Original Article

Echocardiographic Evaluation of Diastolic Dysfunction in Patients with Type-2 Diabetes Mellitus in a Tertiary Care Centre of North Bengal

Bapilal Bala[1], Biswadev Basu Majumdar[2], Debanjan Roy[3], Jyotirmoy Pal[4], Achintya Narayan Ray[5], Debasis Chakrabarti[6] , Sekhar Chakraborty[7]

Aim : India shelters the most number of people with Diabetes Mellitus Worldwide. Diabetic Cardiomyopathy has a complex etiopathological causation and manifests commonly as Diastolic Heart Failure (DHF). Keeping the above result in consideration, the present research was done following proper scientific guidelines to determine the proportion of Ventricular Diastolic Dysfunction among Type-2 DM patients and to find an association between LV Diastolic Dysfunction and other indices such as age, HbA1c, DM duration and obesity.

Methods : In an observational case control study 172 subjects were evaluated for One year. The information obtained become analyzed using specific statistical techniques consisting of general deviation, mean, percent, multivariate evaluation, Z test, student 't'-test, and Chi square test, by the usage of SPSS-20 software program (Statistical package for the Social Sciences) for windows (SPSS, Chicago, IL). Some statistical exams like Chi-square tests and 't'-test has been achieved to have a look at qualitative and quantitative statistics with 'P' value <0.05 changed into measured statistically sizable.

Results : In our study out of 172 study subjects, majority (35.5%) belonged to 50-54 years age group and mean age of the study subjects was 49.02 (SD±7.628) years. The proportion of male population was higher (65.1%). Among the study subjects majority (46.5%) were overweight with Body Mass Index (BMI) between 25-29.9 kg/m2. In our study 12.2% study subjects had Fasting Blood Sugar (FBS) level more than 126 mg/dl and only 7.6% subjects had HbA1c level ≥7.5%. The proportion of Diastolic Dysfunction (DD) was much higher among the diabetic persons (60.46%) than the non diabetics (12.79%). Most of the study subjects had Grade I DD (61.9%) followed by Grade II DD (30.2%) and least having Grade III and IV DD. DD was much higher among persons having increasing Age,BMI, FBS and HbA1c level.

Conclusion : In this study we conclude that there has been a very significant connection of LV diastolic dysfunction with HbA1c levels, duration of Diabetes, Retinopathy, BMI, hypertriglyceridemia and autonomic neuropathy, as obtained by multivariate analysis. Earlier diagnosis and institution of treatment for DD will effect in better decline of the morbidity and Diastolic HF improvement.

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Key words **: Type 2 Diabetes, Diastolic Dysfunction.**

Type-2 Diabetes is the commonest type of Diabetes constituting 90% of the diabetic population in any country. The global prevalence of Diabetes is estimated to increase, from 4% in 1995 to 5.4% by year 2025[1]. A National Study of Diabetes Mellitus conducted in six major cities in India in 2000 showed that the prevalence of Diabetes among Urban adults was 12.1%. Prevalence of Impaired Glucose Tolerance (IGT) was also high (14.0%)[2]. Prevalence of diabetes was found to be lower in the low Socio-economic group living in urban areas compared with the high income group (12.6% *versus* 24.6% in subjects >40 years)[3]. The World Health Organization has predicted that the major burden will occur in the developing countries. There

Editor's Comment :

- The proportion of Diastolic Dysfunction was much higher among the Diabetic persons than the non diabetics.
- Most of the study subjects had Grade I DD followed by Grade II DD.
- DD increases with increment of ages of the study subjects, highest dysfunction was observed between ages 55-59 years.
- DD was much higher among persons having increasing BMI, FBS and HbA1c level and increase in duration of diabetes.

[1]MD (General Medicine), Associate Professor, Department of Medicine, Maharaja Jitendra Narayan Medical College and Hospital, Cooch Behar 736101

[2]MD(Medicine), DM(Cardiology), Senior Resident, Department of Cardiology, North Bengal Medical College and Hospital, Sushrutnagar 734012 and Corresponding Author

[3]MD (General Medicine), Consultant Physician, General Medicine, Desun Hospital, Siliguri 734012

[4]MD (General Medicine), Professor, Department of Medicine, RG Kar Medical College, Kolkata 700004

[5]MD (General Medicine), Associate Professor, Department of Medicine, Cooch Behar Government Medical College and Hospital, Cooch Behar 736101

[6]MD (General Medicine) Associate Professor, Department of Medicine, North Bengal Medical College and Hospital, Sushrutnagar 734012

[7]MD (Medicine), Consultant Physician and Diabetologist, Medical Director of Kins Care and Research Foundation and Kins Hospital, Siliguri 734005

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will be a 42% increase from 51 to 72 million in the developed countries and 170% increase from 84 to 228 million, in the developing countries[5].

