Original Article

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Comparison of left ventricular global longitudinal strain by speckle tracking echocardiography in patients with and without diabetes mellitus asymptomatic for coronary artery disease at a tertiary hospital in Nepal

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Abstract

Background: Diabetes mellitus is a major risk factor for cardiovascular events. A significant proportion of diabetics are asymptomatic for ischaemic heart disease either because of the early stage of ischaemia or silent myocardial ischaemia. Global longitudinal strain (GLS) of the left ventricle measured by speckle tracking echocardiography (STE) is a novel method of detecting left ventricular dysfunction due to myocardial ischaemia.

Objectives: This study aimed to compare the GLS of type-2 diabetes mellitus (T2DM) and non-diabetic patients who were asymptomatic for coronary artery disease (CAD).

Methods: An analytical cross-sectional study was conducted among 52 diabetic and 49 non-diabetic individuals asymptomatic for CAD presenting to a tertiary hospital, between 2022 September to 2022 October. The STE was performed to measure left ventricular GLS of the participants. Their blood and urine samples were sent for measuring glycosylated haemoglobin (HbA1c), total cholesterol, and microalbuminuria. Data were entered and analysed using SPSS v23.

Results: Twenty-five (48.1%) diabetics had left ventricular dysfunction (GLS ≤18) compared to two (4.1%) non-diabetics. GLS was significantly lower among the diabetic patients, and exhibited significant inverse correlation with the duration of diabetes, age, HbA1c, and microalbuminuria ($p < 0.001$). In multiple linear regression model for GLS, only the duration of diabetes ($B = -0.27$, $p < 0.001$) and the age of patients ($B = -0.057$, $p = 0.004$) retained statistical significance, after adjusting for other covariates.

Conclusion: Left ventricular GLS has a significant negative correlation with the duration of diabetes and age of the patients.

Key words: Coronary artery disease; Diabetes mellitus; Global longitudinal strain; Silent myocardial ischaemia; Speckle tracking echocardiography.

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INTRODUCTION

The burden of chronic non-communicable diseases (NCDs) including diabetes mellitus has increased staggeringly in the last two decades, globally as well as in low-and-middle-income countries.[1] In Nepal, the overall prevalence of diabetes is 8.5%.[2] Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases, the leading cause of death among NCDs.[3] It is associated with macrovascular coronary artery diseases (CAD) and

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stroke, and microvascular complications like neuropathy, retinopathy, nephropathy, and coronary microvascular disease (CMD) - reported in 72% of diabetics.[4]

Early identification and treatment of left ventricular (LV) dysfunction, which is among the early manifestation of diabetic heart disease, is vital for preventing full-blown CAD.[5] However, a significant proportion of T2DM patients do not experience the typical symptoms of CAD because of concomitant autonomic neuropathy, making its early diagnosis challenging. This silent myocardial ischaemia (SMI) is reported in around 22% of T2DM patients,[6,7] and in 30-55% of diabetics with additional risk factors.[8] Estimation of global longitudinal strain (GLS) by speckle tracking echocardiography (STE) can predict early LV dysfunction due to subclinical myocardial ischaemia not detected by traditional echocardiographic studies.[9,10] This study aimed to compare the GLS of T2DM and non-diabetic patients who were asymptomatic for CAD.

METHODOLOGY

An analytical cross-sectional, single-centre study was conducted at Kathmandu Medical College Teaching Hospital (KMC), Sinamangal, Kathmandu, Nepal. The study population included 49 non-diabetic patients and 52 diabetes mellitus patients under regular treatment, asymptomatic for CAD presenting to the Department of Cardiology at KMC for echocardiography. The study duration was from 2022 September to 2022 October. Ethical clearance was taken from the Institutional Review Committee of KMC (Ref. 09092022/05) and written informed consent was taken from all participants. The participants were informed that their participation in this study was voluntary, and that they could leave the study at any point.

The sample size was calculated using the formula for comparing two proportions as, $n = (Z_\alpha+Z_\beta)^2\ P\ (1-P)\ /\ (P_1-P_2)^2$. Considering the prevalence of SMI in T2DM patients (P_1) as 0.20,[7] prevalence of SMI in the general population (P_2) as 0.4,[11] Z_α as 1.96 at 95% confidence interval (CI), Z_β as 1.28 at 90% power, and a non-response rate of 15%, the final sample size was calculated as 49 patients per group. Patients were selected using a consecutive sampling method. The inclusion criteria were T2DM patients without any history, symptoms, or subjective evidence of obstructive CAD. The exclusion criteria were as follows: dyspnoea corresponding to New York Heart Association (NYHA) classification III or IV, symptoms suggestive of CAD, left ventricular ejection fraction (LVEF) less than 50%, atrial fibrillation, moderate-to-severe aortic or mitral valve stenosis or regurgitation, poor echocardiographic acoustic window, evidence of obstructive CAD in a coronary angiogram, a history of myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Controls taken were age and sex-matched nondiabetic individuals without any history or subjective evidence of CAD.

