasive Studies
Cardiac catheterisation.
Elevated Left Ventricular End Diastolic Pressure (LVEDP) >16 mmHg.
Mean pulmonary capillary wedge pressure > 12 mmHg.
Normal coronary angiogram is suggestive of diabetic cardiomyopathy.

AIM AND OBJECTIVES
To assess the correlation of HBA1C levels with Left Ventricular Diastolic Dysfunction (LVDD) in newly diagnosed Type 2 diabetic patient.

MATERIALS AND METHOD
Place of Study
Department of General Medicine, OPD, Medical wards.
Stanley Medical College and Hospital, Chennai.

Study Population
100 consecutive patients of newly diagnosed Type 2 diabetes mellitus.

Study Design
Prospective study.

Ethical Committee Approval
Ethical committee approval was obtained for the study.

Study Period
March to September 2015.

Diagnostic Criteria (American Diabetes Association).[11]
FBS ≥ 126 mg/dL.
2 hr. plasma glucose ≥200 mg/dL during an OGTT.
RBS ≥200 mg/dL with symptoms (polyuria, polydipsia, polyphagia, weight loss).
HbA1C >6.5%.

Left Ventricular Diastolic Dysfunction
Reduction in peak velocity of early mitral flow (E) increase over peak velocity of late mitral flow (A) with E/A ratio of <1 and increase in Left Atrial (LA) size with preserved ejection fraction were considered as the evidence of left ventricular diastolic dysfunction.

Inclusion Criteria
All newly diagnosed Type 2 diabetes mellitus patients, who clinically had no cardiovascular symptoms and blood pressure of < 130/80 mmHg with normal ECG.

Exclusion Criteria
- Known diabetic patients on insulin and OHA.
- Ischaemic heart disease.
- Hypertensive heart disease.
- Congestive heart failure.
- Valvular heart disease.
- Cardiomyopathy.
- Connective tissue diseases.
- Renal failure.
- Thyroid dysfunction
  were excluded from the study.

METHODOLOGY
Patients with newly diagnosed Type 2 diabetes presenting to the Medicine Outpatient Service and those admitted to the medical wards at Stanley Medical College Hospital, Chennai, were included in the present study. Informed consent was obtained from the subjects. Detailed medical history was collected from each patient. Patients were subjected for clinical examination followed by relevant investigations.

The Patients Underwent the following Investigations
a. FBS, PPBS.
b. Glycosylated haemoglobin (HbA1c).
c. Urea, creatinine.
d. Fasting lipid profile.
e. Urine routine.
f. ECG.
g. Doppler Echo was done in each patient and 3-4 cardiac cycles were analysed to get best phase for better outcome of results.

In Doppler Echo Study following Values Were Evaluated
1. E-peak velocity of early mitral flow (N: 50-90 cm/sec).
2. A-peak velocity of late mitral flow (N: 30-70 cm/sec).
3. E/A ratio (N: 1-2).
4. Left atrial size (N: 3–4 cms).
5. EF (N: >60%).

Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase in left atrial (LA) size with preserved Ejection Fraction (EF) were considered as the evidence of left ventricular diastolic dysfunction.

Human Subject Protection
The full protocol along with draft questionnaire and Informed consent was kept in Institutional Ethical Committee and approval was obtained.

Informed Consent
Consent form was written in both English and Tamil and consent was obtained from the participant, confidentiality was maintained.

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired 't' test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as P < 0.05. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

RESULTS

SEX	Index	Frequency
	Female	44
	Male	56
AGE	Sex	mean age
	All	45.23
	Female	44.9
	Male	45.48
	Female without LVDD	43.89
	Male without LVDD	44.02
	Female with LVDD	46.86
	Male with LVDD	47.72
Table 1: Age and Sex Distribution of LVDD		

LVDD (Both Gr1 & Gr2)	Frequency	Frequency
	yes	No
All	37	63
Female	15	29
Male	22	34
LVDD Grade 1 only	**Frequency**	**Frequency**
	yes	No
All	33	67
Female	14	30
Male	19	37
LVDD Grade 2 only	**Frequency**	**Frequency**
	yes	No
All	4	96
Female	1	43
Male	3	53
Table 2: Sex Distribution of LVDD, LVDD Grade 1 and Grade 2		

	LVDD		
Age Group	No	Yes	Total
31 to 40 years	20	7	27
41 to 50 years	34	19	53
51 to 60 years	9	11	20
Total	**63**	**37**	**100**
Table 3: Age Group Wise Distribution of LVDD			

Sex	Mean Age
All	46.57
Female without LVDD grade 1	44.4
Male without LVDD grade 1	44.7
Female with LVDD grade 1	46
Male with LVDD grade 1	47
Table 4: Sex and Mean Age Distribution of LVDD Grade 1	

