Research Article

Early detection of Asymptomatic left ventricle Dysfunction in diabetic and pre diabetic Patients

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Abstract
Diabetic patients with normal left ventricular ejection fraction (LVEF) are frequently associated with asymptomatic left ventricle systolic dysfunction, that LVEF is not known to be a sensitive marker for the early detection of subclinical LV systolic dysfunction The aim of this study is to use a new echocardiographic technique (Speckle tracking echocardiography) for early detection of left Ventricle systolic Dysfunction in diabetic and pre diabetic patients
Keywords left ventricular ejection fraction, speckle tracking echocardiography, prediabetic

Introduction
Diabetes Mellitus is one of the most important diseases in the modern society and represents not only a medical but social problem In Industrialized countries. The prevalence of diabetes mellitus is 2%-4% in the general population and up to 10% in the age group over 65, its incidence showing an increasing tendency recent surveys predict increase in the prevalence of diabetes in adults from 4% in 1995 to 6.4% by the year 2025[1]

Diabetes Mellitus represents an important independent risk factor for development of cardiovascular disease and mortality from coronary heart disease (CHD) increasing the risk by 2 to 4 times, According to WHO, more than 75% of patients with non-Insulin dependent DM die due to vascular accident.[2]

Aim: The aim of the Work was to use a recent echocardiographic technique (speckle tracking echocardiography) for early detection of left Ventricular systolic dysfunction in diabetic and pre diabetic patients.

Patients and Methods
The study included Seventy patients and thirty five age matched healthy persons as a control group Patients group included 35 diabetic (17 males -18 females) and 35 pre diabetic (15 males -20 females). Classification into pre diabetes was done according to American diabetes association 2017 All included patients have Normal resting electrocardiogram (ECG), Normal left ventricle systolic function by Conventional echocardiography, Negative stress ECG for diagnosis of coronary artery disease.

Exclusion criteria were: Type I and Newly diagnosed type II diabetes Mellitus ,Ischemic heart disease.

Obese patients (Body mass index >30 (KG/m2), Hypertensive patients, Patients with Microalbuminuria which defined as an abnormal increase in albumin excretion rate within the specific range of 30–299mg of albumin/g of creatinine.[3], Renal impairment: Patients with estimated creatinine clearance rate ≤ 60 ml/ min using Cockcroft-Gault formula.[4], Connective tissue disorders (Rheumatoid arthritis, Systemic lupus erythematosus, Scleroderma, Ankylosing spondylitis, Behcet's disease, Psoriasis)

All studied groups were subjected to:
1- Thorough history taking including: Age, History of diabetes
2- Clinical examination General examination and Local cardiac examination.
3- 12-Leads Resting Electrocardiogram (ECG)
4- Laboratory Investigation: Fasting plasma glucose., 2-h plasma glucose., Hb A1c, Serum Creatinine to estimate creatinine clearance rate, Urine Albumin ⁄ Creatinine rate
5- Trans-thoracic Echocardiography (TTE): Echocardiographic examination was performed by using Philips IE 33 ultrasound: For assessment of left ventricular ejection fraction (LVEF) by M- mode, For exclusion of significant valvular heart disease, Images from the apical four-chamber, two-chamber and three-chamber views are required for the measurement of LV longitudinal strain, Images from

parasternal short-axis views at basal.mid and apical levels are needed for the measurement of radial and circumferential strain.

6- 2 D Speckle Tracking Echocardiography (STE)

Measurement of GLS was made using the same image loops of the apical 4 chamber, apical 2 chamber views as used in the 2D EF measurement as well as the apical 3 chamber view. The three image loops required were selected from the stored dataset on the Philips Echo machine and the automated cardiac motion Quantification (aCMQ) software was applied. The operator visually assessed the accuracy of the software in tracking the ventricular motion and made any small manual adjustment necessary to rectify any machine misinterprettation, Images from the apical four-chamber, two-chamber and three-chamber views are required for the measurement of LV longitudinal strain Images from parasternal short-axis views at basal, mid and apical level are required for the measurement of LV radial and circumferential strain.