The only published nationally representative study on burden of DM in India is Prevalence of Diabetes in India Study – PODIS (2002), a multi-centric study (49 Urban and 59 Rural centers) on 41,000 Indian people. PODIS has estimated the age and gender standardized prevalence of DM in India to be 3.3 percent[6]. The International Diabetes Federation (IDF) also reported that the total number of diabetic subjects in India is 41 million in 2006 and that this would rise to 70 million by the year 2025[7]. Diastolic Heart Failure (HF) failure is the most common form of HF in DM with preserved ventricular systolic function. Studies have suggested an important increase in pre-clinical dysfunction among subjects with DM[8]. The purpose of this research would be to identify the amount of Diastolic Dysfunction in diabetes studies and its relationship to age, obesity symptoms, glycosylated Hb level and DM.

Materials and Methods

This study was conducted at the Cardiology Department of North Bengal Medical College for patients attending indoor and outdoor of Department of General Medicine for 1 year (July 2014- June 2015) . The age and sex matched controls will be selected from the persons who will accompany the patient.

Study Design : It is a observational case control study.

Inclusion Criteria :

All Type-2 DM subjects who are suffering from DM more than 5 years with normal left ventricular systolic function (LVEF:0.50%) having systolic blood pressure(SBP)<140 mmHg and diastolic blood pressure <90 mmHg not taking any anti-hypertensive medication.

Exclusion Criteria :

(a) All patients with indication of Coronary Artery Disease excluded by h/o angina and by ECG.

(b) All patients with indication of valvular Heart Disease.

(c) Hypertensive patients.

(d) Subjects with age > 60 years.

(e) Patients who will not provide consent for participation in the research study.

A similar type of study was done in Surat[9] which showed that among all cases of type-2 DM 66% had diastolic dysfunction.

Based on this, assuming P=66%, confidence interval= 95% and absolute precision of 10% sample size becomes:

Anticipated proportion of the population -P =66%

Confidence level -100(1-α) % =95%

Absolute correctness required on either side of proportion (in % points) -d =10%

Sample Size : $n = Z^2 1 - \alpha/2P(1-P)$

$d^2 = (1.96)^2 \times 0.66 \times 0.34$ $(0.1)^2$

= 86

Similar number of controls will be taken in 1:1 ratio. So, final sample size will be = 86+86 = 172.

Parameters to be Studied :

- History taking including duration from initial diagnosis of DM.
- General clinical examination:
- Anthropometric evaluation.
- Lipid profile

Echocardiographic Parameters :

(1) Peak E velocity in m/sec - peak early transmitral filling velocity during early diastole (normal: 0.5-0.8).

(2) Peak A velocity in m/sec – peak transmitral atrial filling velocity through late diastole (normal: 0.3-0.5).

(3) Deceleration Time (DT) in msec – time intervened among point where extrapolation of slowing slope of E velocity and peak E velocity crosses the zero baseline (normal:150-220).

(4) Isovolumetric Relaxation Time (IVRT) in msec – duration among mitral valve opening and aortic valve closure (normal: 60-100).

(5) Ratio of Peak E to peak A (E/A) (normal:1-2)

(6) E/e' ratio = mitral peak velocity of initial filling (E) to primary diastolic mitral annular speed (e') ratio (normal : >15)

Study Tools :

- Pre-designed and pre-tested interview schedule was used,
- The Consent Form is duly signed by the participant
- Sphygmomanometer,
- 2D, pulse wave Doppler and Tissue Doppler echocardiography.
- Electronic weighing machine,
- Measuring tape,

Study Techniques :

All patients who meet the informed consent procedure will be included in the study and data will be collected from a detailed history using a pre-test procedure; a complete clinical examination including routine tests, systemic tests and anthropometric tests will be performed. This will be followed by biochemical investigation using full Autoanalyser Machine (Transasia Biomedicals Limited ModeL XL-600). After twelve hours of fasting, the sample of blood has been collected and despatched to the laboratory of Biochemistry for added evaluation of the subsequent parameters:

- Plasma glucose level;
- GlycatedHbA1c;

- Lipid profile by crest biosystems reagent.

