Advanced Role of LV GLS to Access Cardiovascular Morbidity in Diabetic Cardiomyopathy Presenting Heart Failure.

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Abstract

Background: Diabetes-associated changes in the structure and function of the myocardium leads to heart failure (HF) that is not directly attributable to other confounding factors such as coronary artery disease (CAD) or hypertension called diabetic cardiomyopathy (DbCMP). NT-pro BNP is an excellent and easy-to-perform biomarker in HF but has limited ability to assess HF in patients with normal ejection fraction.

Objectives: To admittance the left ventricular global longitudinal strain in DbCMP with HF for justification to access cardiovascular adverse events.

Methods: Retrospective study between 2017 to 2020 followed by 12 months of observation for morbidity and mortality. We enrolled 370 cases of DbCMP patients and compared them with the control (n=350). We included adults, age 58+/- 16.5 years, with New York Heart Association (NYHA) class I through IV. Specially LV Global Longitudinal Strain (LVGLS) was assessed by velocity vector imaging using 2-, 3-, and 4-chamber views apart from routine LV diastolic function; IVRT, DT, E/A ratio, E/e', LA Volume, LV Systolic function.

Results: We initiate considerable difference of left LVGLS in the DbCMP group -10.6 ± 4.3% as compared to the control group LVGLS was -18.7 ± 2.3%. Left ventricular ejection fraction (LVEF) was assessed in the case versus the control group (46±11% vs 59±6%). LV GLS <-9% was significantly associated with higher 12 months mortality and HF patients with DbCMP, not only in reduced LVEF but also in fair LVEF.

Conclusions: LVGLS has a more significant value to assess heart failure and mortality among DbCMP.

Keywords: Diabetic Cardiomyopathy, heart failure, left ventricular global longitudinal strain.

1. INTRODUCTION:

Diabetes mellitus affects almost every tissue in the body and causes significant organ dysfunction those results in diabetes-related morbidity and mortality. Cardiovascular disorders account for about 60-65% of diabetes-related mortality and therefore, the American Heart Association (AHA) accepted diabetes as coronary heart disease equivalent towards the turn of the 20th century [1]. Diabetic cardiomyopathy defines diabetes-associated changes in the structure and function of the myocardium lead heart failure (HF) that is not directly attributable to other confounding factors such as coronary artery disease (CAD) or hypertension. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is an excellent and easy-to-perform biomarker in patients with established HF but has limited ability to assess HF in patients with normal Ejection Fraction. Previous studies showed the importance of left ventricular (LV) global longitudinal strain (GLS) as a reliable prognostic indicator in patients with HF. Approximately 50% of patients with clinical heart failure Heart failure are presenting with preserved ejection fraction (HFpEF). Mortality rates after the first hospitalization are as high as 43%, similar to patients with heart failure with reduced ejection fraction (HFrEF)[2-3]. HFpEF, unlike HFrEF, proven therapies to reduce mortality and hospitalization rates in HFpEF are lacking because of the complex and poorly understood pathophysiology of HFpEF. Patients with HFpEF

represent a heterogeneous population that may not be adequately characterized by LVEF; many HFpEF patients may have unrecognized systolic dysfunction and may be better risk stratified by an alternative tool for assessing myocardial contractile function such as left ventricular (LV) global longitudinal stain (GLS)[4-5].

Assessment of myocardial deformation using 2D speckle-tracking echocardiography for measurement of GLS has emerged as a more sensitive and objective modality than LVEF to quantify LV contractile performance [6] and may represent a useful tool for the HFpEF population.4 In patients with chronic HFpEF, GLS has been shown to be a potential predictor of HF-related hospitalizations and cardiovascular (CV) death. [7-9] However, these studies have generally been small, restricted to clinical trial enrollees, and excluded patients who were acutely hospitalized with HFpEF. The complex pathophysiology of diabetic cardiomyopathy with acute HFpEF coupled with poor stratification tools and lack of available therapies provides the rationale for assessing the utility of LV GLS in HFpEF. In our study, we retrospectively identified diabetic cardiomyopathy patients hospitalized with acute heart failure either HFpEF or HFrEF who clinically required diuretic and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)& ARNI treatment. In this study, our aim is to assess the prevalence, distribution & clinical importance of LV GLS in diabetic cardiomyopathy patients, especially with HFpEF, and evaluation for the association of LV GLS on 30-day and 1-year mortality and rehospitalizations.

