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Original Article

Internal Medicine Section

Association of Severity of Coronary Artery Disease with Left Ventricular Diastolic Dysfunction among Diabetics with Stable Ischaemic Heart Disease: A Cross-sectional Study from Odisha, India

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ABSTRACT

Introduction: Ischaemic Heart Disease (IHD) is one of the most common co-morbidity among Indian population, so is Diabetes Mellitus (DM). IHD is associated not only with systolic, but also with Diastolic Dysfunction (DDFx) of Left Ventricle (LV). However, there is scarcity of data correlating the severity of Coronary Artery Disease (CAD) with LV DDFx.

Aim: To assess the severity of CAD in diabetic stable IHD patients with normal LV systolic function (LV Ejection fraction ≥50%) and it's association with degree of DDFx.

Materials and Methods: A prospective cross-sectional study was conducted over a period of one year, in a tertiary care hospital of Odisha, India among diabetic stable IHD patients. Grades of DDFx were assessed among the study population, using Transthoracic Echocardiography (TTE). Subsequently, severity of CAD was assessed, using invasive Coronary Angiography (CAG) using The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score. Next, grades of DDFx were correlated with severity of IHD.

Results: Among a total of 93 diabetic stable IHD patients with normal LV ejection fraction, 76.3% were males and the mean age was 60.7±8.9 years. Majority presented with chronic stable angina (59, 63.4%). Hypertension (50, 53.7%), followed by dyslipidaemia (36, 38.7%) and renal dysfunction (19, 20.4%) were the most common co-morbidities. Majority of patients had grade I (39.8%), followed by grade II (17.2%), and grade III (9.7%) DDFx. On invasive CAG, 39.8% had a SYNTAX score of ≤22, 36.6% had a score of 23-32, and 23.6% had a score of ≥33. Grades of DDFx were found to be significantly higher among the patients with greater SYNTAX score.

Conclusion: Among diabetic stable IHD patients, greater the severity of CAD on CAG, higher were the grades of DDFx.

Keywords: Coronary angiography, SYNTAX score, Transthoracic echocardiography

INTRODUCTION

According to the Global Burden of Disease study age-standardised estimates (2010), nearly a quarter (24.8%) of all deaths in India is attributable to Cardiovascular Diseases (CVD). The age-standardised cardiovascular death rate in India is 272 per 100000 population, which is greater than the global average of 235 per 100000 population. IHD and stroke are responsible for majority of the CVD deaths in India (83%) with IHD being the most common cause [1]. The World Health Organisation (WHO) data showed IHD was the top cause of death globally in both 2000 and 2019; and it is responsible for the largest increase in deaths - more than 2 million- over the last two decades [2]. The spectrum of Stable Ischaemic Heart Disease (SIHD), which is currently designated as chronic coronary syndrome, is broad and includes individuals with chronic stable angina, asymptomatic ischaemia, prior myocardial infarction, prior coronary revascularisation, as well as individuals with non obstructive coronary atherosclerosis. It is also known that ischaemia or infarction occurring due to CAD causes left ventricular systolic and DDFx. DM speeds up the process of coronary atherosclerosis as well as functional and structural cardiac impairments, exhibiting DDFx at the early stages. Several studies have shown high incidence of DDFx among DM patients [3-5].

Severity of CAD is best assessed using invasive CAG although other non invasive method like Computed Tomography Coronary Angiography (CTCA) is available. The Gensini score and SYNTAX score are commonly used as angiographic grading tools to assess severity of CAD, and help in decision making for treatment. In the literature, studies evaluating the relation between these scores and LV function are scarce.

Recently, Sahin DY et al., demonstrated that although the LV systolic function remained normal, myocardial performance index value was impaired in proportion to the severity of CAD in patients with SIHD [6]. Du LJ et al., concluded that elevated LV end-diastolic pressure was significantly associated with extent and severity of CAD [7]. Data from Korean Women's chest pain registry also showed an association between LV DDFx and severity of CAD among women [8]. However, Abali G et al., showed that diastolic function did not demonstrate any impairment according to the severity of CAD among SIHD patients [9]. Also, Jamiel AR et al., suggested that severity of CAD by CTCA, is not independently associated with echocardiographic measures of DDFx among patients without prior CAD or LV dysfunction [10]. Therefore, there are conflicting reports regarding relationship of DDFx and severity of CAD.

