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Original Research Article

Evaluation of Subclinical Atherosclerosis and it's Association with LV Strain and Volume in Patients with Type 2 DM: A Speckle Tracking ECHO Study

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Abstract

Background: Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide with continuously increasing prevalence. Macroangiopathy, a relatively serious complication of DM. Carotid intima-media thickness (CIMT) is an established marker of atherosclerosis. Left ventricular global longitudinal strain (LVGLS) is an echocardiographic measure of left heart function, which can unmask subclinical left heart abnormalities. However, it is unknown whether increased CIMT and FMD are independently associated with subclinical left heart dysfunction assessed by speckle-tracking echocardiography.

Aim: To detect subclinical atherosclerosis and LV Strain and Volume in type 2 diabetes patients.

Methods: 100 consecutive adult patients (> 18 years of age) with type 2 diabetes (T2DM) referred for cardiovascular risk assessment as part of regular patient care attending the OPD of the Department of Cardiology, SCBMCH, Cuttack were selected as observational group and subsequently compared with control group of 100 age and gender matched healthy subjects.

Results: Average CIMT was 0.071 ± 0.01cm, higher and statistically significant among the DM cases in comparison to controls (0.043 ± 0.010 cm, p=<0.001). No difference in, septal s', and lateral a' between the groups was found. Subjects with diabetes showed a reduced GLS (-17.78 ± 2.86) as compared to controls (- 23.29 ± 1.82) [p <0.001]. Finally, Pearson correlation coefficient between FMD % and GLS is 0.401 indicating a significant positive weak linear relationship between these two.

Conclusion: Adding GLS, the most robust deformation marker, to LVEF increases the accuracy of predicting early ventricular functional decline and future cardiovascular events in the risk population.

Keywords: *Subclinical Atherosclerosis, LV, Type 2 DM*

Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide with continuously increasing prevalence. [1] Cardiovascular disease is the major complication of diabetes, accounting for 50% of all diabetes mortality. [2] Patients with type 2 DM are at increased risk of heart failure and there is evidence for the distinct clinical entity of diabetic cardiomyopathy, independent of traditional cardiovascular risk factors. [3] This entity is characterized by microvascular disease, altered myocardial metabolism, and increased myocardial fibrosis that lead to gradual decline in left ventricular (LV) function with impairment in LV relaxation first and then followed by systolic dysfunction that may progress over time to congestive heart failure (CHF). [4]

Macroangiopathy, a relatively serious complication of DM, often represents a leading cause of life-threatening complications and even clinical death of the patients, resulting from atherosclerosis-induced acute myocardial infarction (AMI), heart failure (HF) or cerebral infarction.[5] Therefore it is of great importance to discover and diagnose intimal lesions in their early stages and treat them. [6]

Carotid intima-media thickness (CIMT) is an established marker of atherosclerosis [7] and serves as an atherosclerotic surrogate end-point for possible therapeutic interventions. [8,9] Indeed, recent studies demonstrated that CIMT predicts the occurrence of HF in various clinical conditions and across races. [10] Likewise endothelial function assessed by non-invasive Flow Mediated Dilation (FMD) of the brachial artery correlates with invasive testing of coronary endothelial function, as well as with the severity and extent of coronary atherosclerosis. This testing has provided valuable insights into early atherogenesis, as well as into the potential reversibility of endothelial dysfunction by various strategies, including pharmacological agents (lipid lowering, ACE inhibition), L-arginine, antioxidants, and hormones. [11]

Left ventricular global longitudinal strain (LVGLS) is an echocardiographic measure of left heart function, which can unmask subclinical left heart abnormalities, even when LV ejection fraction and left atrial volume are in the normal range. In fact, LVGLS has prognostic value for cardiovascular events and mortality, which is independent of and additive to that of LV ejection fraction [12,13] However, it is unknown whether increased CIMT and FMD are independently associated with subclinical left heart dysfunction assessed by speckle-tracking echocardiography. Accordingly, the present study is aimed to investigate the association of CIMT and FMD with subclinical LV dysfunction in a large sample of the type 2 diabetes population without overt cardiac disease.

Aim and objectives

Aim:

To detect subclinical atherosclerosis and LV Strain and Volume in type 2 diabetes patients.

Objectives:

- To evaluate subclinical atherosclerosis in patients with type 2 diabetes mellitus using ultrasonography to detect carotid intima-medial thickness (CIMT) and brachial flow mediated dilation (FMD) at baseline.
- To evaluate LV regional tissue velocity, strain, strain rate, and volume variables in diabetic patients using 2D echocardiography and tissue Doppler imaging.

Materials and Methods

100 consecutive adult patients (> 18 years of age) with type 2 diabetes (T2DM) referred for cardiovascular risk assessment as part of regular patient care attending the OPD of the Department of Cardiology, SCBMCH, Cuttack were selected as observational group and

subsequently compared with control group of 100 age and gender matched healthy subjects.

Materials:

The study group included 100 consecutive adult subjects >18 years age attending the OPD of the Department of Cardiology, SCBMCH, Cuttack from August 2020 to August 2021.

Patients Selection:

Inclusion Criteria –

- Adult patients (> 18 years of age) diagnosed with T2DM.
- Age and sex similar healthy controls.

Exclusion Criteria -

- Patients with any pre-existing heart disease.
- Patients with known cardiovascular risk factors:
  - Hypertension
  - Dyslipidemia
  - Tobacco usage
  - Chronic smoker
  - Alcohol abuser
- Patients belonging to vulnerable groups such as pregnant or lactating women, patients younger than 18 years or older than 60 years, critically sick or terminally handicapped patients.
- Patients refusing consent.

Controls were selected from healthy healthcare workers. Written informed consent was obtained from the participants after being briefed about the objectives of the study and the non-invasive assessment method. Follow up evaluation was not conducted in this study.

A baseline demographic data was collected at the time of recruitment and patients were evaluated by taking history, clinical examination, electrocardiography, routine blood investigations, cardiac markers and echocardiography to determine eligibility for enrolment in the study.

Anthropometic analysis including height, weight, Body mass index (BMI) (kg/m2), waist circumference, hip circumference, waist to hip ratio were measured in both cases and control groups. BMI of >25 kg/m2 but <29.9 kg/m2 was defined as overweight and a BMI> 30 kg/m2 as obesity. A waist circumference >90 cm in men and>80 cm in women was taken as abnormal. Waist to hip ratio >0.88 in men and >0.80 in women was considered abnormal.

