**CORRELATION BETWEEN LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND HbA1c LEVELS IN KERALITE DIABETICS**

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**ABSTRACT**

**BACKGROUND**

India has world's second largest number of diabetics. Much of the excess mortality among diabetics is because of cardiovascular diseases, including heart failure. Left ventricular diastolic dysfunction (LVDD), the earliest subclinical manifestation of diabetic cardiomyopathy, can worsen to heart failure. Some studies reported relation between LVDD and hyperglycaemia. There are no such studies on Keralite population. Ethnic variations occur in susceptibility to diabetes mellitus and cardiovascular diseases. Our study aims to examine whether LVDD in Keralite diabetics is related to the glycaemic status reflected by HbA1c.

**METHODS**

This is a cross sectional analytical study. Thirty diabetics between 21-50 years of age without hypertension, obesity and other comorbidities were selected. Parameters of left ventricular diastolic function (Iso-Volumetric Relaxation Time, ratio of peak velocity of early filling phase to peak velocity of late filling phase, deceleration time and ratio of peak velocity of early filling phase to early diastolic mitral annular velocity) were assessed by echocardiography and pulse wave tissue Doppler imaging. Venous blood HbA1c% (glycated haemoglobin A) was estimated.

**RESULTS**

54.5% of the diabetics had Left Ventricular Diastolic Dysfunction (LVDD). HbA1c levels accounted for 88% variance in LVDD. There was a strong correlation between LVDD and HbA1c levels.

**CONCLUSIONS**

There is a strong correlation between LVDD and hyperglycaemia, as reflected by high HbA1c levels. So, rigorous control of blood glucose levels is needed to prevent heart failure in diabetes mellitus.

**KEYWORDS**

Diabetes Mellitus, Hyperglycaemia, Glycated Hemoglobin A, Left Ventricular Diastolic Dysfunction, Echocardiography

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**BACKGROUND**

In 2011, India had the world's second largest number of adult diabetics (61.3 million); and the mean annual increment exceeded 2.1 million. So, in India, the number of adults having diabetes mellitus in 2019 would be about 78.1 million. Kleinman JC et al reported that the death rate of diabetics was twice that of nondiabetics and that the excess mortality was attributable mainly to cardiovascular diseases including diabetic cardiomyopathy. Diabetic cardiomyopathy comprises structural and functional abnormalities of the myocardium in diabetic patients without coronary artery disease or hypertension. Left ventricular diastolic dysfunction (LVDD) represents the earliest preclinical manifestation of diabetic cardiomyopathy. Diastolic dysfunction (DD) is the inability of the left ventricle (LV) to fill during rest or exercise, to a normal end-diastolic volume without an abnormal increase in LV end diastolic pressure (LVEDP). LVDD can progress to symptomatic heart failure. In DD, the abnormality in LV relaxation and/or compliance (i.e. increase in ventricular stiffness) alters the onset, rate, and extent of LV pressure decline and filling during diastole. In DD, during diastole the left ventricle is unable to accept sufficient volume of blood at normal diastolic pressures. So, higher filling pressures are needed to maintain normal LV end-diastolic volume and cardiac output. This produces elevated filling pressures resulting in pulmonary congestion and dyspnoea often during exercise; and in severe cases, even at rest. Diastolic heart failure is associated with elevated morbidity and mortality.