2. METHODS AND STUDY MATERIALS:

2.1 Aim of the study:

To access the left ventricular global longitudinal strain in diabetic cardiomyopathy with HF to reduce cardiovascular morbidity and mortality

2.2 Design of the Study & Ethical Committee Approval

Multi center retrospective analysis of left ventricular global longitudinal strain comparison between case (diabetic cardiomyopathy) versus the control group and correlation with LV ejection fraction & NT pro-BNP level. Further cohort analysis of hospitalization rate with mortality at 30 days and at 12 months.

2.3 Data collection

We assessed adult patients of diabetic cardiomyopathy with heart failure (HF) related hospital admission between 2017 through 2020 at HG SMS Hospital, Jaipur(India) NHICS, Jaipur (India)& BYNH Hospital, India who had a 2D Echocardiography anytime for the duration of the hospitalization with a visually predictable and deliberate biplane LVEF and were discharged on a loop diuretic, either torsemide or furosemide , SGLT2 inhibitors like empagliflogin and ARBs or ACE inhibitors/ARNI. All 2D echocardiograms performed at NH since 2017 are prospectively archived in the NH non-invasive cardiology Lab Database. Baseline clinical variables, including laboratory data, medications, and billing codes, for each patient were obtained from the registry. Follow-up data were obtained from patient's medical records and through the registry of diabetic cardiomyopathy, an ongoing databank of all patients who undergo a cardiac catheterization at NH, Jaipur. This study was approved by the NH ethical committee and the head of the cardiology department. we collected samples based on the following criteria.

(**Table-1**)

Inclusion criteria:	**Exclusion criteria:**
Age> 18 Years Left Ventricular Ejection Fraction- LVEF >25% Diabetic Patients- HBA1C >7 Coronary Angiogram- Normal Coronaries	Hypertension, Coronary Artery Disease Congenital Heart Diseases, Pregnancy, Valvular heart disease. Previous history of Viral Myocarditis.

Inclusion and exclusion criteria

2.4 Echocardiographic assessment

For LV GLS analysis, all echocardiograms were transferred in Digital Imaging and Communications in Medicine (DICOM) format from Vivid T8 (GE cardiac ultrasound Systems, 2D Cardiac Performance Analysis NEW software version) at a frame rate of 30–50/s. Retrospective speckle-tracking LV global longitudinal strain assessments on 2D images have been validated using DICOM structural reporting (SR), even when the original study was not intended for this aim. [10] Our analyses were performed by a single experienced operator blinded to other patient characteristics and outcomes. LVGL strain assessments for the LV were performed in the apical 4-chamber, 3-chamber, and 2-chamber view (Figure-1.3). Evaluation of speckle tracking, the endocardial border was manually traced in end-systole

(Figure-1.4). The reliability of speckle tracking was visually ascertained.

For the small number of studies in which patients were actively in atrial fibrillation, the previously validated index beat method was used to obtain longitudinal strain. [11] LVGL strain was evaluated as the change in length divided by the original length of the speckle pattern over the cardiac cycle and expressed as a percentage; longitudinal lengthening of myocardium was revealed as positive strain and shortening as negative strain at mode of strain imaging by support of special software. LV GLS for the whole LV was averaged from the consequences of 18 segmental peak systolic strains. Based on previous literature, normal LV GLS was defined as ≤−16%, where normal LV GLS ranged from −15.9 to −22.1%.(Yingchoncharoen T et al) [5,12].

We analyzed diastolic dysfunction as per American Society of Echocardiography guidelines(23) and included measurement of early (E) and late (A) diastolic mitral inflow velocities, mitral inflow deceleration times, isovolumic relaxation time(IVRT) and spectral Doppler tissue velocities of the septal mitral annulus (es). Ratios for E/A and E/e' were subsequently calculated; E/A > 0.96 and E/e' > 15 were considered abnormal, per American Society of Echocardiography guidelines (Figure-1.1A &1.1B). Heart failure in patients of diabetic cardiomyopathy with dynamic atrial fibrillation, deprived image quality, E/A fusion, or omitted Doppler images were excluded from the examination of diastolic dysfunction.