ECG will be done in all subjects.

Diagnostic Criteria :

Dyslipidemia: defined if TC >200 mg/dL; LDL cholesterol >130 mg/dL; HDL cholesterol 40 mg/dL: and TG >150 mg/dL.

Obesity indices: cut-off for high BMI >25 for female and>27 for males. Cut-off for excess Waist to Hip Ratio (WHR) > 0.9 for males and >0.8 for females. Cut-off for excess WC >80 cm for females and >90 cm for males.

Diabetes mellitus (DM): If a person is a identified diabetic on diabetes treatment or having FBS ≥126 mg/dL.

Diastolic dysfunction: LV diastolic dysfunction should be considered if any of the following is present.

- E/A ratio <1 or >2
- DT <150 or >220 ms
- IVRT <60 or >100 ms, or
- E/e' ratio >15

Statistical Methods : Data were collected, assembled and transferred to Excel Spread sheet (MS Excel 2007) and analyzed using IBM-SPSS 20 Chicago, IL .The t test and Chi Square Tests were used. All the statistical significance tests were done assuming Level of Significance at 95% confidence intervals.

Analysis and Results

Section 1: Background characteristics of the study subjects

Table 1 shows that, among 172 study subjects majority (35.5%) belonged to 50-54 years age group, followed by 31.5% in 55-59 years. Mean age was 49.02 (SD ±7.628) years of the study subjects.

Mean age of the study subjects was 49.02 (SD ±7.628) years. Majority of the population were males.

Among 172 study subjects majority (46.5%) of the study subjects had BMI between 25-29.9 kg/m² (overweight), 44.2% were of normal BMI. Whereas, obese were 2.9% and undernourished were 6.4%. Table 2 depicts that among all study subjects 12.2% had their fasting blood sugar level more than 126 mg/dl during the time of examination. This table shows that only 7.6% had their HbA1c level 7.5 or more than that.

Table 1 — *Distribution of the study subjects according to age group*

Age Group (years)	Frequency	Percent
40-44	19	11.0
45-49	38	22.0
50-54	61	35.5
55-59	54	31.5
Total	172	100.0

Section 2 : Characteristics of the Diabetic and Non-diabetic subjects.

Table 3 shows that though there is statistically significant difference with some important laboratory indices and BMI but there is no such difference in respect to age (Fig 1).

Table 4 shows there is statistically significant difference in Lipid Profile between Diabetic and Non diabetic subjects (p=0.000).

Section 3 : Diastolic dysfunction: proportion, grade and some important associated factors.

Table 5 shows that among all study subjects, 36.6% had Diastolic Dysfunction.

Table 6 shows that proportion of Diastolic Dysfunction was much higher among the diabetic patients (60.46%) than Non-diabetic persons (12.79%).

It is seen from Table 7 that Diastolic Dysfunction was found most using IVRT parameter.

Table 8 depicts that most of the subjects had Grade I Diastolic Dysfunction (61.9%), followed by Grade II DD among 30.2% and least having Grade III and IV DD.

Table 9 shows that proportion of DD increases with the increment in age of the subjects. Highest Dysfunction was observed among subjects having age of 55 to 59 years (31.5%). This finding is statistically non-significant.

This Table 10 shows that proportion of DD was much higher (60.9%) among the subjects having HbA1c level

Table 2 — *Baseline Characteristics of the population*

Age (Mean ± SD)	49.02 (SD±7.628) years		
Gender (M: F= 1.86)	Male : 112 (65.1%)		Female : 60 (34.9%)
BMI	<18.5 ; 11(6.4%)	18.5-24.9 ; 76(44.2%)	25-29.9 ; 80 (46.5 %) ≥30 ; 5 (2.9 %)
Fasting Blood Sugar (FBS)	<100 mg/dl ; 97(56.4 %)	100-125 mg/dl ; 54(31.4 %)	≥126 mg/dl ; 21 (12.2 %)
HbA1c	<6.5 ; 124(72.1 %)	6.5 – 7.4 ; 35(20.3 %)	≥7.5 ; 13 (7.6 %)

Table 3 — *Association of some important parameters between diabetic and non-diabetic patients* (n=172)