The clinico-demographic details of the patients including age, gender, smoking habit, height, and weight were collected through one-to-one interviews, and the body mass index (BMI) was calculated. Patients or controls under regular antihypertensive medications or the average of three systolic and or diastolic blood pressures above 140 and 90 respectively, measured after fifteen minutes of rest, were taken as hypertensive. Duration of diabetes mellitus was recorded as a continuous variable where the value zero meant non-diabetic, and the remaining natural number indicated the number of years of diabetes.

Blood and urine samples were collected from all patients for assessing the biochemical parameters such as glycosylated haemoglobin A1c (HbA1c), total cholesterol (TC), and microalbuminuria. The HbA1c level of ≥6.5 was considered as poor glycaemic control (hyperglycaemia), and total cholesterol ≥200 mg/dL as hypercholesterolaemia. Microalbuminuria levels of >30mg/L were taken as a surrogate marker for nephropathy.

Transthoracic echocardiography was performed using a General Electric Vivid E95 machine with a 5.2-MHz transducer. All measurements were performed by one observer (cardiologist). Conventional measurements including 2D, M-mode, color Doppler, and spectral Doppler were obtained, and left ventricular ejection fraction (LVEF) was determined by Ticholz's method.

For the assessment of left ventricular GLS, peak systolic longitudinal strain was measured using automated function imaging in EchoPAC software version 202, revision 50 (GE Healthcare). Three standard 2D grey-scale images of apical four-chamber (4C), two-chamber (2C), and apical long axis (ALAX) with an optimised frame rate of 60-80 frames were obtained and stored for offline analysis. To delineate the endocardial borders in each of these three standard images, three points were manually selected on the endocardial border; two were placed at the basal segments along the mitral valve annulus and one at the apex. The region of interest (ROI) within the myocardial tissue was automatically demarcated by the

software system once the three points were selected. Further adjustment was done manually to obtain the best possible ROI. Based on previous findings, GLS of ≤ -18% was considered abnormal, and suggestive of left ventricular dysfunction.[12,13]

The data was entered and analysed using IBM SPSS Statistics for Windows, version 23.0 (IBM corp., Armonk, N.Y., USA). Continuous variables were summarised as mean ± standard deviation (SD) if normally distributed; and as median and interquartile range (IQR) if they showed non-normal distribution. Categorical variables were expressed as numbers and percentages. Student's independent t-test, Independent samples Mann-Whitney U test, and Pearson's Chi-square test were used where appropriate, to test for differences between the two groups. To assess the bivariate correlation between GLS and the continuous variables (including the age of patients, HbA1c, duration of diabetes, total cholesterol, BMI, and microalbuminuria), Pearson's product moment correlation coefficient (r) was used. Similarly, Spearman's rank order correlation coefficient (rho) was used for the correlation of GLS with the categorical variables.

Bivariate simple linear regression analysis was used to test whether diabetes mellitus (including duration of diabetes), hypertension, smoking status, gender, age, BMI, HbA1c, total cholesterol, and microalbuminuria significantly predicted the GLS score. A multiple linear regression model was computed using the significant predictors from the bivariate regression analysis as the independent variables and the GLS score as the dependent variable. The regression model was used in analysing GLS versus diabetes, adjusting for different confounders. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

RESULTS

Out of the total 101 participants, 52 (51.49%) were diabetic and 49 (48.51%) were non-diabetic. The mean age ± SD of the patients was 56.64 ± 14.17 years. There were no significant differences between the diabetic and non-diabetic groups in their clinico-demographic characteristics, besides the prevalence of hypertension (Table 1). Among the 52 diabetic patients, 45 (86.54%) were hypertensive compared to only 29 (59.18%) non-diabetic patients (p=0.002). The socio-demographic and clinical characteristics of the patients are summarised below:

The HbA1c and urine microalbumin levels were significantly higher in the diabetic group (p <0.001), whereas total cholesterol and GLS were significantly higher in the non-diabetic group (p <0.001). The proportion of poor glycaemic control (HbA1c ≥6.5%) and microalbuminuria (≥30mg/L) was significantly higher in the diabetic group (p <0.001). The prevalence of left ventricular dysfunction based on GLS ≤18 among the diabetics was 48.08% (25 patients), compared to 4.08% (2 patients) among the non-diabetics (Table 2).