7- Stress Electrocardiogram:

The stress ECG was done according to Bruce treadmill test protocol.

Methods of statistical analysis:

Data were collected, revised, verified, coded, then entered Personal computer for statistical analysis done by using statistical package for social sciences (SPSS) version 20.

The following had been done:

Descriptive statistics: For qualitative data: number (N) and percentage (%), For quantitative data: mean (X~) and standard deviation (SD), Kolmogorov- Smirnov for normality test was used to differentiate between parametric data and non-parametric data.

Analytical statistics: Normally distributed variables (parametric) between study groups were analyzed using: Student (t) test for analysis of quantitative variables, Chi – square (x^2), Fischer's exact test for analysis of qualitative data.

For all tests probability (p) was considered: Non-significant if ≥ 0.05, Significant if < 0.05, Highly significant if <0.01, Very highly significant if <0.001

For all tests correlation (r) was considered ; Weak correlation if from 0.00 to 0.24**,** Fair correlation if from 0.25 to 0.49**,** Moderate correlation if from 0.50 to 0.74**,** Strong correlation if ≥0.75

Results

1-Demographic data of study groups: There was no statistically significant difference between the three groups as regard the age and the gender (Table 1)

Table (1): The demographic characteristics of the studied patients.

Demographic Characteristics	Diabetic group (n= 35)	Pre diabetic group (n=35)	Control group (n=35)	P-value
Age	41.3±8.3	45±6.2	40.8±6.1	0.07
Sex:-				
Male	17 (48.6)	16 (45.7)	18(51.4)	0.2
Female	18 (51.4)	19 (54.3)	17(48.6)	

2-Trans-thoracic Echocardiography

Regarding Left ventricle ejection fraction, no significant difference was present between the three groups (table2)

Table (2): Comparison between the three groups regarding EF%

	Diabetic group (n= 35)	Pre-diabetic group (n= 35)	Control group (n= 35)	p*	P**	P ***
Mean ± SD	**64 ±5.8**	**63 ±5.2**	**64 ±6.2**	**0.7**	**0.5**	**0.6**

EF ejection fraction P*comparison between diabetic and Pre diabetic group p** comparison between diabetic and control group P*** comparison between Pre diabetic and control group

3- Speckle tracking echocardiography

Regarding global longitudinal strain (GLS) measured by speckle tracking echocardiography, results revealed that GLS was significantly lower in diabetic patients when compared to pre diabetic and control groups . Also, GLS was significantly lower in pre diabetic group when compared with control group (Table 3)

GLS global longitudinal strain P* comparison between diabetic and Pre-diabetic group p** comparison between diabetic and control group P*** comparison between Pre-diabetic and control.

Regarding Global Circumferential strain (GCS) and Global radial Strain (GRS) measured by Speckle tracking echocardiography, no statically significant difference was present between the three groups (tables 4- 5)

Table (3): Comparison between the three groups regarding GLS

GLS	Diabetic group (n= 35)	Pre-diabetic group (n= 35)	Control group (n= 35)	P*	P**	P***
Mean ± SD	-14.1±1.9	-16.8±1.6	-17.7±1.3	0.0001	0.0001	0.01

Table (4): Comparison between the three groups regarding Global Circumferential strain

GCS	Diabetic group (n= 35)	Pre-diabetic group (n= 35)	Control group (n= 35)	P-value
Mean±SD	-23.6±2.3	-24.3±3.3	-24.2±2.7	0.2

GCS; global circumferential strain

Table (5): Comparison between the three groups regarding Global Radial strain

GRS	Diabetic group (n= 35)	Pre-diabetic group (n= 35)	Control group (n= 35)	P-value
Mean±SD	48.9 ±4.6	49.9 ±5.4	50.1±3.9	0.5