Definitive assessment of diastolic function requires simultaneous measurements of intraventricular pressure and volume by cardiac catheterization. But cardiac catheterization is invasive and is impractical to be performed in the majority of patients with suspected DD in daily clinical practice. So, exposing the patients to the risks implied in cardiac catheterization solely for the purpose of research is...
unjustifiable. Two-dimensional and pulsed wave Doppler echocardiography together will non-invasively provide reliable information about diastolic performance.6 Usual evaluation of diastolic function includes peak velocity of transmittal flow during early diastolic filling (E wave), peak velocity of transmittal flow during late diastolic filling (A wave), E/A ratio, deceleration time (DT) of early filling velocity and the isovolumic relaxation time (IVRT, time from aortic valve closure to onset of mitral inflow).5 Characteristic abnormalities in diastolic function, include prolonged isovolumic relaxation period, delayed mitral valve opening, impairment in rapid early diastolic filling, increased atrial contribution of LV filling, and a reduced E/A ratio. E/A ratio in normal recumbent young adults is >1, but <2. In grade I (delayed relaxation) DD, E/A is <1. (The other changes in grade I DD, include increase in A velocity due to increased LA contraction and increase in DT and IVRT due to relaxation abnormality). To compensate, LA pressure may rise, increasing E-wave height, leading to grade II (“pseudonormal”) or grade III (“restrictive”) DD filling pattern, with consequent risk for pulmonary congestion.5 Grade II pattern represents impaired relaxation as well as reduced compliance of LV occurring with increased LA pressure when there is a moderate compromise in diastolic function and is called pseudo normalization because the E/A is normal, i.e., >1, but reversal of E/A to <1 occurs with Valsalva manoeuvre. Restrictive filling pattern, in which E-wave morphology suggests a rapid increase and decay and the A-wave is blunted as the atrium contracts against an increasingly stiff ventricle, occurs in the more advanced DD with severely decreased left ventricular compliance and elevated ventricular filling pressures.6 LA pressure is increased more than in grade II, and there is significant decrease in DT (<150 ms) and IVRT (<60 ms). When this pattern remains fixed with Valsalva manoeuvre, it is grade IV DD (fixed restrictive filling).5 E-Wave Deceleration Time (DT) is the deceleration time of early filling velocity from peak E wave velocity to zero. Normal DT is >150 ms, but <220 ms. E-wave DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening and LV compliance.5 The rate at which the E-wave velocity decreases is inversely proportional to the net compliance of the LA and LV. The stiffer the ventricle, the shorter the DT. Short DT (<150 ms) occurs in grade III DD and is associated with an adverse prognosis.6 Isovolumic relaxation time is the time from the end of systolic ventricular outflow (aortic valve closure) to onset of mitral inflow (mitral valve opening). With normal diastolic function, IVRT = 70–90 ms.5 The most sensitive echocardiographic technique for the relatively load independent assessment of DD is pulsed Doppler tissue imaging (DTI) which measures low velocity, high amplitude intrinsic myocardial tissue velocity with high spatial and temporal resolution.5 DTI early diastolic mitral annular velocity (e’) reflects relaxation of the long axis of the LV and represents the early diastolic lengthening velocity of longitudinal LV fibres. e’ velocity is easily measured with low inter-observer variability, relatively preload independent, and has close correlation with invasive indices such as τ (an exponential time constant), LV dP/dt (the rate of pressure decay when LV pressure falls below LA pressure which is the growth in the pressure gradient across the mitral valve at the start of left ventricular filling and drives early, passive filling of the LVp), and LVEDP over a wide range of filling pressures, both at rest and during exercise. Decreased e’ is one of the earliest markers for DD and e’ progressively decreases with the worsening of LVDD. Diabetes mellitus can lead to impaired myocardial relaxation, thus delaying the longitudinal motion and decreasing the e’ velocity. E/e’ < left atrial pressure. So, E/e’ correlates with mean left atrial pressure and can be used to predict LV filling pressure.8 E/e’ ratio increases with the worsening of LVDD. Using the sepal e’ velocity, Ommen and colleagues10 found that PCWP (pulmonary capillary wedge pressure) is normal if E/e’ ratio is <8 and likely elevated if >15. E/e’ >15 is a powerful prognosticator of adverse cardiac events. LVDD may be considered to be present if any of the following findings are seen: E/A ratio <1 or >2, DT <150 or >220 ms, IVRT <60 or >100 ms, or E/e’ ratio >15.10,11

A relationship has been found between hyperglycaemia and LVDD in diabetes mellitus.12 Manish Gutch et al,13 Raghib Hasan et al,14 Kumar VS et al,15 Ashour K,16 Virendra C. Patil et al,11 Rajesh Kumar Meena et al,17 Jain S et al,18 Michaela Kozakova et al,19 Markuszewski L et al,20 Dhar R et al,21 Perumal V et al,22 Abhay Kumar Chaudhury et al,23 Sriinivasa S. V. et al24 and Suresh G et al25 reported that more of those who had higher HbA1c levels had LVDD compared to those who had lower HbA1c levels. Holzmann M et al26 detected that concentrations of fasting plasma glucose, glucose post load and glycated haemoglobin even below the threshold of diabetes, but already in the upper end of the normal range, had negative impact on LV diastolic function. In their study, HbA1c had independent significant contribution to the prediction of global Em velocity, global peak Am velocity and global Em/Am ratio. Celentana et al27 also reported that the E/A ratio was significantly lower not only in those with NIDDM, but also in those with impaired glucose tolerance than in participants with normoglycemia. A clinical trial by von Bibra H et al28 reported that improvement in the glycemic control by increasing the dose of insulin significantly increased the diastolic myocardial velocity at rest in correlation with the decrease in fasting β glucose. Grandi AM29 and co-researchers demonstrated that there was a close relation between glycaemic control and LV diastolic function in type 1 diabetes; and that the LVDD improves when glycaemic control improves. In the diabetic patient, better glycaemic control can improve myocardial performance by improving myocardial microcirculation,28 decreasing serum free fatty acids, decreasing myocardial FFA oxidation, decreasing myocardial triglyceride overloading and increasing glucose utilization.30 Better the glycaemic control, less will be the formation of advanced glycation end products (AGEs), AGE cross-linking induced stiffening of myocardium, impairment of active relaxation by RAGE (receptors for AGEs)-mediated alterations in calcium signalling, and impairment of mitochondrial ATP production by AGE-induced reactive
oxygen species;\(^{31,32}\) so, less will be the impairment of diastolic function. Ethnic variations occur in susceptibility to diabetes mellitus and cardiovascular diseases. There are no published studies on the relation between LVDD and glycaemic control of Keralite diabetics. The present study aimed to address this lacuna.

