Research Article

Assessment Of Diastolic Function In Diabetic Patients Using Conventional Echocardiogram & Tissue Doppler Imaging

Zainab Atiyah Al Zubeidy, *FICMS, CABM* [1]
Prof. Abdul Hameed Al Qaseer, *FICMS*, **Arshad Fuad Ridha**, *FICMS, CABM, FICMS (Cardiol)* [2]
[1] *Al Kindey Medical College*
[2] *Al Mustansiriyha Medical College*

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Address for Correspondence:
Zainab Atiyah Al Zubeidy, FICMS, CABM Al Kindey Medical College

Abstract

Background: Left ventricular diastolic dysfunction (DD) is considered the first stage of diabetic cardiomyopathy; it occurs in absence of coronary artery disease, hypertension or valvular heart disease &can precede the systolic dysfunction in these patients.

Objectives of the study: The purpose of this study is to assess the diastolic function in diabetic patients of both types 1&2 using conventional, Doppler echocardiograghy and tissue Doppler imaging, and to reveal the impact of age, gender & duration of diabetes on prevalence and grading of DD.

Patients and methods: This is an observational case control analytic study in which 100 persons were enrolled, 50 of them were diabetic patients, and the other 50 were age, sex matched healthy control subjects. In both groups` systolic and diastolic functions were assessed by conventional, Doppler and tissue Doppler echocardiography.

Results: Among the 50 patients, 27 (54%) of them were females and 23 (46%) were males, 27 (54%) of them were type1 diabetes and 23(46%) were type2 diabetes. Control group consisted of 50 subjects including 24(48%) females and 26(52%) males. Patient's age ranges from 15 to 70 years with mean age (39±16.09), control subject's age ranges from 15 to 72 years with mean age (37.64±14.53).

There was significant relationship between aging and prevalence of DD (P value=0.02).Gender not related to prevalence of diastolic dysfunction. There was significant decrease in E/A ratio between both groups (P value=0.0007), while E/É ratio between both groups was not significant.

DD also was higher in type2 diabetes compared with type1 (P value<0.001).Diabetic duration has no impact on prevalence of DD.

Conclusion: Diabetic patients have significant DD detected on both conventional and tissue Doppler echocardiography. Diastolic function is affected with increasing age, but not with gender. The diabetic cardiac changes as well as the echocardiographic parameters seem not to be affected with diabetic duration.

Key words: diabetic cardiomyopathy, diastolic dysfunction, tissue Doppler imaging

INTRODUCTION

Diabetes is considered one of the most common diseases in the world and the main cause of mortality and morbidity in those patients are cardiovascular complications especially in females as more than75% of all diabetic patients die from cardiovascular causes.[1-6]

Ischemic heart diseases and cardiomyopathy increased in those patients.[7, 8]

Many mechanisms have been suggested to explain the abnormal myocardial function in diabetes, and microangiopathy is one of them, it is caused by structural vascular abnormalities &functional disturbances (like endothelial dysfunction which is a

possible determinant of coronary flow reserve (CFR) and it is impaired in early stage of diabetes)

Sympathetic activity increase may be implicated for abnormal CFR in diabetic patients.[9,10] Also abnormal myocyte function is another mechanism, due to changes in substrate supply & utilization. Apoptosis & myocardial fibrosis with accumulation of collagen can cause stiffening of ventricular wall which is seen in diabetes, these changes reflect the changes in the angiotensin and aldosterone system. Finally autonomic neuropathy which is a common complication in diabetes can also lead to left ventricular dysfunction.[7,11,12,13]

Diastolic function is usually affected before systolic function [1] as diabetic patient can have hyperatrophic & noncompliant left ventricles even without obvious signs of heart failure.[14,15,16,17,18]

Framingham heart study revealed the high prevalence of congestive heart failure in diabetic men (2.4:1) and women (5:1) aged 45-74 years regardless the other traditional risk factors.[19,20] Coronary heart disease is more common in diabetes when associated with hypertension, obesity, dyslipidemia, etc…So diabetes is considered a risk factor for the development of heart failure.[21,22,23]

Coronary microvascular damage plays an essential role for diastolic dysfunction or even vice versa, as DD is the main expression of myocardial fibrosis.