Routine biochemistry [complete haemogram, urea, creatinine, CRP, urine examination including routine and microscopy-active sediment], fasting blood sugar. post-prandial blood sugar, HbA1c, fasting lipid profile and viral markers such as hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) was done in all patients.

Blood pressure was recorded in left arm in supine position with an appropriately sized cuff using a sphygmomanometer. Hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic ≥ 90 mmHg and/or on anti-hypertensive treatment.

Diabetes mellitus (DM) was defined as patients having fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/L) and/or two-hour plasma glucose level of ≥ 200 mg/dL (11.1 mmol/L) during a 75gm OGTT and/or an HbA1c level of 6.5% or higher. [14] Risk factors such as age, sex, diabetes, hypertension was evaluated in both cases and control group.

Carotid intimal-medial thickness (CIMT):

Carotid intimal-medial thickness was performed by a high resolution, electronic linear array and high frequency (7.5 MHz) transducer, attached to echocardiography system. The CIMT was measured by the caliper as the distance between the inner echogenic line representing the intima blood interface and the outer echogenic line

representing the adventitia-media junction. A minimum of three measurements of the common carotid artery were taken 1 cm proximal to the bifurcation to derive mean CIMT, on the left side (CIMT LA) and on the right side (CIMT RA) and average of both the sides (CIMT AV). The mean value of each set of the readings represented the mean CIMT that was taken for final analysis.

Flow mediated dilatation of brachial artery:

Arterial endothelial function of the brachial artery was assessed noninvasively by ultrasound examination of the vasodilation response to endothelium-dependent and -independent stimuli. The right brachial artery, proximal to the antecubital fossa, was imaged longitudinally using the linear-array transducer. Flow-mediated endothelium-dependent (FMD) vasodilatation was assessed by measuring the brachial artery diameter at baseline and during reactive hyperemia, the cuff was inflated to at least 50 mm Hg above systolic pressure to occlude arterial inflow for 5 minutes. Flow mediated dilatation of the artery was expressed as maximum percentage change in arterial diameter during the phase of hyperemia with reference to baseline diameter.

$$FMD\% = \frac{Maximum\ Diameter - Baseline\ Diameter}{Baseline\ Diameter} * 100\%$$

The parameters were measured for 3 consecutive cardiac cycles, and the average was taken. Same protocol was followed in both cases and controls.

Echocardiographic evaluation:

Detailed echocardiographic evaluation was performed using a GE healthcare Vivid 8 ECHO machine. Conventional echo-Doppler parameters including LV end-diastolic dimensions and LV end-diastolic volumes, LV end-systolic dimensions and LV end-systolic volumes, interventricular septal thickness (IVST in diastole), LV posterior wall thickness (PW in diastole), LV fractional shortening (LVFS), LV stroke volume (LVSV) and LV ejection fraction (LVEF) were measured according to the American Society of Echocardiography guidelines.[15] The LV dimensions were obtained from M-mode parasternal long-axis views while LV volumes were obtained from the apical four- and two-chamber views using standard transducer positions. Using the modified Simpson's rule, ejection fraction (EF) was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume.

Diastolic Doppler parameters were recorded including early and late trans-mitral diastolic velocities (E velocity and A velocity) and their ratio (E/A) and deceleration time (DT) of the trans-mitral diastolic flow. Tei index or myocardial performance index (MPI), a load independent index of combined systolic and diastolic function, was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Measurements were performed over three heartbeats, and an average of the three measurements was taken.

Tissue doppler imaging (TDI) measures:

TDI analysis of the mitral annulus was performed in the apical four-chamber window. A 5 mm sample volume was placed at the desired area of interest and systolic myocardial velocities (Sm) at the basal segments of the lateral LV wall (LV-Sm), septal wall (septal-Sm), early and late diastolic myocardial velocities (e', a'), and their ratio (e'/a') of the same basal segments of lateral LV wall and septal were also recorded.

Stain and strain rate imaging:

GLS was measured using speckle tracking echocardiography at a frame rate of 43 to 60 fps. 2D Grey scale echo image from 3 standard planes 4 chamber, 2 chamber and 3 chamber were acquired. The AFI algorithm tracks the percent of wall lengthening and shortening in a set of three longitudinal 2D-image planes

(apical long, two chambers and four chambers) and displays the results for each plane. It then combines the results of all three planes in a single bull's-eye summary (agreeing with the standard 17-segment model), which presents the analysis for each segment along with a global peak systolic value for the LV.

Result

Table 1: Distribution of the subjects based on the age group

AGE GROUP	DM CASES N (%)	CONTROL N (%)
30-40	6 (6)	26 (24)
41-50	43 (43)	45 (45)
51-60	50 (50)	29 (29)
>60	1 (1)	0 (0)
TOTAL	100 (100)	100 (100)
MEAN AGE	50.23 ± 5.68	45.94 ± 7.37

The age of the patients included in the study were >18 years. A majority of the subjects in the study group belonged to the age group of 51-60 years, comprising a total of 50% followed by age group of 41-50 years (43%). Only 6 % of subjects were below 40 years of age. Majority in control group belonged to 41-50 (45%) age group. The mean age of the study group was 50.23 ± 5.68 years as against 45.94 ± 7.37 years in controls.