GRS; global Radial strain

Regarding blood sugar level, moderate correlation was present between Global longitudinal strain with Fasting plasma glucose, 2-h plasma glucose and HbA1c in diabetic and pre diabetic groups (figures1-3)

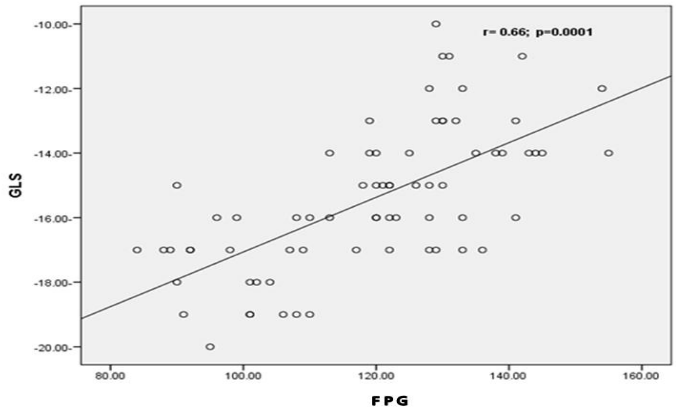


Figure (1): Correlation between GLS and FPG

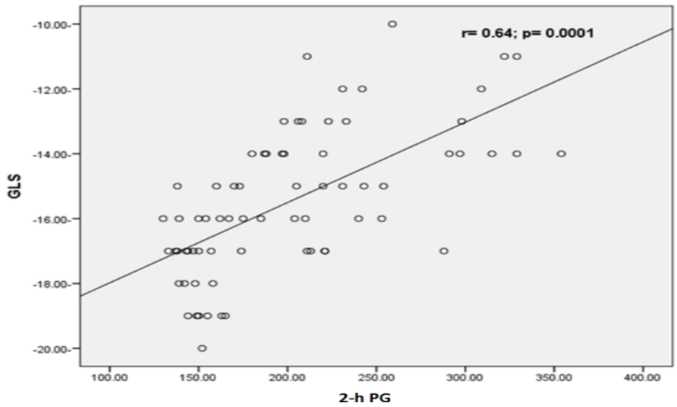
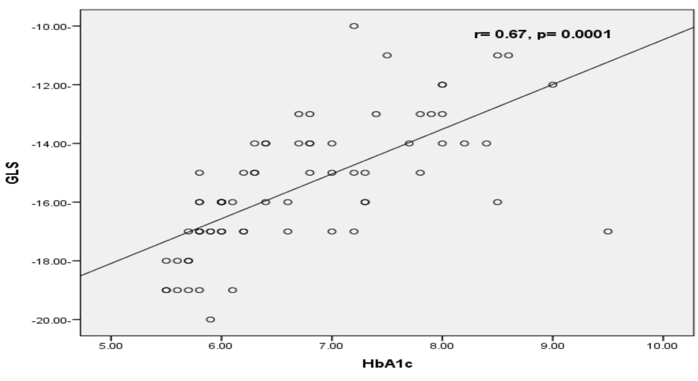


Figure (2): Correlation between GLS and 2-h PG



Figure(3):Correlation between GLS and HbA1c

3- Duration of Diabetes

There was a strong correlation between duration of diabetes and GLS in diabetic group (figure 4)