Moreover, correlation between the LV DDFx and CAD in diabetic patients has not been studied thoroughly. Escaned J et al., found that there appeared to be a relationship between LV diastolic function impairment and structural changes in microcirculation among diabetic CAD patients [11]. Overall, there is insufficient data regarding association of CAD and LV DDFx among diabetics. Further, there is lack of data from Indian subcontinent on this particular issue although here are huge numbers of diabetic IHD patients from this part of the world. Therefore, the present study was conducted to assess severity of CAD in diabetic SIHD patients with normal LV systolic function (LV Ejection fraction ≥50%) and its association with degree of DDFx.

MATERIALS AND METHODS

This observational cross-sectional prospective study was conducted among diabetic SIHD patients presenting to the Department of Cardiology, MKCG Medical College and Hospital, Berhampur, Odisha, India, during the period of one year (March 2019 to February 2020). Institutional Ethics Committee (IEC) approval was taken (IEC approval letter no. 665/2019).

Inclusion criteria: Adult diabetic patients (newly detected as per American Diabetes Association guideline or previously diagnosed cases of DM already on anti-hyperglycaemic therapy) with features of SIHD based on clinical presentation, Electrocardiography (ECG) and echocardiography were included in the present study after obtaining necessary consent.

Exclusion criteria: Patients with current Acute Coronary Syndrome (ACS) or ACS within one month were excluded. Also, patients with prior history of percutaneous coronary intervention or coronary artery bypass grafting surgery were excluded. Patients with severe valvular stenosis or primary regurgitation, LV systolic dysfunction (LVEF <50% on TTE), constrictive/restrictive/hypertrophic cardiomyopathy, congenital heart disease, cardiac arrhythmia were excluded. Patients without any demonstrable lesion in coronary arteries on CAG were excluded. Patients with poor TTE window were eliminated from the study due to unsatisfactory assessment of diastolic function parameters. All the diabetic patients fulfilling inclusion and exclusion criteria were included in the study.

Study Procedure

Following hospitalisation, detailed history was documented (symptoms, signs, co-morbidity, addiction, treatment history) and clinical examination was carried out. Routine haematological investigation (complete blood count) and biochemical investigation (fasting plasma glucose, renal function test, electrolytes, lipid profile) were carried out including HbA1c. ECG was done by a standard 12-lead ECG machine (BPL Cardiart 6108T).

Subsequently, TTE was done using Philips HD7XE echocardiography machine with 3.5 MHz transducer probe. All measurements were obtained as per American Society of Echocardiography (ASE) guideline [12]. LVEF was measured in apical four-chamber (A4C) and two-chamber (A2C) view using modified Simpson biplane method of disc. Out of four major parameters of diastolic function (mitral E/A ratio, mitral E/e' ratio, peak tricuspid regurgitation velocity and left atrial volume index), if majority (at least two of four parameters) were abnormal, diastolic function was considered as abnormal. LV diastolic function was documented as normal, grade I, grade II and grade III DDFx as per the criteria set by ASE using different parameters of diastolic function [12].

Subsequently, CAG was done to determine the extent of CAD. Radial access was used for most of the patients under conscious sedation and local anaesthesia with subcutaneous injection of 2% lignocaine. Femoral access was used only if radial access failed or if there was any contraindication to use radial route. A low-osmolar iodinated contrast medium Iopromide (Ultravist 300) was used to obtain the angiographic image. Severity of CAD was assessed using SYNTAX score [13]. CAD severity was documented as no CAD with SYNTAX score 0, low SYNTAX score (score between 1 and 22), intermediate SYNTAX score (score between 23 and 32) and high SYNTAX score (score ≥33). Lastly, grades of diastolic functions (normal, grade I, grade II, grade III) was compared with angiographic severity of CAD (low, intermediate and high SYNTAX score) to find out whether greater severity of CAD was associated with a greater degree of DDFx.