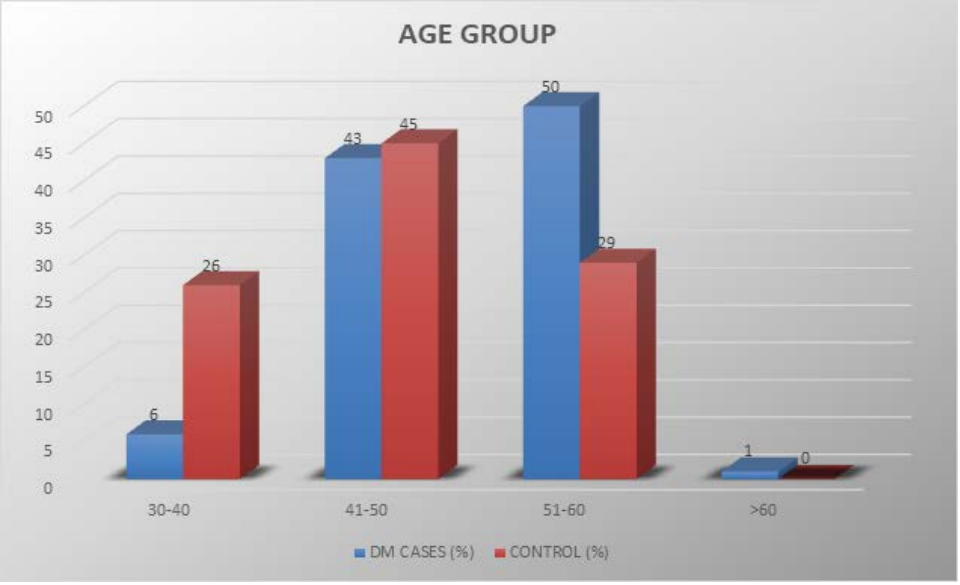


Table 2: Distribution of the subjects based on gender

GENDER	DM CASE N (%)	CONTROL N (%)
MALE	63 (63)	66 (66)
FEMALE	37 (37)	34 (34)
TOTAL	100 (100)	100 (100)

Out of 100 diabetic subjects 63% were male and 37% female. On the other hand, control group had 66% male and 34% female.

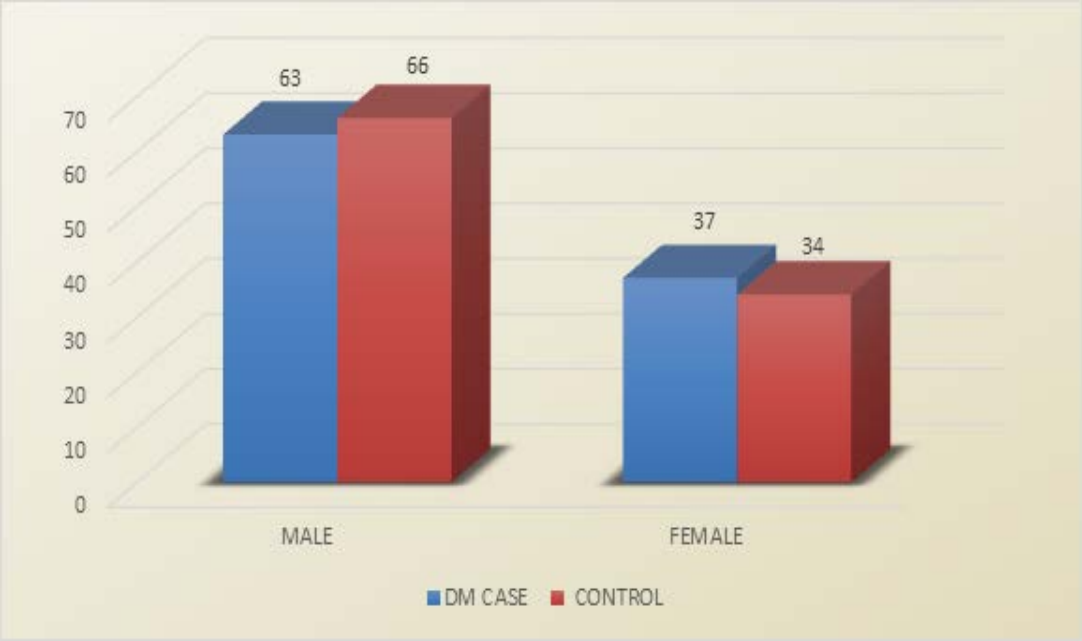
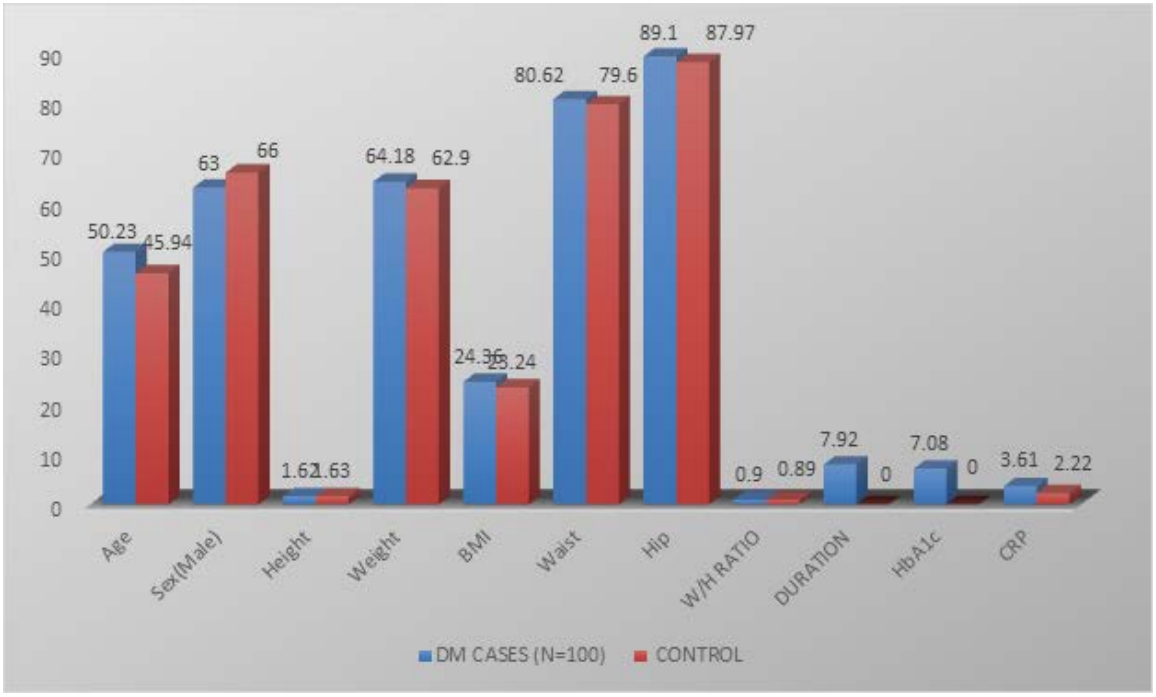


Table 3: Baseline Characteristics, Anthrpometric Measurements znd Dm Disease Characteristics