We wanted to determine as to whether there is any correlation between left ventricular diastolic dysfunction (LVDD) and HbA1c levels in Keralite patients who are on treatment for diabetes mellitus from the diabetic clinic in Government Medical College, Kottayam.

**METHODS**

**Study Design**
Cross sectional analytical study.

**Sample Size**
33

**Inclusion Criteria**
Patients aged between 21 to 50 years who had been diagnosed to have diabetes according to American Diabetes Association criteria for diabetes mellitus: \(^{33}\) Fasting plasma glucose concentration \(\geq 126\) mg/dL or 2-hour plasma glucose concentration \(\geq 200\) mg/dL during oral glucose tolerance test or HbA1C \(\geq 6.5\)% or in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose concentration \(\geq 200\) mg/dL.

**Exclusion Criteria**
Hypertension, valvular heart disease, congenital heart disease, ischemic heart disease, pericardial disease, thyroid dysfunction, renal failure. Obesity, age more than 50 years, age less than 21 years.

**Study Tools**
Semi-structured interview schedule, echocardiograph. (Clinical mercury sphygmomanometer, weighing machine, stadiometer, and medical records were used to rule out exclusion criteria).

**Methodology**
Permission was obtained from ethics committee of Govt. Medical College, Kottayam (IRB No. 120/216 dated 20/12/2016). By non-probability convenient sampling, thirty three diabetics between 21-50 years of age without hypertension, obesity and other comorbidities were selected and subjected to echocardiographic and pulse wave tissue Doppler imaging assessment of the parameters of LVDD: Iso-Volumetric Relaxation Time (IVRT), ratio of peak velocity of early filling phase to peak velocity of late filling phase (E/A), deceleration time (DT) and ratio of peak velocity of early filling phase to early diastolic mitral annular velocity (‘e’). From each patient, venous blood sample was obtained in which the percentage of the glycated haemoglobin HbA1c was estimated by high-performance liquid chromatography (HPLC). LV diastolic dysfunction was considered to be present if any of the following findings are seen: E/A ratio \(<1\) or \(>2\), DT \(<150\) or \(>220\) ms, IVRT \(<60\) or \(>100\) ms, or E/e’ ratio \(>15,10,11\) HbA1c = \(\leq 7\)% was considered as adequate glycaemic control, 7.1%-8% as inadequate control, and \(\geq 8.1\)% as poor control.

**Statistical Analysis**
Data were entered in Microsoft Office Excel and analysis was done using SPSS (Statistical Package for Social Sciences) Version 16. Correlation between the nominal variable, LVDD (presence/absence) and the continuous variable, HbA1c level was analysed using Eta statistic.

**RESULTS**

![Figure 1. Gender](image1)

![Figure 2. Left Ventricular Diastolic Dysfunction](image2)

![Figure 3. Glycaemic Control of Diabetics Having LVDD](image3)

<table>
<thead>
<tr>
<th>Adequate Control (HbA1c% (\leq 7)%)</th>
<th>4</th>
<th>22.22%</th>
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<tbody>
<tr>
<td>Inadequate Control (HbA1c% 7.1% - 8%)</td>
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<td>5.56%</td>
</tr>
<tr>
<td>Poor Control (HbA1c% (\geq 8.1)%)</td>
<td>13</td>
<td>72.22%</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>100%</td>
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| Table 1. Glycaemic Control of Diabetics Having LVDD |
The mean age of the studied patients was 44.42 years with a standard deviation of 5.766. 54.5% of the patients had Left Ventricular Diastolic Dysfunction (LVDD). Only 12.1% (n=4) patients had adequate glycaemic control reflected by HbA1c% ≤7%. 81.8% had poor control (HbA1c% ≥8.1%) and 6.1% (n=2) had inadequate control (HbA1c% =7.1% - 8%). Eta statistic was used to measure the correlation between the nominal variable, Left Ventricular Diastolic Dysfunction (presence/absence) and the continuous variable, HbA1c level. Eta squared is the correlation coefficient = (0.937)^2 = 0.877. This implies that 88% of the variance in LVDD can be accounted for by HbA1c levels. Thus, LVDD has a strong correlation with HbA1c levels.