Diastolic dysfunction is defined as functional abnormalities that occur during LV relaxation and filling, these changes cause the clinical syndrome of heart failure with a normal LV ejection fraction, it can be caused by hypertension, diabetes or aging. It has a mortality rate that is comparable to that of systolic heart failure, even when it is preclinical or asymptomatic, as mortality rate in DD is about 15% per year in elderly patients.[27-33]

Diastolic dysfunction causes 30%-50% of all patients hospitalized for heart failure especially in elderly.[34,35]

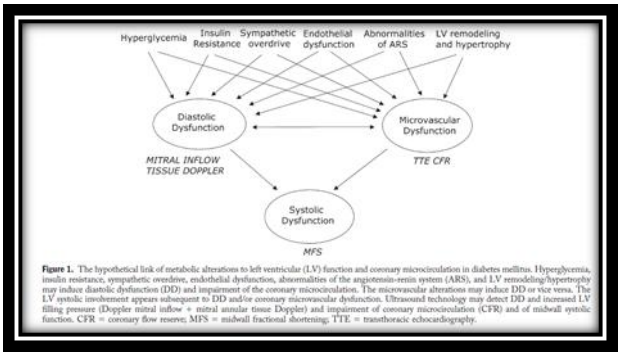

Figure 1. The hypothetical link of metabolic alterations to left ventricular (LV) function and coronary microcirculation in diabetes mellitus. Hyperglycemia, insulin resistance, sympathetic overdrive, endothelial dysfunction, abnormalities of the angiotensin-renin system (ARS), and LV remodeling/hypertrophy may induce diastolic dysfunction (DD) and impairment of the coronary microcirculation. The microvascular alterations may induce DD or vice versa. The LV systolic involvement appears subsequent to DD and/or coronary microvascular dysfunction. Ultrasound technology may detect DD and increased LV filling pressure (Doppler mitral inflow + mitral annular tissue Doppler) and impairment of coronary microcirculation (CFR) and of midwall systolic function. CFR = coronary flow reserve; MFS = midwall fractional shortening; TTE = transthoracic echocardiography.

Diastolic dysfunction represents the first stage of diabetic cardiomyopathy which explains the importance of assessment of diastolic function in diabetes as routine echocardiographic examination.[1,36]

Pulsed-wave Doppler echocardiography has been used for diagnosis of DD because it is widely available, less expensive, and non-invasive tool (if compared to old diagnostic modalities like cardiac catheterization).

Tissue-Doppler imaging (TDI)offers better assessment detection of DD than PW Doppler.[40] It is not affected by the loading conditions and can assess thoroughly the myocardial tissue velocities, TDI reveals the presence of subclinical LV diastolic dysfunction in diabetic patients even if asymptomatic and is more sensitive than PW Doppler.[41] TDI can be combined with pulse Doppler to estimate left ventricular filling pressures.[42] Thus, TDI has an obvious complementary role in the assessment of DD and this role should be applied clinically, and in addition to its diagnostic use it can give us a prognostic guide depending on LV filling indices.[43-48]

Definitions and grading:[49,50]

* E-wave [early left ventricle (LV) filling - reflects the period of active LV relaxation.

* A-wave (late LV filling) - reflects LV-LA pressure gradient in diastole , influenced by LV relaxation.
* IVRT- isovolumetric relaxation time is the period from aortic valve closure to the opening of the mitral valve.
* DT (deceleration time) of E-wave, is the time for which reduction of transmitral pressure gradient occurs. DT reflects the capillary pressure in the left atrium and lungs.

* É - wave (early diastolic velocity) reflects LV relaxation in TDI.