Parameters	Diabetic (mean ± SD)	Non-diabetic (mean ± SD)	Statistical test (95% CI, t-test, p value)
AGE	49.01 ± 7.438	49.02 ± 7.856	- 2.315 to 2.291, t value = -0.010, p= 0.992
BMI	26.41 ± 1.886	21.12 ± 2.305	4.654 to 5.922, t value = 16.466, p= 0.000
FBS	110.16 ± 21.101	91.56 ± 13.882	13.228 to 23.98, t value = 6.831, p= 0.000
PPBS	185.53 ± 50.419	121.45 ± 10.861	53.103 to 75.060, t value = 11.521, p= 0.000
HBA1C	6.53 ± 0.846	5.14 ± 0.434	1.184 to 1.589, t value = 13.519, p= 0.000

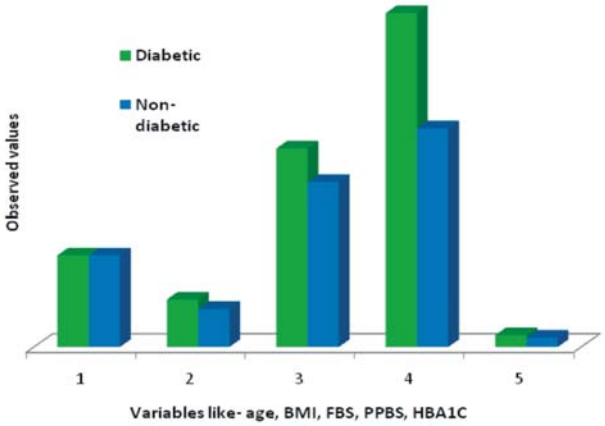

Fig 1 — *Mean values of some baseline parameters between diabetic and non-diabetic patients*

more than 7. The above result is statistically significant ($p<0.05$).

Table 11 shows that proportion of DD increases with the increase in duration of diabetes of the subjects. This finding is statistically significant ($p<0.05$).

From the Table 12 it is seen that, diastolic dysfunction is much higher among the subjects who had increased BMI, Fasting blood sugar and HbA1c.

Table 13 shows that occurrence of diastolic dysfunction is suggestively associated with many of the echo parameters, except the IVRT value.

Discussion

Our result reveal that Asymptomatic Cardiac Dysfunction is common in subjects with DM. It has been widely described as DiastoliC Dysfunction in subjects with normal Systolic function, and there are not any signs and symptoms of heart failure (HF). It reveals that fasting BSL, HbA1c, serum TC, serum TG and LDL cholesterol in case the values are higher versus the control group. A total of 52 subjects (60.46%) among the trial group had diastolic dysfunction, on the other hand 11 (12.79%) within the control group showed Diastolic Dysfunction. The duration of diabetes mellitus of ≥15 years was significantly higher than Diastolic Dysfunction ($P<0.05$). Patients having HbA1c more than 7.0% had a surge in Diastolic Dysfunction than patients with HbA1c less than 7.0% ($P<0.05$). Diastolic dysfunction was proportionally high in subjects with more than 55-year age compared to less than 55-year age subjects.

We have compared our study findings with many studies. Soldatos *et al*[10]. In their study of 55 control subjects with type 2 DM it has been found that diastolic dysfunction has been present in a big proportion of patients with Type-2 DM. Equally, in our study, 60.46% of patients among the study group had Diastolic Dysfunction and 11 (12.79%) among the control group had Diastolic Dysfunction ($P<0.05$). Diabetes is thought to increase strength through myocardial collagen placement and high-end glycation end products.

In the case control study of 77 normotensive

Table 4 — *Association of some important parameters related to Lipid Profile between diabetic and Non-diabetic patients (n=172)*

Parameters	Diabetic (mean ± SD)	Non-diabetic (mean ± SD)	Statistical test (95% CI, t-test, p value)
LDL	130.48 ± 19.986	118.05 ± 8.435	7.812 to 17.048, t value= 5.314, p= 0.000
TC	208.12 ± 22.037	176.08 ± 12.711	26.62 to 37.45, t value =11.678, p= 0.000
HDL	40.60 ± 4.625	48.85 ± 5.416	-9.76 to -6.728, t value= -10.735, p= 0.000
TG	151.07 ± 15.756	133.72 ± 10.435	13.32 to 21.37, t value= 8.513, p= 0.000

Table 5 — *Proportion of Left Ventricular Diastolic Dysfunction among patients and controls (n=172)*

Diastolic dysfunction	Frequency	Percentage
Present	63	36.6
Absent	109	63.4
Total	172	100

**Assessed using all echo parameters*

Table 6 — *Distribution of Diastolic Dysfunction among Diabetic and Non-diabetic Study Subjects (n=172)*