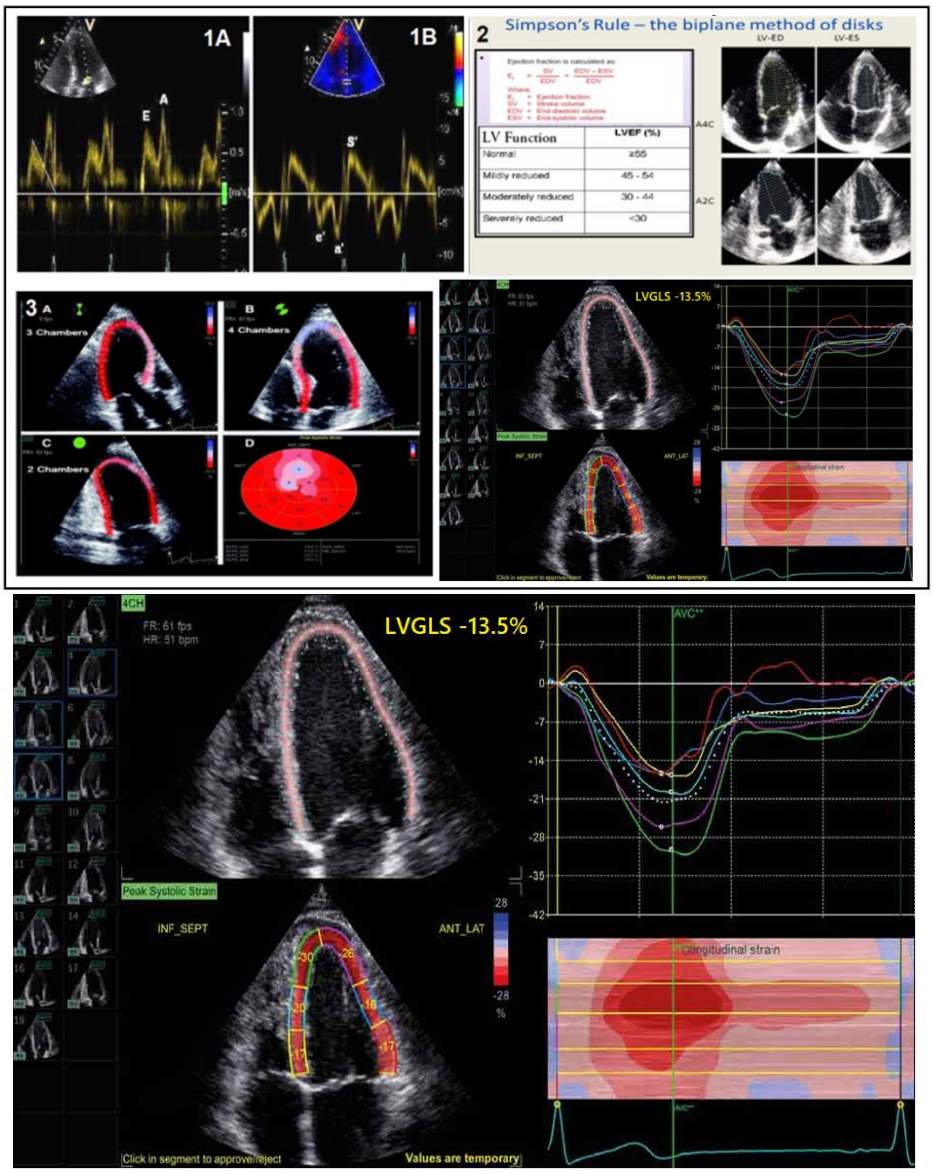

Figure- 1 (1.1A showed E/A ratio&1.1B E/e' for diastolic function , 1.2 showed LVEF calculation by simpsons method for systolic function , 1.3 showed LV GLS calculation 2chamber, 3 chamber, 4 chamber view. And 1.4 showed LV Global longitudinal strain rate and graph for systolic function. (Figure1.4)

2.5 Outcomes of Interest

Our interest was to get primary outcomes for the analysis of mortality at 30 days and 1-year post-discharge with a correlation of LV GLS. The secondary outcomes were a composite endpoint of mortality or rehospitalization at 30 days and a 1-year comparison between diabetic cardiomyopathy patients with HFpEF or HFrEF.