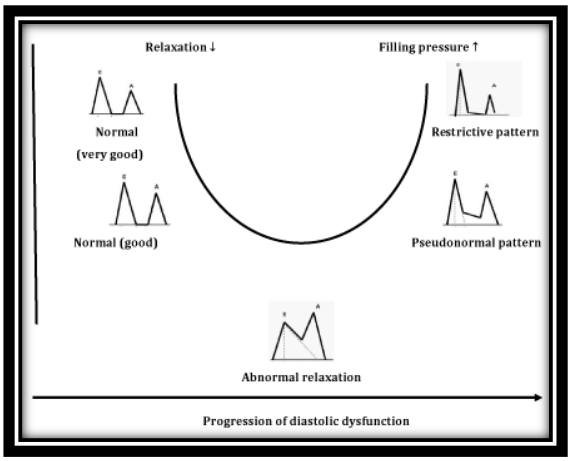

Figure 2: demonstrates E/A ratio changes with progression of diastolic dysfunction

Table 1: Defining the Stages of Diastolic Dysfunction: Normal and abnormal values in adults

			Stage I	Stage II	StageIII	Stage IV
Parameter	Impaired relaxation	Pseuddonormal	Units	Normal	Restrictive filling(reversible)	Restrictive filling(irreversible)
IVRT	>90	60-90	ms	70-90	<70	<70
E/A ratio	<0.9	0.9-1.5	Unit-less	0.9-1.5	>1.8	>2.0
Deceleration time	>240	140-200	ms	140-240	<140	<130

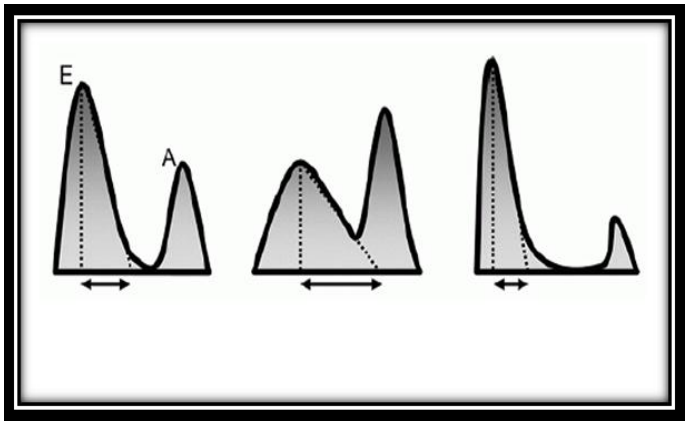

Figure 3: demonstrates three types of mitral inflow velocity curves and shows how DT should be determined in each case. Note in the middle panel that velocity curves does not reach baseline and DT must be extraploted in order to determine the DT

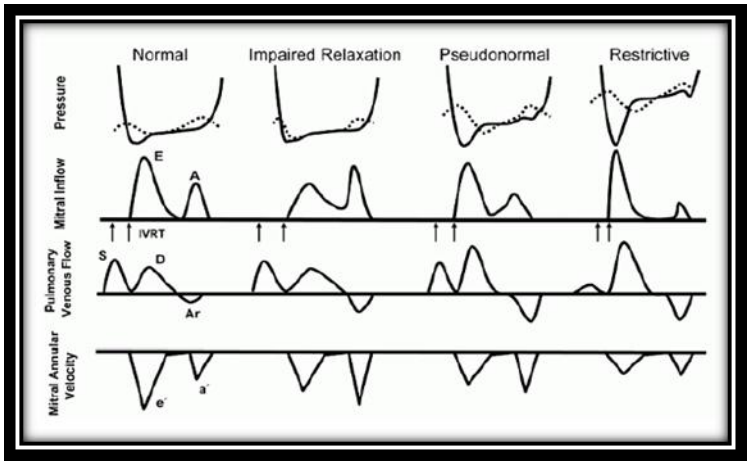

Figure 4: The schematic demonstrates typical mitral inflow velocity, pulmonary venous flow, and mitral annular velocity patterns in the setting of normal diastolic function, impaired relaxation, pseudo normal filling, and restrictive physiology .