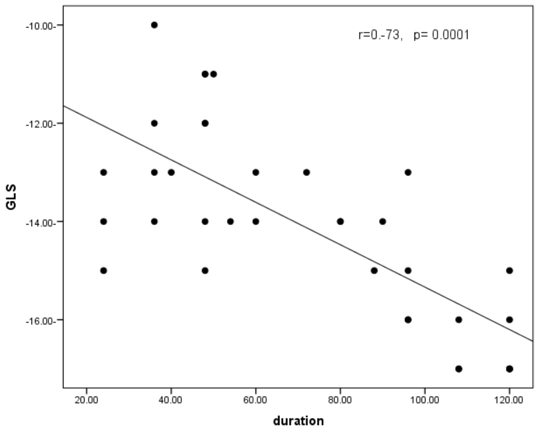


Figure (4): Correlation between GLS and duration of diabetes in months

Discussion

Diabetes mellitus is often associated with coronary risk factors, resulting in significant cardiac morbidity and mortality. Early detection of diabetic heart disease is of paramount importance, because timely life-style modifications and medical interventions could prevent or delay the subsequent development of heart failure which is considered one of major burdens for health insurance costs., Diabetic patients with normal left ventricular ejection fraction(LVEF) are frequently associated with asymptomatic left ventricle dysfunction. However, LVEF is known not to be a sensitive marker for the detection of subclinical Left ventricle (LV) systolic dysfunction.[5]

Early manifestation of diabetic LV systolic dysfunction can be detected longitudinally, because sub-endocardial fibers which are prone to myocardial ischemia, have a longitudinal trajectory.[6]

Regarding impairment of global longitudinal strain in diabetic and pre diabetic groups:

In 2009 Nakai et al., studied the Subclinical left ventricular dysfunction in 60 asymptomatic diabetic patients and 25 age matched health volunteers using two dimensional speckle tracking echocardiography . They found that subclinical LV longitudinal dysfunction is preferentially and frequently observed in asymptomatic diabetes patients with normal LVEF That 2D STE has the potential for detecting subclinical LV systolic function and might provide useful information of the risk stratification in a asymptomatic diabetic population[7].

In 2014, Zoroufian et al., evaluated subclinical LV systolic dysfunction in diabetes mellitus patients using two-dimensional speckle tracking echocardiography (STE) for early detection of changes in LV longitudinal strain (ST) or synchronized contraction. They studied 37 normal coronary and normotensive diabetes mellitus patients with LV ejection fraction >50% and compared to 39 non diabetic normal coronary and LV function subjects. They found a significant reduction in global and segmental ST adjusted for age and body mass index .Diabetes mellitus remained an independent correlate of reduced LV global longitudinal ST (R = 0.688, P = 0.003). These results suggest that there might be early detectable changes in systolic function in the natural course of diabetes mellitus by STE study[8].

In 2016 Bakhom et al., studied the usefulness of STE in detecting subclinical LV dysfunction in asymptomatic T1DM patients . They found that young asymptomatic patients with T1DM have the evidence of impaired LV both systolic and diastolic functions compared to control subjects and STE allowed early detection of abnormal systolic longitudinal deformation before overt Impairment of indices of LV systolic function. Despite the similarity in the results between this study and ours, but Bakhom et al., study investigated T1DM patients while the included patients in our study were pre diabetic and T2DM[9].

In 2016, Akcay et al., evaluated the longitudinal function of LV but by the pulsed wave tissue doppler imaging. They evaluated 94 patients with pre diabetes (mean age of 50.8 ± 6.9 years, 78 female) without known cardiovascular diseases and 70 healthy volunteers with similar demographic characteristics. Systolic and diastolic function of the left ventricle was evaluated with transthoracic echocardiography according to the latest consensus recommendations including TDE. The mean results of septal and lateral parts of the mitral annulus Pulsed wave TDE showed that myocardial systolic wave (Sm), myocardial early diastolic wave (Em) and Em to atrial peak velocity (Am) ratio were significantly lower while myocardial isovolumetric contraction time (IVCTm) and myocardial performance index (MPI) values were significantly higher in patients with prediabetes (preDM). They concluded that PreDM is associated with subclinical LV systolic and diastolic dysfunction as evaluated by TDE[10].

This is a concordance between the results of the before mentioned study and ours despite the difference in the method of measuring strain.

Although, Nakai et al., reported that circumferential and radial strains was significantly reduced in diabetic patients compared with age matched group in contrary to our results[7] .The included patients in Nakai et al., study were diabetic and hypertensive while the patients in our study were normotensives.