STATISTICAL ANALYSIS

All results for continuous variables were expressed as Mean±SD (Standard Deviation). Data were compared for statistical significance using Fisher's-Exact test, Chi-square test, Student's t-test and one-way Analysis of Variance (ANOVA), as appropriate. All analyses were performed using the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). A p-value <0.05 was considered statistically significant.

RESULTS

As per inclusion criteria, 213 diabetic patients presented with features of SIHD during the study period. Based on exclusion criteria, 120 patients were excluded (14 prior PCI/CABG, 16 significant valvular stenotic or regurgitant lesion, LVEF less than 50% in 36, significant cardiac arrhythmia in nine, no demonstrable CAD on CAG in seven and unsatisfactory echocardiographic image in 38). Therefore, a total of 93 patients were included in the final analysis. Demographic and baseline characteristics of the patient population are described in [Table/Fig-1].

Characteristics	Male (n=71)	Female (n=22)	p-value
Age (years)	58.7±8.4	62.3±7.8	0.077#
<50	19 (26.8%)	8 (36.4%)	0.686*
50-69	41 (57.7%)	11 (50%)	
≥70	11 (15.5%)	3 (13.6%)	
Clinical presentation			
Chronic stable angina	43 (60.6%)	16 (72.7%)	0.568*
Prior myocardial infarction	17 (23.9%)	4 (18.2%)	
Asymptomatic myocardial ischaemia	11 (15.5%)	2 (9.1%)	
Risk factors			
Hypertension	40 (56.3%)	10 (45.4%)	0.46*
Peripheral artery disease	6 (8.4%)	1 (4.5%)	1.00*
Renal dysfunction	16 (22.5%)	3 (4.2%)	0.54*
History of heart failure	4 (5.6%)	0	0.57*
History of CVA	4 (5.6%)	0	0.57*
Smoking	27 (38.0%)	0	0.0003*
Obesity (BMI >30 kg/m^2)	6 (8.4%)	5 (22.7%)	0.12*
Dyslipidaemia	27 (38.0%)	9 (40.9%)	0.80*
Symptoms	**Male (n=60)**	**Female (n=20)**	
Angina	50 (83.3%)	11 (55.0%)	0.015*
Mid-epigastric discomfort	12 (20.0%)	7 (35.0%)	0.225*
Dyspnoea	31 (51.7%)	13 (65.0%)	0.437*
Effort intolerance	12 (20.0%)	8 (40.0%)	0.133*
Excessive fatigue	9 (15.0%)	6 (30.0%)	0.185*
ECG changes	**Male (n=71)$^{\$}$**	**Female (n=22)**	
Features of myocardial ischaemia	66 (92.9%)	18 (81.8%)	0.207*
Evidence of prior MI	17 (23.9%)	4 (18.2%)	0.772*

[Table/Fig-1]: Demographic and baseline characteristics of the study population. *Chi-square test; #unpaired t-test; p-value <0.05 is statistically significant; CVA: Cerebrovascular accident; MI: Myocardial infarction; $patient may have ECG features of both current myocardial ischaemia and prior MI

Among the study population, 76.3% were males and 23.7% were females. Majority of the male (57.7%) as well as female (50%) patients were in the age group of 50-69 years. Mean age was 60.7±8.9 years. There was no statistically significant difference in age distribution (p=0.686) between males and females. Majority of enrolled patients presented with chronic stable angina (63.4%). Nearly one-fourth of diabetic SIHD patients had prior documentation of myocardial infarction (22.6%) and 13.9% patients had asymptomatic myocardial ischaemia who were incidentally detected during ECG.

Hypertension (53.7%), followed by dyslipidaemia (38.7%) and renal dysfunction (eGFR <60 mL/min/1.73 m^2 as per CKD-EPI formula; 20.4%) were the most common co-morbidities among the population. Duration of diabetes was significantly longer in male than their female counterpart (4.5±3.4 years vs 2.7±2.9 years, p=0.027). Overall, 38% of the males were smoker (either active or former). Most of the female patients (81.8%) were postmenopausal.