PATIENTS AND METHODS

An observational, case control analytic study is conducted at Al-Yarmouk Teaching Hospital in Baghdad during the period from 1st of May 2013 to 1st of December 2014.The study consisted of 100 subjects 50 asymptomatic patients with diabetes mellitus, constitute the diabetic group, 27 of them are females and 23 are males, 27 of them are type1 diabetic and 23 of them are type2 diabetic. Patients` age ranges from 15 to 70 years. Control group consisted of 50 healthy subjects including 24 females and 26 males, their age ranges from 15 to 72 years. Diabetic group were all asymptomatic and free of dyspnea, fatigue, exercise intolerance, and chest pain.

Inclusion criteria were being diabetic patient (type 1 or 2), with normal 12-leads ECG (no pathological Q waves, no ST-T changes, no LBBB, no LVH criteria).

Exclusion criteria were having known coronary artery disease, hypertension, valvular heart disease, diagnosed heart failure, cardiac dysrhythmia, thyroid disease or any stage of renal failure or being on drugs that can cardiac function like ACEI,ARBS, B-blockers or digoxin ,obesity and patients with poor transthoracic window.

The studied subjects were informed &their acceptance was obtained.

The study lead groups subjected to the following:

A. Careful and detailed medical history and clinical examination.

B. Echocardiographic and Doppler studies: were performed using PHILLIPS machine with 1-5 MHz phased array imaging transducer with pulsed and continuous wave Doppler and color flow imaging capabilities. All patients were examined in supine and left lateral recumbent position.

1. M-mode echocardiography: M-mode indices were recorded by visualizing the heart with 2 dimensions echocardiography from the parasternal view while an ECG is monitoring the cardiac cycle. The following parameters were obtained from the M-mode study in the parasternal long axis view: Left ventricular internal dimension at the end of diastole (LVEDd), thickness of interventricular septal wall at end of diastole (IVSd),these recordings were all in mm.

2. Pulse Wave Doppler echocardiography: The peak early filling velocity across mitral valve (E) and peak mitral atrial velocity in late diastole(A) & their ratio(E/A) were measured to assess the left ventricular diastolic function. Tracing of mitral flow in diastole was viewed in the apical four chamber view by using PW Doppler echocardiography with sample volume sited at the tips of mitral leaflets.

3. Tissue Doppler imaging measurements (TDI): This was assessed by using the same device to acquire color tissue Doppler data &the imaging angle was regulated to ensure a parallel alignment of the beam with the myocardial segment of interest.

All the echocardiographic workup was done following a defined protocol; according to the American Society of Echocardiography.(37)

Statistical analysis:

Statistical analysis was performed using t-test. Numerical values are expressed as mean ± SD. The chi-square test is used to compare frequency ratios between groups. The results are considered statistically significant when $P<0.05$.

RESULTS

On hundred subjects were included in this study, fifty of them constitute the patients group who fulfill the forementioned inclusion criteria, 27 (54%) of them were females and 23 (46%) were males, 27 (54%) of them were type1 diabetes and 23 (46%) were type 2 diabetes. Control group consisted of 50 subjects including 24 (48%) females and 26 (52%) males .Patients age ranges from 15 to 70 years with mean age (39 ± 16.09) , control subjects age ranges from 15 to 72 years with mean age (37.64 ± 14.53) ,the results of the study shown in the following tables and figures .

Table 2: Impact of age on prevalence of diastolic function both in diabetic & control groups:

AGE	DM		CONTROL	
	NORMAL	DD	NORMAL	DD
15-25	13	2	11	1
26-35	5	1	15	0
36-45	5	7	8	2
46-55	4	4	5	1
56-65	0	5	3	2
>65	1	3	2	0