DISCUSSION

The present study included only nonobese, non-hypertensive Keralite diabetics aged 21-50 years, with no detected heart disease and no history of thyroid. Diabetics aged >50 years were excluded to avoid the confounding effect of age-associated decline in LV function. Hypertensives and obese diabetics were also excluded to avoid the confounding effects of the myocardial dysfunction known to be associated with these morbidities. Avoiding the hypertensives among the diabetics having <50 years amounted to excluding more of the males than the females. So, only 39.4% of our study group were males. The mean age of our patients was only 44.42 years, i.e., before the usual age of menopause, after which many females develop hypertension? Abhay Kumar Choudhary et al,23 Srinivasa S. V. et al24 and Perumal V et al22 had reported that more of those aged > 50 years have LVDD, than those aged < 50 years. Because of the exclusion of diabetics aged >50 years, and the hypertensives, most of the studied patients were having only short duration of diagnosed diabetes. With this background we expected that less percentage of the diabetics in our study group would have LVDD.

But we detected that 54.5% of the diabetics in our study group had Left Ventricular Diastolic Dysfunction (LVDD). Our finding is similar to the 53.3% of diabetics having LVDD reported by Rajesh Kumar Meena et al,17 Abhay Kumar Choudhary et al23 and Manish Gutch et al,13 reported that only 41% of diabetics had LVDD. Their studies were on people from Uttar Pradesh; and Keralites are known to have higher prevalence of diabetes and heart disease, in general, than North Indians. This ethnic vulnerability might have contributed to the relatively higher percentage of our study group having LVDD compared to those reported by these studies as well as the 30% reported by Karan Jain et al24 from Maharashtra and the one-third reported by Michaela Kozakova et al19 from Italy. Though Swapnil Jain et al18 reported from Rajasthan that 63% of the diabetics had LVDD, their study group consisted of patients much older than ours, with age up to 79 years and a mean age of 57.04±10.17 years. The higher age of their patients may be the reason for the higher percentage of their patients having LVDD.

77.78% (n=14) of the diabetics having LVDD did not have adequate glycaemic control (HbA1c% ≤7%). 72.22% (n=13) had poor glycaemic control (HbA1c% ≥8.1%) and 5.56% (n=1) had inadequate glycaemic control (HbA1c% =7.1% - 8%). Eta statistic revealed that 88% of the variance in LVDD in the studied group of diabetics could be accounted for by HbA1c levels and thus a significant correlation existed between LVDD and HbA1c. Raghib Hasan et al14 had also reported significant correlation between diastolic dysfunction and HbA1c. Our finding is in accordance with the findings of various previous studies that higher the HbA1c%, higher was the prevalence (Rajesh Kumar Meena et al,17 Jain S et al,18 Ashour K,16 Kumar VS et al,15 Virendra C Pabli et al,11 Michaela Kozakova et al,19 Markuszewski L et al20) and the chance of developing (Dhar R et al,21 Perumal V et al22) LVDD. Suresh G et al25 observed that glycated HbA1c value > 8.1% showed increased prevalence of diastolic dysfunction in diabetic patients with a sensitivity of 80.6% and specificity of 71.4%. Srinivasa S. V. et al,24 Abhay Kumar Choudhary et al23 and Manish Gutch et al13 found that the mean HbA1c of diabetics with LVDD was significantly higher than that of diabetics without LVDD. HbA1c is glycated HbA1c, the percentage of which undergoes glycation increases with the degree and duration of exposure to glucose. Because the average lifespan of erythrocyte is about 120 days, HbA1c level is a rough indicator of the average glycaemic status of the preceding 120 days and reflects the tissue exposure to glucose during that period. Thus, HbA1c is superior to the plasma glucose level which varies with time in vivo and in vitro reflects only the degree of glucose exposure of body tissues at the time point of collection of the blood sample. The reports of many studies that HbA1c level has statistically significant relationship with LVDD indicates the important contributory role of hyperglycaemia to the development of LVDD in diabetic patients. Our study indicates that this holds true for Keralite diabetics also.

![Figure 4. Correlation Between HbA1c Level and LVDD](image-url)
CONCLUSIONS
In Keralite diabetics, LVDD has strong correlation with HbA1c levels, with HbA1c levels accounting for 88% of the variance in LVDD among them. Hyperglycaemia reflected by high HbA1c being the main contributor to its development, rigorous glycaemic control as reflected by low HbA1c levels may prevent the onset, or arrest the progression of LVDD in diabetics.

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