Diabetes Mellitus	Diastolic dysfunction		Total
	Present	Absent	
Yes	52 (60.46)	34 (39.54)	86 (100)
No	11 (12.79)	75 (87.21)	86 (100)
Total	63 (36.6)	109 (63.4)	172

Z test value = 6.33, 95% CI value= 33.99 to 61.35
P value = 0.000

Table 7 — *Diastolic dysfunction according to various Echo parameters (n=172)*

Echo parameters	Frequency	Percent
E/A	44	25.6
IVRT	85	49.5
DT	68	39.5
E/e'M	26	15.1
E/e'L	8	4.7

Table 8 — *Pattern of Left Ventricular Diastolic Dysfunction among Patients and Controls* (n=63)

Grades of diastolic dysfunction	Frequency	Percentage
Grade I	39	61.9
Grade II	19	30.2
Grade III and IV	5	7.9
Total	63	100

Table 9 — *Relationship of Diastolic Dysfunction with age group (n=172)*

Age group (years)	Diastolic dysfunction		Total
	Present	Absent	
40-44	4 (21.1%)	15 (78.9%)	19 (100.0%)
45-49	10 (26.3%)	28 (73.7%)	38 (100.0%)
50-54	13 (21.3%)	48 (78.7%)	61 (100.0%)
55-59	17 (31.5%)	37 (68.5%)	54 (100.0%)
Total	44 (25.6%)	128 (74.4%)	172 (100.0%)

Chi-square value= 1.787, p value= 0.618

Table 10 — *Relationship of Diastolic dYSFUNCTION WITH HBA1C (N=86)*

HbA1c	Diastolic dysfunction		Total
	Present	Absent	
< 7	20 (31.7%)	43 (68.3%)	63 (100.0%)
≥7	14 (60.9%)	9 (39.1%)	23 (100.0%)
Total	34 (39.5%)	52 (60.5%)	86 (100.0%)

Chi-square value= 5.987, p value= 0.014

Table 11 — *Relationship of Diastolic Dysfunction with Duration of diabetes (n=86)*

Duration of diabetes (years)	Diastolic dysfunction		Total
	Present	Absent	
5 - 9	17 (29.8%)	40 (70.2%)	57 (100.0%)
10 -14	14 (56.0%)	11 (40.0%)	25 (100.0%)
≥15	3 (75.0%)	1 (25.0%)	4 (100.0%)
Total	34 (39.5%)	52 (60.5%)	86 (100.0%)

Chi-square value= 7.188, p value= 0.027

Table 12 — *Association of left ventricular diastolic dysfunction with some baseline parameters (n=172)*

Baseline Parameters	Diastolic dysfunction (mean ± SD)		Statistical test (95% CI, t-test, p value)
	Present	Absent	
BMI	26.15 ± 2.68	22.94 ± 3.21	-2.134 to 4.265, t value = 5.929, p= 0.000
FBS	108.3 ± 21.97	98.3 ± 18.84	3.202 to 16.780, t value = 2.905, p= 0.004
HbA1c	6.46 ± 1.08	5.62 ± 0.82	0.531 to 1.150, t value = 5.369, p= 0.000

Table 13 — *Correlation of some important parameters related to echocardiography findings between patients having diastolic dysfunction or not (n=172)*

Echo Parameters	Diastolic dysfunction (mean ± SD)		Statistical test (95% CI, t-test, p value)
	Present	Absent	
IVRT	77.82 ± 32.178	72.35 ± 20.173	-2.740 to 13.673, t value = 1.315, p= 0.190
DT	225.30 ± 48.760	199.84 ± 34.313	12.176 to 38.727, t value = 3.785, p= 0.000
E/e'M	13.67 ± 5.39	9.73 ± 2.78	2.687 to 5.190, t value = 6.212, p= 0.000
E/e'L	11.44 ± 4.41	8.91 ± 2.33	1.496 to 3.564, t value = 4.832, p= 0.000
E/A	0.99 ± 0.56	1.27 ± 0. 17	-0.398 to -0.177, t value = -5.156, p= 0.000

patients Masugata ET AL observed that diastolic dysfunction without LV systolic dysfunction in subjects with accurately controlled Type-2 DM was not linked to high blood pressure or LV hypertrophy, but rather type 2 DM and aging. Likewise, in the current study, a 60.46% of patients from the study group without hypertension and CAD had diastolic dysfunction with normal LV systolic function.Ordinary LV systolic and diastolic activity are related with the period of diabetes and other diabetic microangiopathies, like diabetic retinopathy and neuropathy.