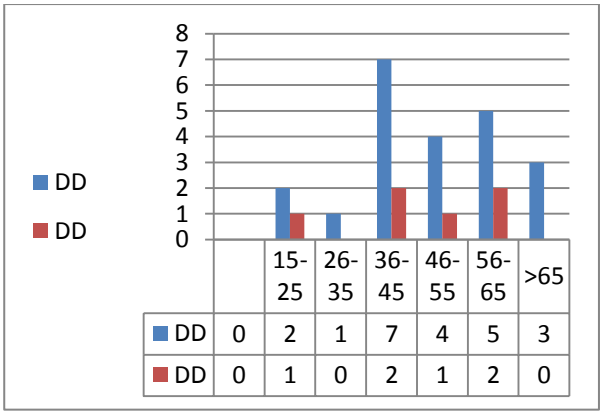

Figure 5: Impact of age on prevalence of Diastolic Dysfunction in diabetic & control groups*

***P value=0.01**

Table 2 & figure 5 reveal that diastolic dysfunction is more prevalent in diabetic patient compared to control groups across all age groups, which was highly statistically significant (P value:0.011)

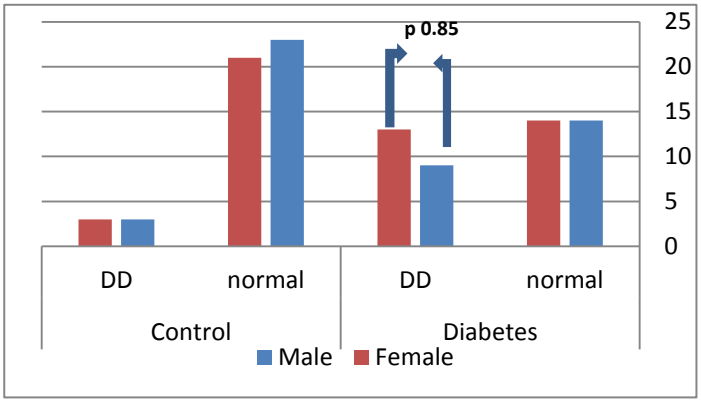

Figure 6: Prevalence of Diastolic Dysfunction in Diabetic Patients According To Gender*

***P value=0.85**

Figure 6 reveals that in both gender (Males& females), diastolic dysfunction was higher in diabetic patients compared to the control groups, & it is slightly higher in female compared to male, although it is not statistically significant (P value:0.085).

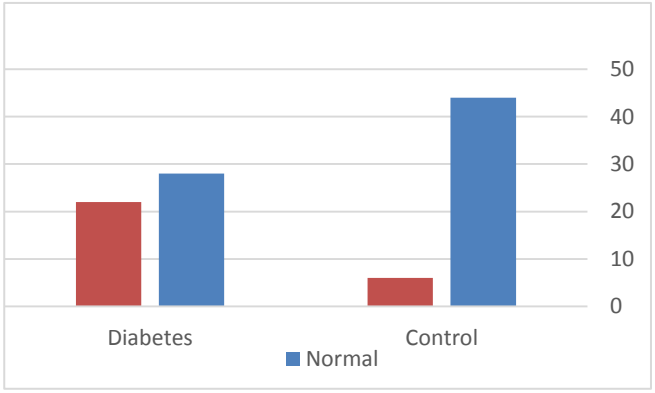

Figure (7) Prevalence of Diastolic Dysfunction in Diabetic and Control Groups*

***P value<0.0001**

Figure 7 reveals that diastolic dysfunction was found in 22 diabetic patients compared to 6 controls, which was highly statistically significant (P value :< 0.0001)

Table 3: Echocardiographic Parameters in Diabetic and Control Group

Parameter	Diabetic	Control	P value
	Mean ±SD	Mean ±SD	
E / A	1.008 ± 0.3	1.24 ± 0.31	0.001
IVRT (ms)	85 ± 21.4	92.9 ± 24.59	0.1
EDT (ms)	189 ± 57.1	180.48 ± 36.67	0.34
E / É	4.8 ± 1.3	4.98 ± 1.22	0.72
IVSd (mm)	7.9 ± 1.6	8.46 ± 1.06	0.09
LVEDd (mm)	44.3 ± 5.8	46.54 ± 5.6	0.06
EF	70.5 ± 8.9	70.75 ± 6.25	0.88

Table 3 reveals that although IVRT is shortened & EDT is prolonged in diabetic patients compared to the controls, they were statistically non-significant. While E: A ratio showed a statistically significant difference between diabetics & control groups (P value:0.001).