2.6 Statistical Analysis

We used IBM SPSS Statistical Package for the Social Sciences (SPSS SOFTWARE) and analysis of variance (ANOVA) for statistical analysis in our study: Patient demographics, medical history, laboratory findings, variables of 2D echocardiogram and in-hospital medical management were summarized as percentages and frequencies for categorical variables & medians (25th and 75th percentiles) for constant variables, and justified by either normal or abnormal LV GLS. Baseline characteristics were compared using the Pearson chi-square or exact tests for categorical variablesas appropriate.

We also used CPHR (cox proportional hazards regression) models to assess the association between LV GLS and mortality and rehospitalization. Candidate variables were selected for use in the multivariable model based on clinical judgment. We calculated data as hazard ratios (HRs) for 1-month & 1-year outcomes that were deliberate with resultant 95% confidence intervals (CIs). Data analysis was performed allowing for a constant LV GLS measure, and HRs reported per 1% increase in LV Global Longitudinal Strain.

3. RESULTS:

We enrolled 370 cases of diabetic cardiomyopathy patients and compared them with the control (n=350). We included adults, age 58+/- 16.5 years, with New York Heart Association (NYHA) class I through IV. Male: Female was 3:2.We found risk variables like sex, body mass index, smoking, blood pressure, cholesterol level (see Table-2) and 2D echocardiography data as diastolic function and systolic function of LV and RV function and comparison data of LV GLS and NT pro-BNP level(see Table-2).

Table-2

Variable	**Case(n=370)**	**Control(n=350)**	**P value**
AGE (Year)	49+/-11.5	46+/-13	<0.002
Male	N=240(64.9%)	N=210(60%)	<0.002
Female	N=130(36.1%)	N=140(40%)	<0.002
BMI	27.2+/-4.5	26+/-7.2	<0.005
SMOKING (%)	32.4(n=120)	37.1(n=130)	<0.004
Systolic BP (mmHg)	132±12	128±9	0.005
Diastolic BP (mmHg)	83±9	78±8	0.005
HbA1c level	**9.5 ±2.5**	**6.5±1.9**	**0.045**
Total Cholesterol (mg/dl)	**225+/-35**	**199+/-24**	**0.040**
LDL (mg/dl)	119 +/-17	91+/-13	0.050
HDL (mg/dl)	39+/-6	45+/-8	0.005
TG (mg/dl)	168+/-14	139+/-16	0.003
NT-Pro BNP (pg/ml)	**436 to 3212**	**156 to 387**	**0.054**
2D Echocardiography data			
LVEDD (cm)	5.2±0.90	4.8±0.84	0.045
LVESD (cm)	4.1±0.96	3.4±0.77	0.042
LVEF (%)	**46±11**	**59±6**	**0.045**
LA Volume (ml)	38+/-5.2	33+/-4.7	0.045
IVRT (msec)	109 +/-7.4	92+/-3.8	0.050
DT (msec)	212 +/-24	202+/-16	0.005
E/A	0.68+/-0.4	1.09+/-0.8	0.005
E/e'	13.5+/-6.2	9.4+/-2.6	0.004
RVEF (%)	61+/-5	62+/-7	0.041

TAPSE	20+/-4	22+/-5	0.032
LV GLS (%)	**-10.6 ± 4.3%**	**-18.7 ± 2.3%**	**0.042**

Risk Variables and Echoacardiography data in Case vs Control.