VARIABLES	DM CASES (N=100)	CONTROL (N=100)	p value
Age (in years)	50.23 ± 5.68	45.94 ± 7.37	0.410
Sex (Male)	63 (63%)	66 (66%)	0.451
Sex (Female)	37 (37%)	34 (34%)	0.350
Height (m)	1.62 ± 0.05	1.63 ± 0.06	0.701
Weight (kg)	64.18 ± 8.36	62.9 ± 7.54	0.061
BMI (kg/m2)	24.36 ± 2.5	23.24 ± 2.45	0.049
Waist (cm)	80.62 ± 8.57	79.6 ± 7.08	0.740
Hip (cm)	89.1 ± 5.11	87.97 ± 5.71	0.220
W/H RATIO	0.90 ± 0.06	0.89 ± 0.07	0.760
MEAN DURATION OF ILLNESS	7.92 ± 2.86	-	-
HbA1c	7.08 ± 1.08	-	-
CRP	3.61 ± 1.97	2.22 ± 0.9	0.310

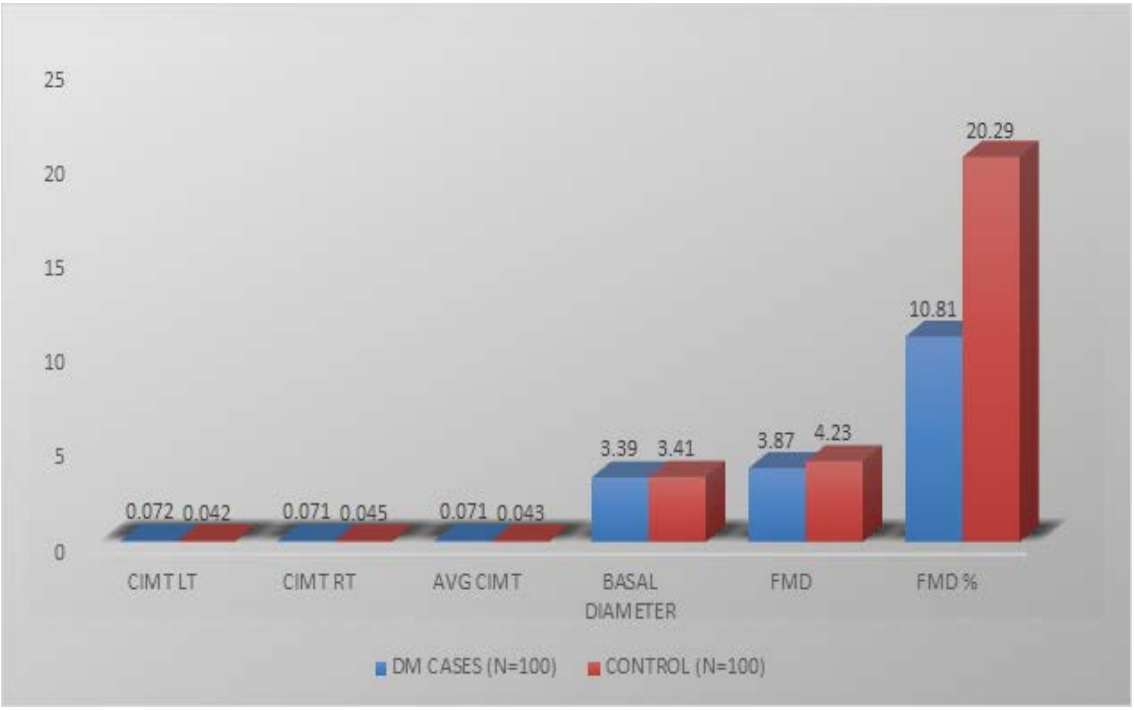


The mean age (50.23 ± 5.68 vs 45.94 ± 7.37 , p= 0.41), gender distribution, height (1.62 ± 0.05 vs 1.63 ± 0.06, p=0.701), weight (64.18 ± 8.36 vs 62.9 ± 7.54, p=0.061), waist (80.62 ± 8.57,p=0.74), hip and W/H ratio (0.90 ± 0.06 vs 0.89 ± 0.07, p= 0.76) are comparable amongst the study group and controls with statistically significant difference found between BMI (24.36 ± 2.5 vs 23.24 ± 2.45, p =0.049) in the subgroups. The mean disease duration was 7.08 ± 3.87 years and HbA1c 7.08 ± 1.08 with a comparable CRP (3.61 ± 1.97 vs 2.22 ± 0.9 p = 0.310) between the two groups

Table 4: Carotid Intima Medial Thickness and Brachial Artery Flow Mediated Dilation:

	DM CASES (N=100)	CONTROL (N=100)	p value
CIMT LT (cm)	0.072 ± 0.01	0.042 ± 0.01	<0.001
CIMT RT (cm)	0.071 ± 0.01	0.045 ± 0.01	0.031
COMBINED CIMT (cm)	0.143 ± 0.02	0.087 ± 0.02	<0.001
AVERAGE CIMT (cm)	0.071 ± 0.01	0.043 ± 0.01	<0.001
BASAL BRACHIAL ARTERY DIAMETER (mm)	3.39 ± 0.48	3.41 ± 0.49	0.056
FMD (mm)	3.87 ± 0.33	4.23 ± 0.68	<0.001
FMD %	10.81 ± 2.30	20.29 ± 4.62	<0.001