Furthermore, among the 52 diabetes mellitus patients, 50 (96.15%) had presence of at least one additional comorbid chronic condition (among hypertension, nephropathy, hypercholesterolaemia , or LV dysfunction), suggestive of multimorbidity. Simlarly, 14 (28.57%) of the non-diabetic patients had at least two chronic conditions, suggestive of multimorbidity (Figure 1). The diabetic patients had higher prevalence of multimorbidity compared to the nondiabetics ($\chi^2 = 49.63$; df = 1, p <0.001).

The GLS showed statistically significant negative correlation with the duration of diabetes, age, HbA1c, urine microalbumin, hypertension, gender, and smoking habit (Table 3). In simple bivariate linear regression of GLS with predictor variables, statistically significant regression coefficients (B) were observed with the duration of diabetes, age, HbA1c, urine microalbumin, hypertension, gender, and smoking habit.

In the linear regression model, the statistically significant predictors of GLS were the duration of diabetes (B = -0.27, p <0.001), and age of the patients (B = -0.057, p = 0.004), after adjusting for HbA1c, urine microalbumin, hypertension, gender, and smoking. The regression equation for predicting the GLS can be summarised as:

$$y = 25.28 + (-0.27)x_1 + (-0.057)x_2$$

In the above equation, the dependent variable (y) is the GLS score, whereas the independent (predictor) variables are duration of diabetes (x_1) and age of the patient (x_2). The overall regression model was statistically significant (F(7,93) = 22.11; p <0.001), with a coefficient of determination (adjusted R^2) of nearly 60% (Table 4).

Table 1: Socio-demographic and clinical characteristics of the patients

		Diabetic patients (N = 52)	Non-diabetic patients (N = 49)	p-value	Statistical test
Age (years)	Mean ± SD	58.73 ± 14.00	54.43 ± 14.16	0.128	Chi-square test
BMI (kg/m^2)	Mean ± SD	27.66 ± 4.66	26.72 ± 3.11	0.236	Chi-square test
Gender	Male, n (%) Female, n (%)	(51.92) 25 (48.08)	31 (63.27) 18 (36.73)	0.25	Independent t-test
Smokers	n (%)	21 (40.38)	23 (46.94)	0.51	Independent t-test
Hypertension	n (%)	45 (86.54)	29 (59.18)	0.002	Chi-square test

Table 2: Clinical and laboratory parameters of the patients

	Statistic	Diabetic patients (N = 52)	Non-diabetic patients (N = 49)	p-value	Statistical test
HbA1c (%)	Mean ± SD	7.42 ± 1.01	5.68 ± 0.41	<0.001	Independent t-test
Poor glycaemic control (HbA1c ≥6.5%)	n (%)	45 (86.54)	3 (6.12)	<0.001	Chi-square test
Urine Microalbumin (mg/L)	Median (IQR)	23.10 (48.53)	6.20 (2.80)	<0.001	Mann-Whitney U test
Microalbuminuria (≥30mg/L)	n (%)	23 (44.23)	-	<0.001	Chi-square test
Total cholesterol (mg/dL)	Mean ± SD	164.62 ± 41.61	205.39 ± 45.22	<0.001	Independent t-test
Hypercholesterolaemia (≥200mg/dL)	n (%)	13 (25)	21 (42.86)	0.58	Chi-square test
GLS	Mean ± SD	18.50 ± 3.86	21.47 ± 2.18	<0.001	Independent t-test
Left ventricular dysfunction (GLS ≤18)	n (%)	25 (48.08%)	2 (4.08%)	<0.001	Chi-square test

Table 3: Bivariate correlation and simple linear regression of GLS with predictor variables

Continuous variables	Pearson's correlation		Regression coefficients			R^2
	r	p-value	Unstandardised B	Standardised β	p-value	
Duration of diabetes	-0.77	<0.001	-0.358	-0.77	<0.001	0.585
Age	-0.05	<0.001	-0.136	-0.555	<0.001	0.308
HbA1c	-0.48	<0.001	-1.429	-0.481	<0.001	0.231
Urine microalbumin*	-0.51	<0.001	-0.029	-0.511	<0.001	0.261
Total cholesterol	0.12	0.206	0.009	0.127	0.206	0.016
BMI	-0.18	0.106	-0.141	-0.162	0.106	0.026
Categorical and Continuous variables with non-normal distribution	**Spearman's correlation**		**Regression coefficients**			**R^2**
	Rho	**p-value**	**Unstandardised B**	**Standardised B**	**p-value**	
Hypertension (Y/N)	-0.357	<0.001	-2.59	-0.378	<0.001	0.143
Gender (M/F)	-0.207	0.037	-1.58	-0.227	0.023	0.051
Smoking (Y/N)	-0.217	0.029	-1.39	-0.2	0.045	0.04
Urine microalbumin*	-0.55	<0.001	-0.029	-0.511	<0.001	0.261

*Since urine microalbumin (mg/L) showed a non-normal distribution, non-parametric Spearman's correlation is more suitable for assessing the correlation.