We further divided two groups based on LVEF, Group 1 HF with reduced ejection failure (HFrEF <50%) and Group 2 HF with preserved ejection failure(HFpEF >50%). We initiate a noteworthy difference in left ventricular global longitudinal strain(LVGLS) in the diabetic cardiomyopathy group -10.5 ± 4.2% as compared to the control group LVGLS was -18.6 ± 2.4%. Left ventricular ejection fraction (LVEF) was assessed in the case versus the control group (46±11% vs 59±6%). Our study revealed a mortality rate comparison between HFrEF versus HFpEF at 30 days(7.1% vs 4.3% p<0.004) and 12 months follow up(28.5 % vs 17.4% p<0.041) see table-3. LV GLS <-9% was significantly associated with higher 12 months mortality and HF patients with diabetic cardiomyopathy, not only in reduced LVEF but also in fair LVEF(see Table-4) and also suggested three fold higher mortality rate in HFpEF group patients who had LVGLS <-9% as compared to HFpEF patients who had >-9%- to -14% strain rate of LV(see Table-4). Data from the unadjusted and adjusted Cox regression models, reporting HRs per 1% increase in LV GLS. On adjusted analysis, LV GLS was associated with increased mortality (HR 1.22 per 1% increase; 95% CI 1.09–1.39; P = 0.004) and a nominal increase in the composite endpoint of rehospitalization at 30 days (HR 1.18 per 1% increase; 95% CI 1.06–1.28; P = 0.002).

Table-3

Variable	**Case- Group1 – HFrEF (n=14)**	**Case- Group 2 – HfpEF (n=23)**	**P Value**
LVEF %	**39±4**	**56±7**	0.005
NT-Pro BNP level pg/ml	1456 to 3212	436 to 1167	0.005
E/e'	15.5+/-5.1	12.4+/-6.9	0.004
TAPSE	19+/-4	20+/-3	0.041
LA Volume ml	37+/-3.2	36.3+/-2.7	0.005
LV GLS %	**-9.7. ± 2.8%**	**-11.4 ± 3.6%**	0.005
Death rate % at 30 days	**7.1(n=1)**	**4.3(n=1)**	0.004
Death rate % at 12 months	**28.5(n=4)**	**17.4(n=4)**	0.041

BNP level, LVGLS and death rate in HFrEF vs HFpEF patients.

Table-4

Variable	**Group-2A – HFpEF (n=12)**	**Group-2B- HFpEF (n=11)**	**P Value**
LV GLS %	< -9 %	-9% to -14%	0.005
NT-Pro BNP level pg/ml	548 to 1167	436 to 967	0.005
Death rate % at 12 months	25(n=3)	9(n=1)	0.004

Mortality rate in group 1 vs group 2 based on LV GLS.

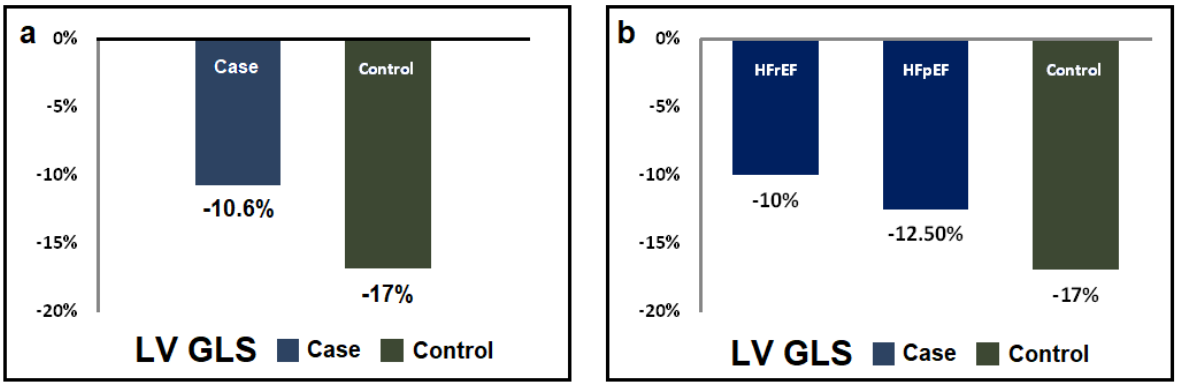

Figure-2: 2a-LV GLS variation between case versus control , 2b-LV GLS in case (HFrEF & HFpEF) versus control