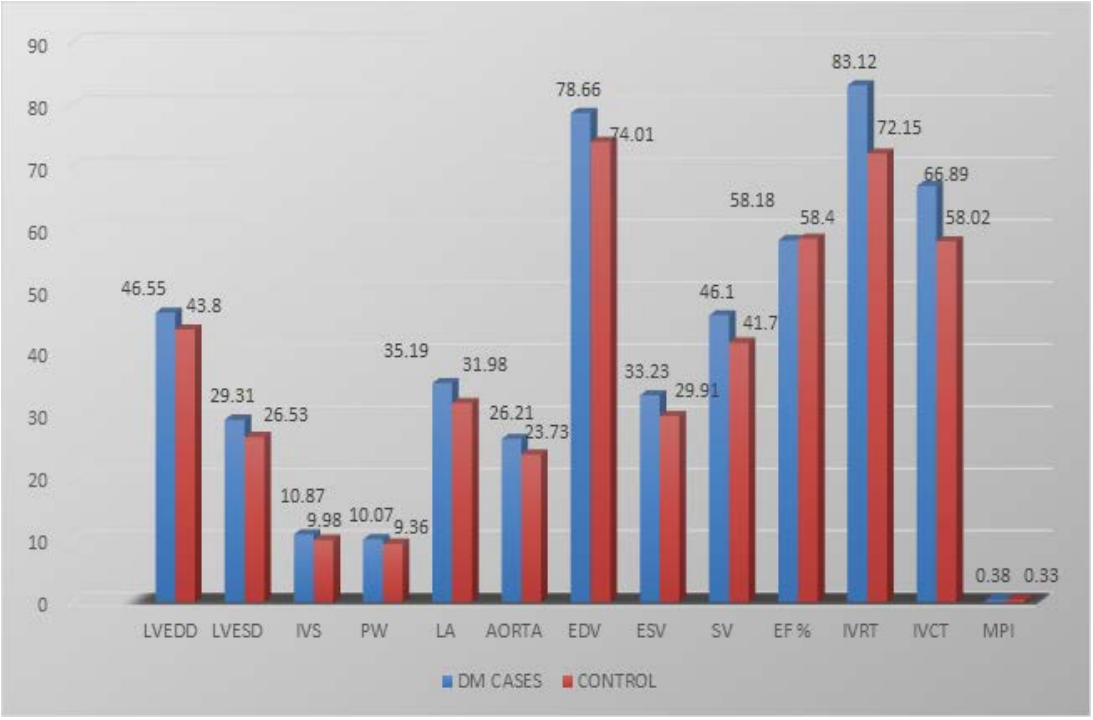
The mean CIMT left was 0.072 ± 0.01 cm in cases which was statistically significant compared to controls (0.042 ±0.01 cm) ($p \leq 0.001$), similar to mean CIMT right (0.071 ± 0.01 vs 0.045 ± 0.011 cm, p = 0.031). Average CIMT was 0.071 ± 0.01cm, higher and statistically significant among the DM cases in comparison to controls (0.043 ± 0.010 cm, p=<0.001).



Even though there was no difference in the baseline Brachial artery diameter [BADB] (3.39 ± 0.48 vs 3.41 ± 0.49, p = 0.056), the mean Brachial artery diameter post-ischemia (BADAV) (3.87 ± 0.33 vs 4.23 ± 0.68, p < 0.001) and change in BADAV which is expressed as FMD% (BADAV-BADB/BADB) (10.81 ± 2.30 vs 20.29 ± 4.62, p<0.001) was significantly lower in DM cases in comparison to controls suggesting lesser vasodilatation in response to ischemia in patients with DM

Table 5: Conventional Echocardiographic Parameters

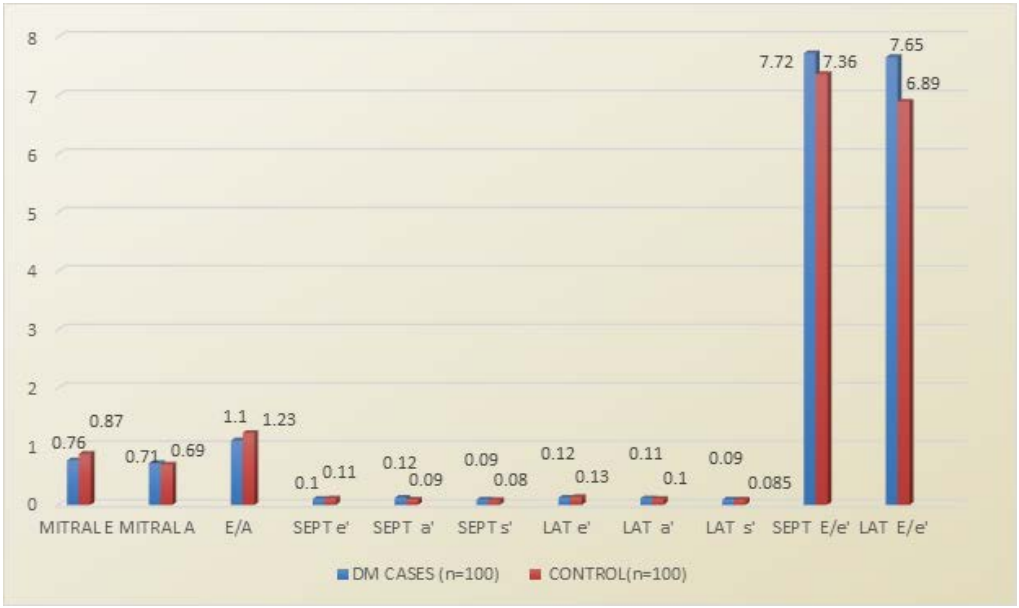
ECHO PARAMETERS	DM CASES (N=100)	CONTROL (N=100)	p value
LVEDD (mm)	46.55 ± 4.35	43.80 ± 3.55	0.058
LVESD (mm)	29.31 ± 4.45	26.53 ± 3.57	0.322
IVS (mm)	10.87 ± 1.4	9.98 ± 0.96	0.204
PW (mm)	10.07 ± 1.14	9.36 ± 0.76	0.247
LA (mm)	35.19 ± 5.77	31.98 ± 3.59	0.415
AORTA (mm)	26.21 ± 3.27	23.73 ±2.58	0.059
EDV (ml)	78.66 ± 13.44	74.01 ± 12.98	0.057
ESV (ml)	33.23 ± 7.45	29.91 ± 6.24	0.076
SV (ml)	46.10 ± 8.91	41.70 ± 9.02	0.145
EF %	58.18 ± 4.99	58.40 ± 5.18	0.178
IVRT (ms)	83.12 ± 8.85	72.15 ± 5.49	0.021
IVCT (ms)	66.89 ± 7.74	58.02 ± 7.92	< 0.001
MPI	0.38 ± 0.05	0.33 ± 0.02	< 0.001