Table (4) Comparison of Echocardiographic Parameters in Diabetic Males and Females

Parameter	Male	Female	P Value
	Mean ±SD	Mean ±SD	
E / A	0.9 ± 0.4	1.009 ± 0.3	0.5
IVRT (ms)	87.7 ± 20.08	85.02 ± 21.4	0.6
EDT (ms)	190.4 ± 55.4	189.7 ± 57.1	0.09
E / É	4.8 ± 1.31	4.8 ± 1.34	0.9
IVSd (mm)	8.07 ±1.6	7.9 ± 1.6	0.033
LVEDd (mm)	45.6 ± 5.6	44.3 ± 5.8	0.231
EF	69.07 ± 8.7	70.5 ± 9.06	0.04

Tables 4 reveals that all echocardiographic parameters showed a non-statistically significant difference between male diabetics & female diabetic patients, except EF which is slightly low in male diabetics compared to female diabetics (P value: 0.04).

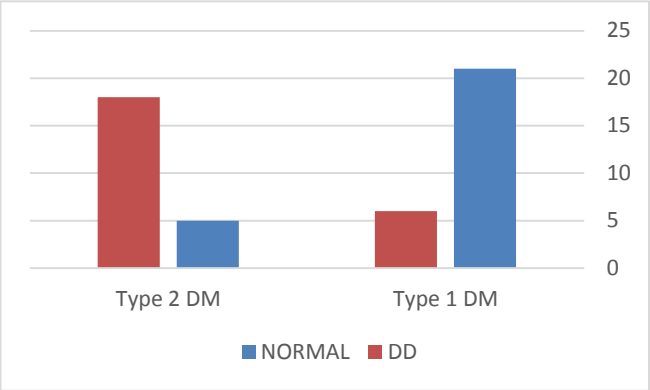

Figure 8: Prevalence of Diastolic Dysfunction in both Types of Diabetes*

***P value<0.001**

Figure 8 reveals that a higher number of patients with Type II diabetes had diastolic dysfunction compared to type I DM (p value: < 0.001).

Table 5: Echocardiographic Parameters in Both Types of Diabetes

Parameter	Type 1 diabetes	Type 2 diabetes	P value
	Mean±SD	Mean±SD	
E / A	1.01 ± 0.3	0.9 ± 0.3	0.01
IVRT (ms)	83.3 ± 21.1	86. 4 ± 20.6	0.1
DT (ms)	186 ± 45	199.3 ± 65.06	0.07
E / É	4.8 ± 1.2	5.04 ± 1.3	0.2
IVSd (mm)	7.9 ± 1.5	8.2 ± 1.6	0.08
LVEDd (mm)	44.4 ± 5.9	45.1 ± 5.6	0.8
EF	70.4 ± 8.2	69.4 ± 9.5	0.4

Table 5 reveals that all echocardiographic parameters showed a non-statistically significant difference between type I & type II DM except for E:A ratio which is significantly lower in Type II DM compared to type I (p value: 0.01)

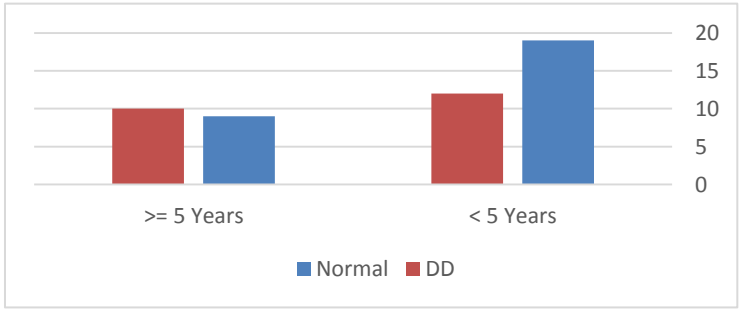

Figure (9) Impact of Duration of Diabetes on Prevalence of Diastolic Dysfunction*

***P value<0.001**

Figure 9 reveal a non-statistically significant difference between duration of DM 7 the development of diastolic dysfunction (P value: 0.335).