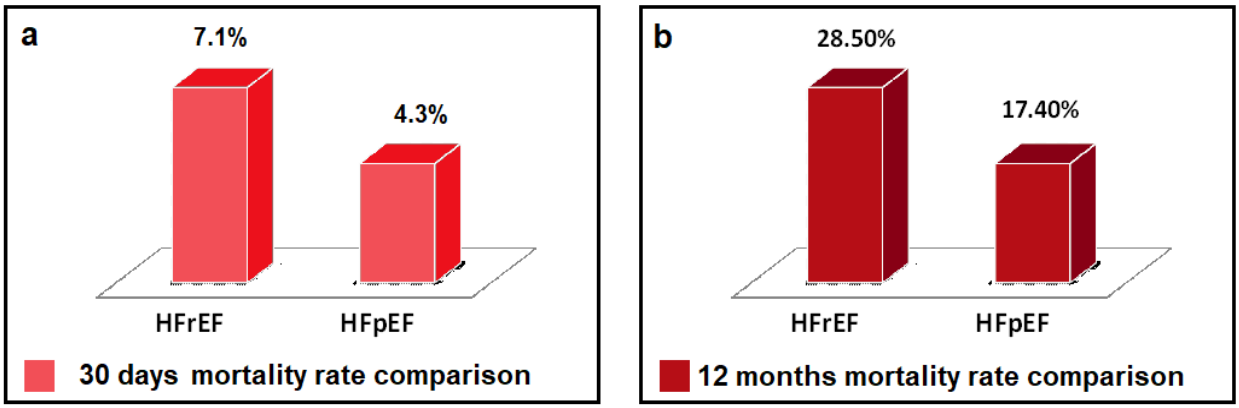

Figure-3: Mortality between HFrEF versus HFrEF patients of DbCMP; 3a- at 30 Days , 3b- at 12 Months)

4. DISCUSSION:

Diabetes mellitus affects almost every tissue in the body and causes significant organ dysfunction that results in diabetes-related morbidity and mortality. Diabetes mellitus describe changes in the heart in different ways like coronary artery disease (CAD) due to accelerated atherosclerosis, cardiac autonomic neuropathy (CAN), and diabetic cardiomyopathy (DbCMP). Although there is high awareness among clinicians about the first two disease entities, DbCMP is poorly recognized by most physicians and diabetologists. [20]

DbCMP was first described by Rubler et al[21] in 1972. DbCMP is defined as myocardial dysfunction occurring in patients with diabetes in the absence of CAD, hypertension, or valvular heart disease[21-22]. Diabetes mellitus is a renowned risk factor for the expansion of heart failure. Heart failure reduces the quality of life of the affected individual and complicates the management of diabetes by alterations in the pharmacokinetics of anti-diabetic medications. Hence, early diagnosis and prompt management of these patients are of paramount importance.

The prevalence of different degrees of heart failure among diabetic subjects was as high as 19%-26% in different major clinical trials[23]. The real prevalence of DbCMP is not yet established, due to the lack of large study data from special populations with diabetic patients. The prevalence of diastolic dysfunction in patients with type 2 diabetes mellitus (T2DM) was shown to be up to 30% in some studies[23] However, there are other studies which reported a prevalence as high as 40%-60%[24] The pathogenesis and pathophysiology of DbCMP is not yet fully defined. The development of diabetic cardiomyopathy is multi-factorial. Different anticipated mechanisms include metabolic turbulence, insulin resistance, microvascular illness, alteration in the renin-angiotensin system (RAS), cardiac autonomic dysfunction , inflammation and myocardial fibrosis[25,28].

Chronic hyperglycemia is thought to play a central role in the development of DbCMP, although multiple complex mechanisms and interplay of many molecular and metabolic events within the myocardium and plasma contribute to the pathogenesis. The chief metabolic abnormalities in diabetes are hyperglycemia, dyslipidemia & chronic inflammation which lead to stimulating reactive oxygen species (ROS) or nitrogen species that reason most of the diabetic complications, including diabetic cardiomyopathy & diabetic nephropathy [26-27] see figure-4. Numerous adaptive responses caused by these metabolic abnormalities leads to cardiac dysfunction resulting in heart failure.