These findings are similar to the current study findings, wherein diastolic dysfunction exist in several patients in long-standing researches. The diabetic length more than 15 years had a greater frequency of diastolic dysfunction linked to the 5 - 9 year group (P<0.05).

In case-control study of 71 patients with type-2 DM, Mishra *et al*[11] found that patients with type 2 diabetes had lesser LV systolic and Diastolic function associated with fit patients. Likewise, in the present study, duration of diabetes more than 15 years had advanced occurrence of diastolic dysfunction compared to the 5–9-year-old age group (P<0.05).

In the study of 114 subjects Exiara *et al*[13] found that the prevalence of LV diastolic dysfunction in subjects with normotensive, asymptomatic and well-controlled DM Type-2 is higher, and rises with age. Almost 63.2% of subjects previously had diastolic dysfunction in their research paralleled 60.46% study subjects in the present study. In the study conducted by Diamant *et al*[14] reveal that early (E) acceleration rate, deceleration peak, high fill rate and E / A ratio, and also many other indicators of diastolic activity, are suggestively lesser in subjects with type 2 diabetes. 2 newly discovered, well-controlled and relatively simple controls (P<0.02). The above results are similar with our findings.

Study conducted by Bonito, *et al*[15] found that impaired LV diastolic dysfunction happens initially in the natural history of Type 2 DM and is associated to clinical proof of microangiopathic conditions. In the study conducted by Aaron *et al*[16] reveal that among the 1,760 patients with diabetic, 411 (23%) patients had diastolic dysfunction which is having high prevalence of adverse outcomes in important number associated to those short of diastolic dysfunction.

The above results are similar with our findings.

In the study conducted by Boyer *et al*[17] reveal that the rate of LV diastolic dysfunction in normotensive subjects without signs with Type 2 Diabetes is higher. Diastolic Dysfunction was present in 75% subjects. In the study conducted with 305 patients with type-2 DM by Poulsen *et al*[18] reveal that, irregular filling of LV was highly linked with abnormal myocardial perfusion scintigraphy.

In the study of 544 consecutive Japanese DM subjects with ejection fraction ≥50%, Takeda *et al*[19] reveal that Diastolic Dysfunction played a major role in HF symptoms with average systolic function in DM subjects, regardless of the blood sugar status or renal dysfunction. Above findings are somewhat comparable to the present study in which diastolic dysfunction was suggestively higher at HbA1c more than 7.0%.

Hameedullah *et al*[20] in their study of 60 patients with Type-2 DM they found a strong association

between HbA1c level and Diastolic indicators (P<0.05). Diastolic dysfunction was further common in highly managed diabetic patients and its sternness was linked with glycemic control. Likewise in the present study, HbA1c>7.0% had a high rate of diastolic dysfunction compared to HbA1c <7.0%.

In the study of 87 patients, CM Schannwell *et al*[21] revealed that even younger patients with Diabetes suffer from diastolic dysfunction, while systolic ventricular function is standard. Accordingly, we say that patients with Type-2 DM is highly linked with duration of Diabetes, HbA1c, age, dyslipidemia and variability in different indicators of obesity.

Our study reveals that cases of pre-clinical diastolic dysfunction are extremely high in patients with Type 2 DM. Our study also reveal that there is a straight link between duration of Diabetes and Diastolic Dysfunction; also, that statistically significant diastolic dysfunction occurs more than five years after the beginning of diabetes irrespective of co-existent coronary artery disease or hypertension. Accordingly, more studies have to be conducted to prove the hypothesis that screening and treatment of subjects with pre-clinical DM can postpone the development of Heart Failure.

Limitations :

(1) The study was conducted on general population in India. Therefore, the results found in our study need further research among different ethnic and racial group.

(2) The Homeostatic Model Assessment (HOMA) test model to investigate fasting insulin concentration has not been involved in our study due to limitations of resources. HOMA index is considered an independent component of Diastolic Dysfunction.

(3) There are both technical and clinical limitations. For technical limitations, proper attention to the location of the sample size, as well as gain, filter and minimal angulation with annular motion, is essential for reliable velocity measurements.

(4) With experience, these are highly reproducible with low variability. Because time interval measurements are performed from different Cardiac cycles, additional variability is introduced. This limits their application to selective clinical settings in which other Doppler Measurements are not reliable.

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