Nearly two-third of the patients (65.6%) presented with angina. A significantly higher percentage of men had angina than women (83.3% vs 55%, p=0.015). Dyspnoea (47.3%) was the second most common presenting symptom. Although non anginal symptoms like dyspnoea, mid-epigastric discomfort, effort intolerance and excessive fatigue were more common among female patients, these differences didn't meet criteria of statistical significance.

All the patients were in normal sinus rhythm as per inclusion/exclusion criteria. Mean LVEF was 59.7±3.6%. Echocardiographic parameters of diastolic function are shown in [Table/Fig-2]. Two third of study population had DDFx (39.8% patient with grade I, 17.2% with grade II and 9.7% with grade III).

Echo parameters	Mean±Standard deviation
LV peak E wave velocity (cm/sec)	71.4±14.6
LV peak A wave velocity (cm/sec)	81.3±15.2
Mitral E/A ratio	0.90±0.21
Average e' (cm/sec)	7.43±3.4
Average E/e' ratio	9.6±2.9
Peak TR velocity (m/sec)	2.1±1.1
LA volume index (mL/m^2)	32.6±6.9
Diastolic dysfunction	**No. of patients (%)**
Nil	31 (33.3)
Grade I	37 (39.8)
Grade II	16 (17.2)
Grade III	9 (9.7)

[Table/Fig-2]: Echocardiographic parameters of diastolic function among study population.
LV: Left ventricle; E wave velocity: Early diastolic mitral inflow velocity; A wave velocity: late diastolic mitral inflow velocity during atrial contraction; e': mitral annular early diastolic velocity in tissue Doppler imaging; TR: Tricuspid regurgitation; LA: Left atrium

Majority of the patients underwent CAG through right radial artery access. Two-third of the patient population had multivessel disease. Severe CAD was found in 23.6% of study cohort [Table/Fig-3]. Different demographic parameters and co-morbidities were compared between three terciles of SYNTAX score [Table/Fig-4]. Patients with uncontrolled diabetes (HbA1C >7%) had more severe CAD (p=0.003). However, other co-morbidities as well as smoking history were similar in between three groups. Patients with higher SYNTAX score had relatively lower LVEF (60.9±2.7%, 58.6±3.6% and 58.3±3.1% with SYNTAX score ≤22, 23-32 and ≥33 respectively, p=0.0002). As diastolic function of study population was compared with angiographic SYNTAX score [Table/Fig-5], it showed that grade of DDFx was significantly higher among the patients with greater SYNTAX score.

Parameters	Cases (n=93)	Percentage (%)
Arterial access		
Radial	78	83.8
Femoral	15	16.2
Number of vessels involved		
SVD	31	33.3
DVD	29	31.2
TVD	33	35.5
LMCA involvement	13	13.9
SYNTAX score		
1-22	37	39.8
23-32	34	36.6
≥33	22	23.6

[Table/Fig-3]: Coronary Angiography (CAG) profile in study population.
SVD: Single vessel disease; DVD: Double vessel disease; TVD: Triple vessel disease; LMCA: Left main coronary artery

SYNTAX score	≤22 (n=37)	23-32 (n=34)	≥33 (n=22)	Total (n=93)	p-value
Male/Female	30/7	25/9	16/6	71/22	0.681*
Age (in years)	58.6±12.7	61.2±10.7	60.3±11.8	60.7±8.9	0.643#
Hypertension	17 (46%)	20 (59%)	13 (59%)	50 (54%)	0.469*
CrCl <60 mL/min	7 (19%)	5 (15%)	3 (14%)	15 (16%)	0.833*
LDL-C >55 mg/dL	17 (46%)	20 (59%)	14 (64%)	51 (55%)	0.352*
Serum TG >200 mg/dL	16 (43%)	17 (50%)	9 (41%)	42 (45%)	0.764*
HbA1C >7%	13 (35%)	8 (23%)	15 (68%)	36 (39%)	0.003*
Postmenopausal	7 (100%)	7 (78%)	4 (68%)	18 (82%)	0.745*
Smoking	13 (35%)	8 (24%)	6 (27%)	27 (29%)	0.548*
LVEF (%)	60.9±2.7	58.6±3.6	58.3±3.1	--	0.002#