	LVDD Grade 1		
Age Group	No	Yes	Total
31 to 40 years	20	7	27
41 to 50 years	35	18	53
51 to 60 years	12	8	20
Total	**67**	**33**	**100**
Table 5: Age Group Wise Distribution of LVDD Grade 1			

Age	Sex	Mean Age
	All	54
	Female without LVDD grade 2	44.58
	Male without LVDD grade 2	45.09
	Female with LVDD grade 2	59
	Male with LVDD grade 2	52.33
Table 6: Sex and Age Wise Distribution of LVDD Grade 2		

	LVDD Grade 2		
Age Group	No	Yes	Total
31 to 40 years	27	0	27
41 to 50 years	52	1	53
51 to 60 years	17	3	20
Total	**96**	**4**	**100**
Table 7: Age Group Wise Distribution of LVDD Grade 2			

LVDD	Odds Ratio	P-value	Females Odds Ratio (P value)	Males Odds Ratio (P value)
HBA1C 6.5 to 8	0.17	0.035	1(NA)	0.36(0.27)
HBA1C 8 to 10	0.3541667	0.021	0.157(0.01)	0.64(0.46)
HBA1C >10	1	NA	1(NA)	1(NA)
Table 8: Odds Ratio with Multi-Nominal Regression for HBA1C Levels with LVDD				

LVDD GR1	Odds Ratio	P-value	Females Odds Ratio (P value)	Males Odds Ratio (P value)
HBA1C65to8	0.2625	0.112	1(NA)	0.66 (0.66)
HBA1C8to10	0.54	0.182	0.204(0.02)	1.17(0.79)
HBA1C10	1	NA	1(NA)	1(NA)
Table 9: Odds Ratio with Multi-Nominal Logistic Regression for HBA1C Levels with LVDD Grade 1				

LVDD	Odds Ratio	P-value
Age 31 to 40	0.286	0.047
Age 41 to 50	0.457	0.142
Age 51 to 60	1	NA
Table10: Odds Ratio with Multi-Nominal Logistic Regression for LVDD with Age Groups		

LVDD Grade 1	Odds Ratio	P-value
Age 31 to 40	0.525	0.309
Age 41 to 50	0.771	0.631
Age 51 to 60	1	NA
Table 11: Odds Ratio with Multi-Nominal Logistic Regression for LVDD Grade 1 with Age Groups		

Patients with age group 31 to 40 have 52% chances to get LVDD grade 1 without significant P value of 0.309. Patients with age between 31 to 40 have 77% chances to get LVDD without significant P value of 0.631.

DISCUSSION

Patients with HbA1c between 6.5 to 8 have 17% chances to get LVDD with significant P value of 0.03. Patients with HbA1c between 8 to 10 have 35% chances to get LVDD with significant P value of 0.02. Patients with HbA1c 6.5 to 8 have double the chances when compared to HbA1c 6.5 to 8 with significant association statistically. Female patients with HbA1c 8 to 10 have 15% chances of having LVDD with significant association statistically (P value 0.02). Male patients with HbA1c between 6.5 to 8 have 36% chances to get LVDD without significant P value of 0.279. Male patients with

HbA1c of 8 to 10 have 64% chances to get LVDD without significant P value of 0.46.

Patents with HbA1c between 6.5 to 8 have 26% chances to get LVDD Grade 1 without significant P value of 0.112. Patients with HbA1c of 8 to 10 have 54% chances to get LVDD grade 1 without significant P value of 0.182. Patients with HbA1c 6.5 to 8 have double the chances when compared to HbA1c 6.5 to 8 without significant association statistically. Female patients with HbA1c 8 to 10 have 20% chances of having LVDD grade 1 with significant association statistically (P value 0.02). Male patients with HbA1c between 6.5 to 8 have 66% chances to get LVDD Grade 1 without significant P value of 0.66. Male patients with HbA1c of 8 to 10 have 117% chances to get LVDD grade 1 without significant P value of 0.79.

Patents with age between 31 to 40 have 28% chances to get LVDD with significant P value of 0.04. Patients with age between 31 to 40 have 45% chances to get LVDD without significant P value of 0.142.

Abay Kumar Chaudhary et al[9] in their study of 100 asymptomatic subjects found the prevalence of diastolic dysfunction in asymptomatic newly diagnosed Type 2 diabetics as 41%.[12] Mean of HbA1C (%) was found higher in group with LVDD (7.67±0.90) as compared to group without LVDD (7.24±0.64). This concludes that HbA1C is strongly associated with presence of LVDD (p=0.0057). Mean FBS found higher in LVDD group (189.80±30.90) as compared to LVDD negative group (179±29.80). Age of the patients was very significantly associated with incidence of LVDD (p=0.0012), meaning that older the age at the time of diagnosis higher the incidence of LVDD.