All the routine echocardiographic parameters including LV dimensions [LVEDD (46.55 ± 4.35 vs 43.80 ± 3.55, p=0.058), LVESD (29.31 ± 4.45 vs 26.53 ± 3.57, p=0.322)], LV volume [ESV (33.23 ± 7.45 vs 29.91 ± 6.24, p= 0.076), EDV (78.66 ± 13.44 vs 74.01 ± 26.0, p=0.057)] and systolic function (LVEF 58.18 ± 4.99 vs 58.40 ± 5.18, p=0.178) were similar between the DM cases and controls. Parameters of diastolic function like IVRT (83.12 ± 8.85 vs 72.15 ± 5.49, p=0.021), IVCT (66.89 ± 7.74 vs 58.02 ± 7.92, p<0.001) and MPI (0.38 ± 0.05 vs 0.33 ± 0.02, p <0.001) were significantly different amongst the study group and controls

Table 6: Tissue Doppler Parameters

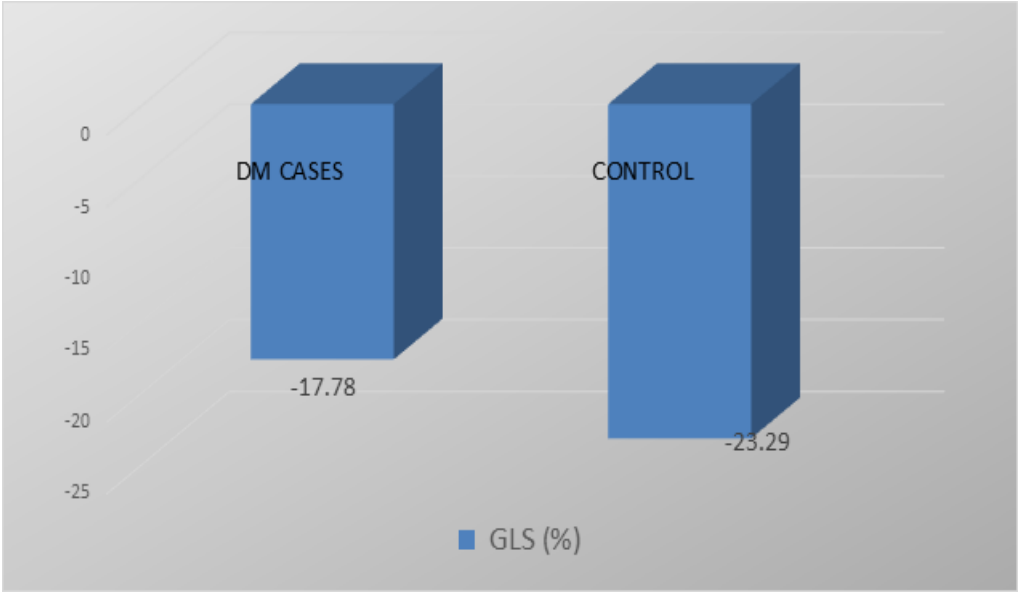
TDI FINDINGS	DM CASES (N=100)	CONTROL (N=100)	p value
MITRAL E	0.76 ± 0.11	0.87 ± 0.16	< 0.001
MITRAL A	0.71 ± 0.18	0.69 ± 0.2	0.039
E/A	1.10 ± 0.30	1.23 ± 0.42	0.012
SEPTAL e'	0.10 ±0.02	0.11 ± 0.02	0.022
SEPTAL a'	0.12 ± 0.03	0.09 ± 0.016	0.031
SEPTAL s'	0.09 ± 0.01	0.08 ± 0.01	0.054
LATERAL e'	0.12 ± 0.02	0.13 ± 0.01	0.010
LATERAL a'	0.11 ± 0.03	0.10 ± 0.01	0.061
LATERAL s'	0.09 ± 0.01	0.085 ± 0.015	0.049
SEPTAL E/e'	7.72 ± 1.75	7.36 ± 2.30	0.014
LATERAL E/e'	7.65 ± 1.91	6.89 ± 2.28	0.022