[Table/Fig-4]: Distribution of demographic characteristics, co-morbidities and LV ejection fraction based on SYNTAX score.
*Chi-square test, #unpaired t-test; p-value <0.05 is statistically significant

SYNTAX score	≤22	23-32	≥33	Total	p-value*
Normal diastolic function	16 (17%)	11 (12%)	4 (4%)	31 (33%)	0.0009
Grade I diastolic dysfunction	14 (15%)	19 (20%)	4 (4%)	37 (40%)	
Grade II diastolic dysfunction	5 (6%)	2 (2%)	9 (10%)	16 (17%)	
Grade III diastolic dysfunction	2 (2%)	2 (2%)	5 (6%)	9 (10%)	
Total	37 (40%)	34 (36%)	22 (24%)	93 (100%)	

[Table/Fig-5]: Distribution of grades of diastolic dysfunction based on SYNTAX score.
*Chi-square test; p-value <0.05 is statistically significant

DISCUSSION

The DDFx refers to an abnormal relaxation of the LV leading to filling impairment during diastole. Despite this simple definition, understanding the cause of DDFx and its inter-relationship with myocardial ischaemia and diabetes is extremely complex. DDFx and CAD are interlinked and DDFx has been shown to alter the clinical course in CAD patients.

Age and gender distribution in this study were corroborative with data published by Abali G et al., who evaluated stable CAD patients with normal LVEF for CAD severity and DDFx [9]. Similar findings have been obtained by Du LJ et al., and Escaned J et al., [7,11]. However, a study from Egypt among 40 patients with known IHD described mean age 48±10 years which was more than a decade younger than the index study cohort [14]. But, such comparisons can't be made as these studies included a limited number of patients; therefore may not be the true representative of the real world scenario.

A good number of the diabetic patients had asymptomatic myocardial ischaemia, detected on routine ECG during health check up or while being evaluated for other causes. Earlier, several studies suggested that silent myocardial ischaemia is more frequent among diabetic patients than in others [15-17]. More than four decades ago, a study from New York showed a high prevalence of silent myocardial ischaemia among asymptomatic diabetic males detected by thallium scintigraphy and exercise ECG [18]. A Finnish study showed that atleast 9% diabetics had asymptomatic CAD with evidence of active myocardial ischaemia [19]. However, this study was not designed to assess such prevalence among diabetics in the community.

Hypertension was found to be the most common co-morbidity among the present study population. This was an expected finding as nearly 70% of the adult patients with DM have concomitant hypertension [20]. Several Indian studies previously described high prevalence of hypertension among diabetics [21,22]. A study among a large number of diabetic patients based on a database of primary health record from United Kingdom (UK) also showed that hypertension was the commonest co-morbid condition [23]. However, they found a higher prevalence of hypertension among

female patients with diabetes; although authors could not find any such gender difference. This may be due to the limited number of female patients in present cohort.

Women, in the present study cohort, had a relatively shorter duration of DM than men, possibly due to delayed diagnosis of DM in women. Possibility of recall bias can't be excluded as the exact timing of diagnosis could not be ascertained in most of the patients due to unavailability of old documents. However, it may also indicate the probability of a more aggressive course of DM in women. In 2014, a meta-analysis showed that the diabetic women had more than 40% higher risk of incident CAD compared with diabetic men [24].

Transthoracic Echocardiography, in the study, revealed presence of normal diastolic function in one-third and some degree of DDFx in remaining two-third patients. Majority of patients with DDFx had grade I (39.8%), followed by grade II (17.2%) and grade III (9.7%) DDFx. A study by El din Behairy NH et al., among 40 known CAD patients found grade I DDFx among 35%, grade II among 30% and grade III among 15% by echocardiography and this finding had excellent correlation with DDFx assessment by cardiac MRI [14]. Although current guideline [12] recommends measurement of diastolic parameters routinely, not only in suspected cases of Heart Failure with Preserved Ejection Fraction (HFpEF), but also in patients with systolic LV dysfunction, often measurement of these parameters is neglected in clinical practice as this is cumbersome and takes a lot of time and precision.