Table 4: Multiple linear regression model for predicting GLS adjusting for different co-variates

Variable	Regression coefficients					Model Summary		
	Unstandardised B	S.E.	Standardised β	t-test statistic	p-value	R^2	Adjusted R^2	p-value
Duration of diabetes†	-0.27	0.051	-0.637	-5.32	<0.001	0.625	0.596	<0.001
Age ‡	-0.057	0.019	-0.232	-2.92	0.004			

†: Adjusted for age, HbA1c, microalbuminuria, hypertension, gender, smoking

‡: Adjusted for duration of diabetes, HbA1c, microalbuminuria, hypertension, gender, smoking

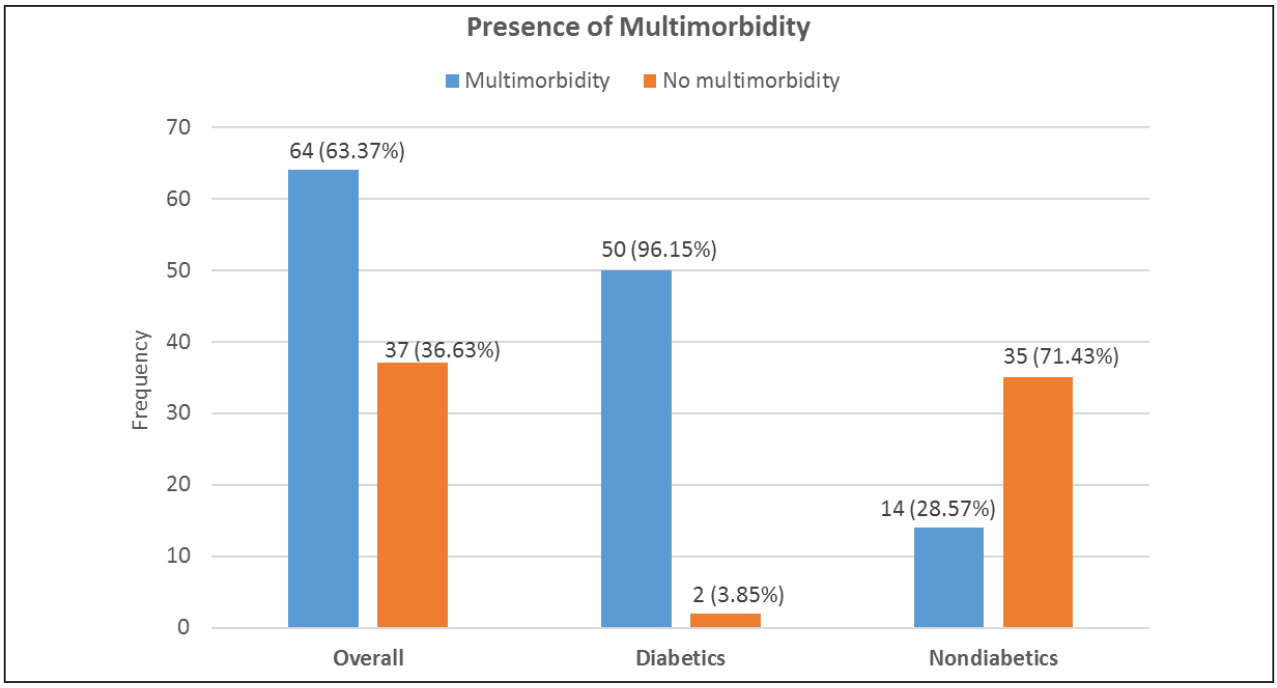

Figure 1: Prevalence of multimorbidity among the patients

DISCUSSION

This study is presumably the first of its kind in the context of Nepal, to use STE based GLS score to predict left ventricular dysfunction among diabetics and non-diabetics, both asymptomatic for CAD. The LV dysfunction is one of the early manifestation of diabetic cardiomyopathy in diabetic subjects, which can be detected at its incipient stage only by sensitive methods such as longitudinal strain and myocardial tissue velocity.[14] The GLS measured by STE using 2D echocardiography is easy to measure and reproducible.[15] The GLS of the left ventricle (LV) is a measure of longitudinal oriented myocardial deformation of the LV during systole, which predominantly reflects the function of subendocardial longitudinal fibres, which are most prone to ischaemic damage and wall stress. This abnormal contraction pattern of subendocardial fibres, normally not detected by the conventional echocardiogram can be detected by STE.[16]