In this single-center retrospective analysis of LV GLS in DbCMP patients with cohort analysis of cardiovascular morbidity & mortality after the medical management. We revealed that the majority of patients of DbCMP who were admitted with acute HFpEF or HFrEF had abnormal LV GLS. As per basic science, LVGLS is a straightforward constraint that expresses longitudinal shortening as a percentage (change in length as a proportion to baseline length) whereas LVGLS is consequent from speckle tracking & accessed by the meting out of apical views of the LV.

Dissimilarity in various software from different manufacturers of Echo machines derives LV GLS differently. However, universal features engage view selection, significant end-systole, tracing the myocardium, analyzing tracking quality, and addition for integrative results. As LV GLS usually varies with age, sex, and LV loading circumstances, significant abnormal GLS is not simple. On the other hand, in adults, GLS <16% (sic) is abnormal, GLS >18% (sic) is normal, and GLS 16% to 18% is borderline. (GLS is uttered as a negative number.)

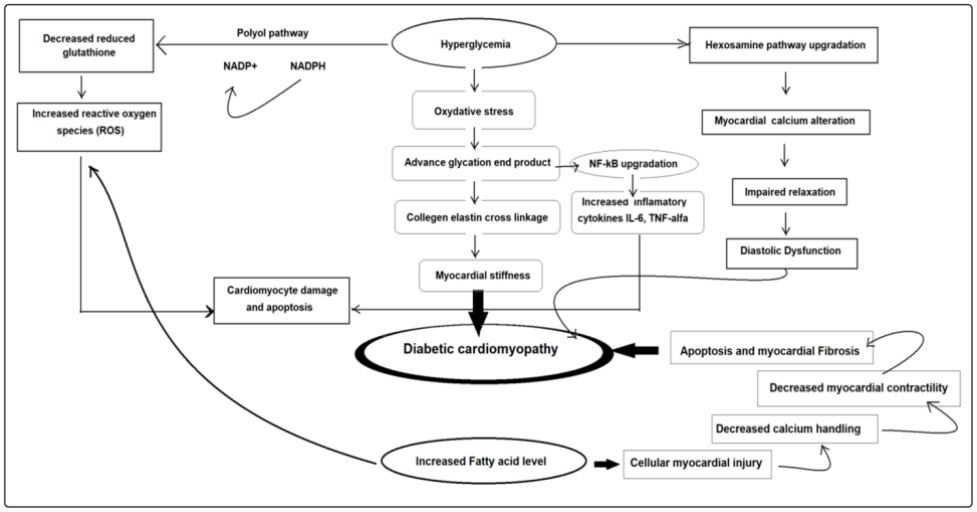

Figure 4- Metabolic abnormalities in diabetes are hyperglycemia, hyperlipidemia and inflammation leads heart failure and describe diabetic cardiomyopathy.

Our study showed a statistically significant association between LV GLS and mortality or a composite endpoint of mortality or rehospitalization at 30 days or 1 year. Raised LV GLS was associated with significantly worse 30-day mortality rates and nominally higher composite outcomes with co-morbid variables; however, there remained no association with clinical outcomes at 12 months post-discharge. To our acquaintance, this is the initial study to evaluate DbCMP hospitalized patients with acute HFpEF or HFrEF and illustrate the association of LV GLS with both 1 month and 12 months clinical outcomes. It is acknowledged that mortality rates subsequent a hospitalization for acute HFpEF are as good as to rates for HFrEF, [13] even up to 5 years after discharge. Data subsist on cardiac biomarkers, clinical features, or 2D echocardiographic variables that may forecast worse short-term outcomes of post-discharge and the relationship of HFpEF echo variables with clinical outcomes focused on measurements of diastolic dysfunction among chronic patients with HFpEF. [13] Therefore, the exploit of LV GLS to recognize a division of acute HFpEF patients with short-term worse outcomes. Self-determining of diastolic dysfunction may express a new advance tool to justify high-risk patients with inimitable cardiac pathophysiology for probable interventions earlier to discharge.