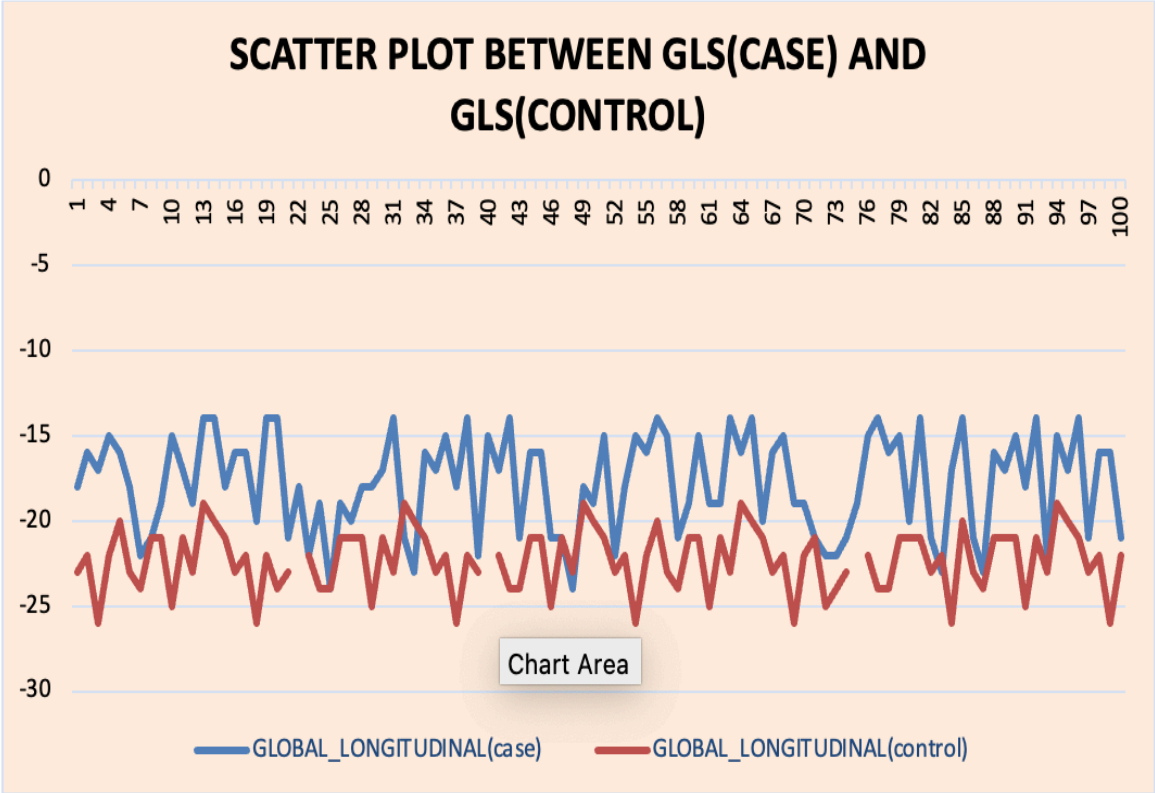


Mitral E velocity, Mitral A velocity, Mitral E/A ratio , Septal e', Septal a', Lateral e', Lateral s', Septal E/e', Lateral E/e' (0.76 ± 0.11, 0.71 ± 0.18, 1.10 ± 0.30, 0.10 ± 0.02, 0.12 ± 0.03, 0.12 ± 0.02, 0.097 ± 0.01, 7.72 ± 1.75, 7.65 ± 1.91 respectively) in cases group had significant difference as compared to control groups (0.87 ± 0.16, 0.71 ± 0.20, 1.23 ± 0.42, 0.09 ± 0.016,0.085 ± 0.015,7.36 ± 2.30, 6.89 ± 2.28 respectively) ($p \leq 0.05$). Furthermore, no difference in, septal s', and lateral a' between the groups was found

Table 7: Global Longitudinal Strain

	DM CASES (N=100)	CONTROL (N=100)	p value
GLS (%)	- 17.78 ± 2.86	- 23.29 ± 1.82	<0.001





There was a significant difference in Global longitudinal strain between the case and the control group. Subjects with diabetes showed a reduced GLS (-17.78 ± 2.86) as compared to controls (23.29 ± 1.82) [p <0.001].

Table 8: Correlation between Cimt and Fmd with Gls

		AVG CIMT	FMD%	GLS
AVG CIMT	Pearson Correlation	-	-.572**	-.571**
	Sig. (2-tailed)	-	<0.001	<0.001
FMD %	Pearson Correlation	-.471**	-	.401**
	Sig. (2-tailed)	<0.001	-	<0..001
GLOBAL LONGITUDINAL STRAIN (GLS)	Pearson Correlation	-.571**	.401**	-
	Sig. (2-tailed)	<0.001	<0.001	-

** Correlation is significant at the 0.01 level (2-tailed).

It is found from the study that Pearson correlation coefficient between Average CIMT and GLS is -0.571, which means there is significant negative strong linear relationship between these two. Similarly, Pearson correlation coefficient between FMD % and GLS is 0.401 indicating a significant positive weak linear relationship between these two.

Discussion

The prevalence of diabetes mellitus (DM) is increasing and is reaching epidemic proportions worldwide, as the population becomes older and is less active and more obese. The association between diabetes and coronary artery disease (CAD) is strong and is the most prevalent cause of mortality and

morbidity in diabetic populations. Atherosclerosis, an end stage of the diabetic process accounts for virtually 80% of all diabetes-related mortality and exists along a continuum from subclinical atherosclerosis to patent clinical atherosclerotic vascular disease. [16] Identification of patients at high risk in the early phase is critical to allow for modification of cardiovascular risk by effective preventive strategies.

Ultrasound measurement of carotid intima-media thickness (CIMT) and brachial artery flow mediated dilation has become a valuable tool for detecting and monitoring progression of atherosclerosis. Likewise, Global Longitudinal Strain (GLS) assessed using automated speckle-tracking echocardiography (STE) is an emerging technique for detecting and quantifying subtle disturbances in LV systolic function and its accuracy has been validated against tagged magnetic resonance imaging (MRI). So in the present study, we assessed subclinical atherosclerosis using CIMT and FMD and tried to find its association with GLS in asymptomatic type 2 diabetic subjects with no co-morbidities.

Age

A majority of subjects in our study belonged to the age group of 51-60 years comprising a total of 50% followed by 41-50 years (43%). The mean age of the patients in our study was 50.23 $\pm$ 5.68 years. Anjana et al in their study on South Indian population in 2015 reported high incidence of T2DM with a mean age of 50.9 ± 12.8 years. [17] Similar to this finding, Vijaykumar et al found mean age of participants was 54.50 ± 14.47 years based on the 10-year follow-up data obtained from the 869 participants of the cohort. [18] The descriptive epidemiological study by Khan et al also demonstrated peak global incidence of diabetes at 55-59 years of age. [19] The mean age of study population in our study was comparable with other studies.

Gender

In the present study males accounted for a total of 63% of the study population, whereas females comprised 37 %. This is similar to findings by Khan et al where males showed higher prevalence than females. Ghorpade et al in their study on Diabetes in rural Pondicherry found the incidence rate was twice as high in males (28.7/1000 PY) when compared to females (14.6/1000 PY; 95% CI: 9.4–21.7), similar to our study. [20] Every study compared has similar proportion of males and females and it doesn't affect the study result.

Other Baseline Charecteristic

The mean Body Mass Index (BMI) of diabetic patients in our study group was 24.36 $\pm$ 2.5 kg/m2 and was statistically significant (p=0.049). However, we didn't find any significance of waist circumference (80.62 ± 8.57, p=0.74), waist by hip ratio (0.90 $\pm$ 0.06, p=0.76) and CRP (3.61 $\pm$ 1.97) between cases and control. The mean duration of diabetes among our cases was 7.92 $\pm$ 2.86 years and mean HbA1c 7.08 ± 1.08 %. Vijaykumar et al in their study reported participants with T2DM had higher baseline BMI which was statistically significant ($p < 0.001$) thus supporting our observation. [18] However, significant changes ($p < 0.001$) were also observed in waist circumference in this study group. This discrepancy in result may be due to selection bias and small sample size of our study.

Subclinical Atherosclerosis and DM

Different studies have reported independent associations between DM and markers of subclinical atherosclerosis such as impaired flow-mediated vasodilation (FMD), increased carotid artery intima-media thickness (CIMT) and increase coronary artery calcification (CAC), after adjusting for cardiovascular risk factors and metabolic syndrome in patients with DM.