In this study, LV dysfunction (GLS ≤18) was prevalent among 25 (48.08%) of diabetic patients. This is similar to the findings of one prospective study which reported a prevalence of LV dysfunction of 47% among T2DM patients who were normotensive and asymptomatic for ischaemic heart disease or heart failure, with normal electrocardiogram at rest and exercise echocardiography.[17] The mean ± SD of the GLS of LV was significantly lower among the diabetic patients compared to the non-diabetic controls in the present study (18.50 ± 3.86% vs 21.47 ± 2.18%; p <0.001). A single-centre study done in China in 2022 reported similar impairment in GLS score among diabetic patients (16.82 ± 2.59% vs. 19.13 ± 1.72%; p <0.001).[18]

The present study also shows that left ventricular GLS has a significant negative correlation with the duration of diabetes, which means that there is significant LV dysfunction as the duration of diabetes increases in T2DM patients. The LV dysfunction could be the result of subclinical myocardial ischaemia or SMI which has been reported in 22% of the asymptomatic diabetic population, detected using adenosine technetium-99 m myocardial perfusion imaging.[7]

The majority (45, 86.54%) of the diabetics had HbA1c ≥6.5%, despite regular diabetes treatment, indicating inadequate glycaemic control in these patients. This requires urgent addressing in managing and preventing the complications of diabetes, such as micro- and macrovascular diseases. Nearly half (23, 44.23%) of the diabetics had microalbuminuria ≥30 mg/L, indicating nephropathy, a surrogate marker of microvascular disease. However, the total cholesterol levels were significantly lower in diabetics than in non-diabetics, which could be due to the aggressive use of lipid-lowering agents like statins.

Multimorbidity has been defined as the coexistence of two or more chronic health conditions in an individual, and is an accelerating global public health problem, associated with increased economic and health care burden.[19] The overall prevalence of multimorbidity among all 101 participants of this study was 63.37% (n = 64). The diabetic patients had higher prevalence of multimorbidity compared to the nondiabetics: 50 (96.15%) vs 14 (28.57%) with p <0.001. These prevalence figures were obtained considering only the chronic conditions measured in this study, viz diabetes mellitus, hypertension, nephropathy, hypercholesterolaemia, and LV dysfunction. These figures could rise much higher if other common chronic conditions like chronic obstructive pulmonary disease (COPD), musculosekeltal disorders such as osteoarthritis, mental disorders, and cancers are included. Nationally representative data of multimorbidity is lacking in the context of Nepal. A similar study done at a tertiary care centre in Nepal in 2022 reported that 70.09% of the diabetes mellitus patients admitted in the centre had multimorbidity.[20]

In this study, HbA1c, microalbuminuria, and hypertension were significantly associated with both diabetes mellitus (predictor) and GLS (outcome), which is suggestive of confounding. Age, gender, and smoking habit were significantly associated with GLS, but not with diabetes. In the final regression model, the duration of diabetes and the age of the patient were identified as significant predictors of GLS, after adjusting for the effect of the above confounders and other independent variables. The regression model was statistically significant (p <0.001), and predicted 60% of the variation in the GLS.

This study had some limitations. Firstly, the cross-sectional observational study design used in this study has obvious drawbacks in establishing a cause-effect relationship, and is prone to temporal bias and survival bias. The study design was suitable to determine the prevalence and predictors of LV dysfunction among the patients, but was inadequate to evaluate the prognosis of the patients and the validity of the tool in our context. Secondly, a non-probability consecutive sampling technique was used to select the study participants, which limits the external validity of the findings. Although there was no significant difference in the age and gender of the two study groups, individual matching for age and gender could not be done due to various constraints. Lastly, the study participants were diabetic and nondiabetic patients presenting to KMC for echocardiography. Hence, the findings may not be generalisable to other settings. Further prospective studies are needed to evaluate the prognosis of diabetic and non-diabetic patients, with different GLS scores.

CONCLUSION

The T2DM is a significant risk factor for silent coronary microvascular disease. Duration of diabetes and age of the patient are significant predictors of a decrease in the left ventricular GLS that reflects left ventricular dysfunction due to ischaemic damage. Further studies are needed to implement the consistent use of STE to measure left ventricular GLS to predict any coronary microvascular events, especially in the diabetic population.

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