This hypothesis was supported by Wang et al., in 2015. They found that Patients with diabetes and hypertension showed significantly lower systolic strains in all directions than controls and patients with diabetes. Also the mean diabetic duration in Nakai et al., study was 8.7 years while in our study was 5.9 years. The Time factor may be responsible for affection of all strains (circumferential and radial beside the longitudinal strain) as its role was investigated and documented in In Roos et al., [11].

Regarding correlation between impairment of global longitudinal strain, with FPG, 2-h PG and Hb A1c in diabetic and prediabetic groups:

In 2014, Zoroufian et al., evaluated subclinical LV systolic dysfunction in diabetes mellitus patients using two-dimensional speckle tracking echocardiography (STE). Among the diabetic patients, reduction in global peak systolic strain, adjusted for age and the body mass index, was independently correlated with glycated hemoglobin ($P < 0.001$), and Fasting Plasma glucose ($P < 0.001$)[8].

In 2015 Wang et al., investigated the myocardial deformation in well treated type 2 diabetes patients with or without hypertension using speckle-tracking echocardiography. Among all strains, GLS showed the highest correlation with three-dimensional LVEF in diabetic patients, FPG and left ventricular end-diastolic volume (LDEDV) were common significant influential factors for GLS in both diabetic groups whatever with or without hypertension[12].

In 2018 Khaleghi et al., studied the longitudinal deformation of the LV myocardium using 2D STE in subjects with impaired fasting glucose with and without increased glycated hemoglobin. They studied 80 subjects with impaired fasting glucose (100–126mg/dL) and without significant epicardial coronary artery stenosis seen on selective coronary angiography were included in their study and were divided into two groups based on their HbA1c levels (<5.7% and 5.7%–6.4%)
They found no correlation between FPG and GLS between subtypes of pre diabetes[13].This is contradictory between the results of the before mentioned study and ours but in Khaleghi et al., study, the mean HbA1c was 5.4± 0.2 %and mean FPG was107.2±6.5mg／dl while in our study, the mean HbA1c was 5.9± 0.2 %and the mean FPG was 110.2±5.5 mg／dl.

Regarding the correlation between duration of diabetes and Global longitudinal strain impairment

Only a few studies have investigated changes of LV dysfunction over time in patients with DM. In 27 type 2 DM patients, Vintila et al., showed progression of subclinical LV dysfunction after 5-year follow-up by a significant reduction in longitudinal velocities measured with TDI echocardiography (mean longitudinal systolic velocity 4.9 vs. 5.6 cm/s, P = 0.001)(14).

In 2013 Roo*s* et al., confirms and extends previous observations by measuring 2Dspeckle tracking echocardiography derived LV systolic and diastolic parameters. Asymptomatic patients with type 2DMshowed subclinical LV systolic and diastolic dysfunction as reflected by impaired CS and LS. More important, after 2-year follow-up and despite remaining clinically stable and asymptomatic, these patients showed progression of subclinical LV dysfunction with further impairment in CS and LS(11).

Nakai et al., showed that diabetic duration was the only independent predictor for the reduction in LS. This highlights the relationship between long-term hyperglycemia and the impairment of LS. Although global LS was reduced, regional RS and CS were paradoxically increased in diabetic patients of long-term duration. This augmentation in regional RS and CS might reflect a compensation to maintain LVEF in diabetic patients with a long history of disease(7).

Limitations

First, the study size was relatively small. but the challenging selection of patients in absence of Comorbidities of cardiac history and a poor acoustic window in obese subjects could represent a partial explanation of this limitation. **Second**, it was not possible for us to conduct a follow-up of the study population

Conclusion

Our study reinforces that Left ventricle ejection fraction (LVEF) is not a sensitive method for early detection of subclinical systolic dysfunction. The results of this study showed that normotensive non ischemic diabetic and pre diabetic subjects with normal LVEF have evidence of impaired left ventricular systolic function compared to control subjects

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