In the present study, we compared the presence of atherosclerosis in the form of CIMT and FMD between patients of DM and controls. We found mean CIMT to be significantly

higher among patients with DM (0.071 ± 0.01 cm) in comparison to controls (0.043 ± 0.01cm) (p <0.001). These findings were similar to study by Temelkova-Kurktschiev et al who found that newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose tolerance subjects matched for age and sex, suggesting that hyperglycemia may cause intimal-medial thickening in the early phases of diabetes. [21] Brohall et al in their review on 21 studies had a similar observation. [22] Compared with healthy controls, CIMT was increased in individuals with type 2 diabetes by 0.13 mm (95% CI: 0.12–0.14) and by 0.04 mm (95% CI: 0.01–0.07) in individuals with IGT. Similarly, Niskanen et al in their study on elderly patients with NIDDM found common carotid and carotid bifurcation IMTs greater in the NIDDM group than in control subjects (P < 0.05 to 0.01). [23]

In addition, our analysis found change in brachial artery diameter post-ischemia (FMD%) to be significantly lower in the DM group (10.81 ± 2.30) in comparison to controls (20.29 ± 4.62, p<0.001). This finding is in sync with the observation by Bhargava et al. [24] Their study on endothelium-dependent brachial artery flow mediated vasodilatation in patients with diabetes mellitus with and without coronary artery disease found FMD to be significantly impaired in diabetics (5.51 +/- 2.12%) compared to non-diabetics (7.03 +/- 2.87%) in absence of CAD. Meyer et al in their study on impaired flow-mediated vasodilation in type 2 diabetes revealed similar findings with FMD% (3.8+/-0.8% vs. 6.9+/-0.9%; p<0.01) reduced in the diabetic patients compared to their control subjects. [25] Thus, increased CIMT and impaired FMD% is associated with DM cases as compared to control in present study which is well correlating with all other studies.

Echocardiographic Indices and DM

Left ventricular involvement in type II diabetes mellitus is poorly understood.

In the present study, the cardiac structure and systolic function parameters in patients with DM were examined which showed no significant differences from the normal population. The end-systolic and end-diastolic dimensions, IVS, posterior wall, left atrium, Aorta dimensions, volumes (ESV, EDV, SV) were similar between the DM patients and healthy controls while IVRT, IVCT, MPI were significantly higher in participants with DM than those without; however, all variables were still within the normal range. No significant differences in LV dimensions and LVEF assessed by conventional echocardiography between the DM and healthy controls was found in the current study. Consistent to our results, a cross-sectional, M-mode and pulsed Doppler echocardiographic study by Porcellati et al on 27 diabetic patients and 27 controls, did not find any statistical differences in left ventricular wall thicknesses and dimensions in diastole and systole, left ventricular mass index and the echocardiographic indices of left ventricular contractility between diabetics and controls. [26]

However, Jorgensen et al on their study on 1030 type 2 DM patients observed echocardiographic abnormalities were present in 513 (49.8%) patients, mainly driven by a high prevalence of left ventricular hypertrophy 213 (21.0%) and left atrial enlargement 200 (19.6%). The prevalence increased markedly with age from 31.1% in the youngest group (<55 years) to 73.9% in the oldest group (>75 years) (p < 0.001) and was equally distributed among the sexes (p = 0.76). [27] The above study had a large sample size and may be the reason for discrepancy in our observation. Also, strict inclusion and exclusion criteria in our study may contribute to this difference.

Diastolic Dysfunction and DM

In present study, patients with DM were characterized by significantly lower e' velocity and higher E/e' ratio in comparison to individuals without DM suggesting the adverse effects of DM on diastolic indices. The

comparison of LVEF between the two groups did not reveal any significant difference, illustrating that the use of this conventional tool would result in missing the early stages of LV systolic dysfunction. Concordant to our results, Scholte et al in their study demonstrated the prevalence of diastolic dysfunction to be higher in diabetics when compared with those without coronary atherosclerosis. [28] In contrast to our present study findings, the Framingham study did not observe any association of atherosclerosis with E/e'. [29] A large sample size and prevalence of relatively low subclinical atherosclerotic subjects in the study could be the reason for this discrepancy.

Subclinical Atherosclerosis, Gls and DM

GLS, an indicator of systolic function, was decreased in patients with DM compared to healthy controls, indicating greater subclinical systolic dysfunction in DM patients. Parallel to our findings, MESA study by Fernandes et al on 58 subjects found increased CIMT to be associated with alterations of myocardial strain parameters reflecting reduced systolic and diastolic myocardial function. [30] These observations indicated a relationship between subclinical atherosclerosis and incipient myocardial dysfunction in a population free of clinical heart disease. In agreements with our results, Mehta et al found a linear relationship between global longitudinal strain obtained from the four-chamber view and global strain rate in systole and carotid intima-media thickness (four-chamber global longitudinal strain: $\beta = 3.0$, CV risk factor-adjusted $R2 = 0.34$; global strain rate in systole: $\beta = 0.0053$, $R2 = 0.21$; $P \leq .0001$) and between four-chamber global longitudinal strain and lower brachial distensibility ($\beta = -0.42$, $R2 = 0.22$; $P < .001$). [30] Similarly , Scholte et al in their study on 234 asymptomatic, type 2 diabetic patients without overt LV systolic dysfunction who underwent coronary artery calcium (CAC) scoring and LV global longitudinal strain (GLS) assessed using automated function imaging, found patients with subclinical coronary atherosclerosis (CAC >0; n = 139) had more impaired GLS when compared with patients without coronary atherosclerosis (CAC < 0; n = 95; P = 0.001). [28] The addition of the LV GLS to other selected independent clinical variables significantly improved the ability to predict coronary atherosclerosis in these patients. [31,32]

Conclusion

Patients with diabetes mellitus are at an increased risk of atherosclerosis and cardiovascular disease and should undergo periodic cardiovascular risk assessment. DM patients have more arterial stiffness compared to general population. Use of global longitudinal strain (GLS) is more sensitive than LV ejection fraction (LVEF) for the detection of LV systolic dysfunction in diabetic patients.

Thus, adding GLS, the most robust deformation marker, to LVEF increases the accuracy of predicting early ventricular functional decline and future cardiovascular events in the risk population. Further studies with larger and less heterogeneous sample volumes are required to elucidate the relationship between cause and effect as well as the underlying mechanism of cardiac dysfunction in DM.

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