As patients were distributed based on their angiographic SYNTAX score, it was found that patients with higher HbA1c (i.e., >7%) had high SYNTAX score. Similar conclusion had been made by Malthesh MK et al., in their study among ACS patients from Karnataka, India [25]. Finding of current study also corroborated with several other studies which showed positive association between HbA1c and severity of CAD [26,27]. Interestingly, Kamal AM et al., showed that higher HbA1c was associated with higher Gensini score not only among diabetics, but also among non diabetics [28]. However, UK Prospective Diabetes Study (UKPDS) failed to show any significant effect of blood glucose lowering on cardiovascular complications although it showed a 25% reduction in microvascular complications [29].

It was also found that degree of DDFx was directly proportional to the severity of CAD, as measured by SYNTAX score. Most of the patients with SYNTAX score ≤22 had either normal diastolic function or grade I DDFx on TTE. 22 patients had SYNTAX score ≥33, out of them 9 had grade II and 5 had grade III DDFx. So, 14 of 22 had either grade II or III DDFx, i.e. 63.6%. Although several previous studies pointed out such relation between CAD severity and degree of DDFx, controversies still remain. Du LJ et al., from China found that, the extent and severity of CAD was closely related to Left Ventricular End-Diastolic Pressure (LVEDP) ($p<0.001$). LVEDP, a marker of diastolic function, was significantly associated with Gensini score as found on linear regression analysis [7]. Lin FY et al., made similar conclusion as they also correlated elevated LVEDP with increased CAD severity measured by CTCA [30]. But, they have not excluded patients with LV systolic dysfunction from their study. Results from several other studies also strengthened such association between CAD severity and grade of DDFx [31,32].

However, Abali G et al., did not show any relation between angiographic severity of CAD assessed by SYNTAX score and Gensini score with impairment of diastolic function [9]. A study from Saudi Arabia tried to correlate CAD burden measured by CTCA with DDFx. They observed a direct relationship between coronary artery plaque burden and measures of DDFx on univariate analysis. However, after adjusting for confounders by multivariate analysis (age, hypertension, DM, dyslipidaemia etc.,), independent association between atherosclerosis and DDFx could not be found [10]. Eleid MF et al., described that in asymptomatic patients with normal LVEF and negative cardiac stress test results, coronary artery calcium score did not correlate with LV diastolic function as defined by established Doppler echocardiographic criteria. In the absence of ischaemia, post infarction LV remodeling, or previous CABG, CAD does not appear be a cause of LV DDFx in asymptomatic patients [33]. However, the result of this study may not be applicable to present study population as they evaluated only asymptomatic patients without any evidence of myocardial ischaemia irrespective of their diabetes status.

Limitation(s)

The present study was a single centre study with a small sample size carried out with limited resources. A larger study with longer duration and more robust design is needed to get the real-world scenario. Only diabetic patients were included in the present study. A control group of non diabetic CAD patients could have been included to compare the diastolic and angiographic parameters between these two groups. The present study was a cross-sectional study; a longitudinal prospective study would have given a clear scenario regarding prognosis of these patients and how the diastolic parameters change with therapy. Finally, invasive assessment of diastolic parameters has not been done. Only TTE was done to assess diastolic function which may affect the accuracy of the diastolic parameters.

CONCLUSION(S)

Coronary Artery Disease is a major determinant of the long term prognosis among patients with DM. It is also well known that myocardial ischaemia can cause systolic as well as DDFx. In the present study, authors have evaluated the association between grades of DDFx (measured by echocardiography) and severity of CAD assessed by SYNTAX score following CAG among diabetic patients with chronic coronary syndrome. It was found that patients with higher SYNTAX score had poorer control of their diabetes status, lower LVEF and greater degree of DDFx.

However, previous studies have shown contradictory results. Moreover, prersent study had several limitations. Hence, there is no conclusive evidence to state that more severe the CAD, greater the degree of DDFx. Therefore, a large prospective randomised controlled trial with appropriate study design is the need of the hour to find out whether severity of CAD is truly a determinant of DDFx.

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