Sanjeev Kumar et al[12] in their study of 100 asymptomatic subjects found the prevalence of diastolic dysfunction in asymptomatic newly diagnosed Type 2 diabetics as 42%. Mean of HbA1C (%) was found higher in group with LVDD (7.69±1.01) as compared to group without LVDD (7.26±0.74). This concludes that HbA1C is strongly associated with presence of LVDD (p=0.0157). Mean FBS found higher in LVDD group (192.05±29.80) as compared to LVDD negative group (173.67±27.71). Age of the patients was very significantly associated with incidence of LVDD (p=0.0012), meaning that older the age at the time of diagnosis higher the incidence of LVDD.

Compared to other studies, our study significantly correlated with elevated HbA1C and elevated FBS to LVDD, whereas age and gender has no statistical significance.[13][14][15]

CONCLUSIONS
- One-fifth to one-third of patients will develop LVDD in diabetic patients.
- Patients with HBA1C 8 to 10 have double the chances to develop LVDD than with HbA1c 6.5 to 8.
- Patients with HBA1C more than 10 have five times the chances to develop LVDD than with HbA1c 6.5 to 8.
- Patients with HBA1C more than 10 have three times the chances to develop LVDD than with HbA1c 8 to10.
- One-fourth to one-half of diabetic patients will develop LVDD grade 1 in diabetic patients.
- Patients with HBA1C 8 to 10 have double the chances to develop LVDD grade 1 than with HbA1c 6.5 to 8.
- Patients with HBA1C more than 10 have four times the chances to develop LVDD grade 1 than with HbA1c 6.5 to 8.
- Patients with HBA1C more than 10 have two times the chances to develop LVDD than with HbA1c 8 to10.
- Older the diabetics, more chances of getting LVDD.
- Age group between 50 to 60 years have 4 times and 2 times more chances to get LVDD when compared with age group 40 to 50 and 31 to 40 years respectively.
- Age group between 50 to 60 years have 2 times and 1.25 times more chances to get LVDD grade 1 when compared with age group 40 to 50 and 31 to 40 years respectively.

REFERENCES
1. Anjana RM, Pradeepa R, Deepa M, et al. Prevalence of diabetes and pre-diabetes in rural and urban India: phase 1 results of the Indian council of medical research-India DIABetes (INDIAB) study. Diabetologia 2011;54(12):3022-7.
2. Isaaz K, Thompson A, Ethevenot G, et al. Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall. Am J Cardiol 1989;64(1):66-75.
3. Rubler S, Dlugash J, Yuceoglu YZ, et al. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30(6):595-602.
4. Cosson S, Kevorkian JP. Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy. Diabetes Metab 2003;29(5):455-66.
5. Von Bibra H, Hansen A, Dounis V, et al. Augmented metabolic control improves myocardial diastolic function and perfusion in patients with non-insulin dependent diabetes. Heart 2004;90:1483-4.
6. Aneja A, Tang WHW, Bansilal S, et al. Diabetic cardiomyopathy: insights into pathogenesis diagnostic challenges and therapeutic options. The American Journal of Medicine 2008;121(9):748-57.
7. Lopaschuk GD. Metabolic abnormalities in the diabetic heart. Heart Fail Rev 2002;7:149-59.
8. Orea-Tejeda A, Colin-Ramirez E, Castillo-Martinez L, et al. Aldosterone receptor antagonists induce favourable cardiac remodeling in diastolic heart failure patients. Rev Invest Clin 2007;59(2):103-7.
9. Chaudhary AK, Aneja GK, Shukla S, et al. Study on diastolic dysfunction in newly diagnosed type 2 diabetes mellitus and its correlation with glycosylated haemoglobin (HbA1C). Journal of Clinical and Diagnostic Research 2015;9(8):OC20-OC22.
   DOI: 10.7860/JCDR/2015/13348.6376.
10. Saadeh B, Jureidini, Cynthia J, et al. Transthoracic Doppler echocardiography of normally originating coronary arteries in children. Journal of the American Society of Echocardiography 1998;11(5):409-20.
11. American diabetes association report of the expert committee on the diagnosis and classification of diabetes mellitus. America: clinical practice recommendation. Diabetes Care 2006;28(Supl 1):S1-S40.

12. Kumar S, Aneja GK, Trivedi A, et al, Glycosylated haemoglobin (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. International Journal of Scientific and Research Publications 2014;4(12):ISSN 2250-3153.

13. Patil VC, Patil HV, Shah KB, et al. Diastolic function in asymptomatic type 2 diabetes mellitus with normal systolic function. J Cardiovascular Dis Res 2011;2(4):213-22.

14. Shrestha NR, Sharma SK, Karki P, et al. Echo evaluation of diastolic function in asymptomatic type 2 diabetes: a cross sectional study. Journal Nepal Medical Association 2009;48(173):20-3.

15. Mishra R, Das JP. Endomyocardial biopsy in diabetes mellitus. Ind Heart J 1981;33-156.