As per past data, the association between LV GLS was no longer statistically significant at 12 months in contradistinction to previous data that revealed LV GLS to be a significant predictor of clinical outcomes such as rate of hospitalizations or mortality in patients of DbCMP with chronic HFpEF. [5] Shah et al. Found that abnormal LV GLS was a predictor of cardiovascular death and HF hospitalizations, [5] As per the TOPCAT trial about aborted cardiac arrest or CV death in 447 patients with chronic HFpEF enrolled with 2.6 years follow-up.

Our data differs from Shah et al. study in many key sectors. The Shah et al. analyses were a theme to firm inclusion and exclusion criteria for the TOPCAT trial. In our study, patients with uncontrolled HTN, severe renal dysfunction, severe COPD, recent myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass grafting were excluded. [14] Relatively, our patient population was paying attention to acute HF and extra envoy of HFpEF patients with the generous co-morbid disease(s) encountered.

Shah et al. revealed worse outcomes beyond 12-24 months; so far, our study did not locate a significant relationship at 12 months post-discharge. Difference between acute & chronic HF; for example, chronic HF therapies target regulation at the neurohormonal level, preventing cardiac remodeling and control of co-morbidities.Although acute HF therapies target decongestion, preventing renal insufficiency, maintaining adequate cardiac output, and reversal of decompensation etiology. Different haemodynamics and states of congestion between acute & chronic HF patients could have essential unrecognized implications concerning the relationship between abnormal LV GLS on long-term clinical outcomes. An additional impending explanation is that HFpEF is principally the elder age group and half of the patients with HFpEF die from non-cardiac causes. [14] Hence, with many rival co-morbidities, abnormalities in LV contractility in acute HF, as determined by LV GLS, may engage in recreation a lesser role in long-term clinical outcomes.

Our study revealed boosted mortality in both groups either HFrEF or HFpEF with abnormal LV global longitudinal strain , as per hazard ratio(HR) increased mortality as 1% increase LV GLS and near parallel to two studies

(Sengelov M et al, [18] & Dalen H et al HUNT study[19]). Our study revealed high levels of NT-proBNP among abnormal LV GLS group, which is in contour with prior data that noted considerably higher levels of BNP or NT-proBNP among chronic HFpEF patients with abnormal LV GLS versus normal LV GLS. [15-17] Therefore, in preserved LVEF sub-population, similar echocardiographic data of diastolic dysfunction and increased levels of NT-proBNP. Left Ventricle Global Longitudinal Strain represents a beneficial tool to justify myocardial dysfunction that contributes to the complex pathophysiology of acute HFpEF at an independency of abnormal diastolic function.

4.Clinical Perspectives:

The study results show that myocardial function in DbCMP patients may be altered even in the absence of clinical symptoms, hypertension, and CAD. This indicates that echocardiographic assessment with 2D strain should be considered to detect subclinical myocardial dysfunction. The problem of potential therapeutic strategies needs further investigation. The relationship between systolic impairment with LDL may suggest cholesterol be the risk factor of cardiac damage and may indicate the need for early treatment of hyperlipidemia accompanying type 1&2 DM. As the diabetic group was relatively small, this subject should be analyzed in a larger population study.

5.Limitations:

We have some limitations in our study; First, this was a single-center retrospective analysis, and our data on subsequent hospitalizations were limited. LV GLS data variation due to different machine software while our statistical models adjusted for variables likely to affect mortality, measured and unmeasured variables may contribute in unknown ways. the majority of patients who had a 2D echocardiogram during hospitalization were included, and inherent bias may subsist regarding which patients received a 2D echocardiogram. In our study we only included data from the index 2D echocardiogram, so we only captured each patient at a single snapshot in particular time & without serial measurements of LV GLS during study. Although 2D echocardiograms were obtained during the acute hospitalization, at hand is expected heterogeneity among our cohort with respective therapy (i.e. ARBs or ACE inhibitors, diuresis, ARNI) acknowledged prior to the evaluation, which may have pretentious our results, as LV GLS residue vulnerable to loading clinical conditions.

6. Conclusion:

Left Ventricular Global Longitudinal Strain has more significant value to access heart failure and mortality among diabetes induced cardiomyopathy.

7. Acknowledgement :

We would like to thank to our patients for their consent and organization team members for collecting data.

8. Conflict of interest:

There are no conflicts of interest and there was no funding and grants for our study.

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