Table 6: Impact of Diabetic Duration on Echocardiographic Parameters

Parameter	DM Duration		P Value
	<5 Years	≥5 Years	
	Mean±SD	Mean±SD	
E/A	1.01±0.4	1.01±0.4	0.2
IVRT (ms)	84.8±21.9	84.4±21.9	0.9
DT (ms)	189.8±58.2	188.6±57.6	0.1
E/ É	4.9±1.3	4.9±1.3	0.2
IVSd (mm)	7.9±1.6	7.8±1.6	0.2
LVEDd (mm)	44.4±5.9	44.6±5.7	0.1
EF	70.6±9.08	70.5±9.06	0.4

Table 6 reveals a non-statistically significant difference between diabetes duration & all echocardiographic parameters.

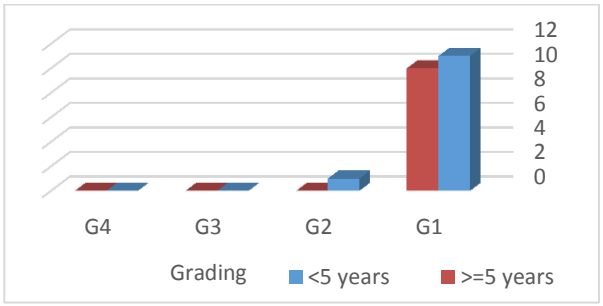

Figure 10: Impact of Duration of Diabetes on Grading of Diastolic Dysfunction

Figure 10 reveals that the majority of diabetic patients with diastolic dysfunction laid in grade I & that diabetes duration had no impact on grading of diastolic dysfunction.

DISCUSSION

Left ventricle diastolic dysfunction is the earliest cardiac change in diabetic patients.There is a strong association between diabetes & cardiovascular morbidity and mortality which is due to the high rate of ischemic heart disease. There is a direct effect of hyperglycemia on the myocardium (diabetic cardiomyopathy) which can cause congestive HF regardless the presence of coronary atherosclerosis.[51, 52,53,54] DD precedes systolic dysfunction in diabetics.[55] Thus, impairment of diastolic function may be used as an early preclinical detector of diabetic heart changes.[40] Risk factors for pre-clinical DD are increasing age, hypertension, diabetes and female sex, as these were all associated with impaired diastolic function.[56,57] The use of non-invasive methods such as conventional Doppler and TDI, correlate favorably with other invasive techniques, it has been suggested to use lateral annular velocity in cases of normal systolic function preferentially,[58,59] also lateral annular velocity is helpful indicator of early diastolic dysfunction.[36] This study studied the impact of age on diastolic function in diabetic patients compared to control subjects, results show that there was statistically significant increase in diastolic dysfunction with increase age of patients, as 30.3% of diabetic patients whose age is 45 years or less have diastolic dysfunction, while 70.5% of patients whose age more than 45 years have diastolic dysfunction, these results was consistent with Hamedulla et al.[7] Virendra C.Patil et al,[35] Exiara T. et al,[60] Masugata H. et al.[61] This study compared the prevalence of diastolic dysfunction in diabetic patients according to gender,13 diabetic females (48%) compared to 9 diabetic male(39%) have diastolic dysfunction, this difference was statistically not significant. Framingham study previously confirmed that all cardiovascular complications increase in diabetic females compared to diabetic males.[19] Also results show that there is statistically significant increase in diastolic dysfunction in diabetic group(88%) compared to (12%) in control group, this is due to relaxation abnormality that is well known finding in diabetic patients and diabetes causes changing structure and contractility of myocardium with stiffening, [62,63] these results are consistent with Soldators G. et al,[64] Sacre et al,[65] Ashraf SM et al,[66] Ojii D. et al,[67] Mishra Y. et al,[68] as left ventricular diastolic dysfunction is the first stage of "diabetic cardiomyopathy"[69]

This study also shows that there was significantly no left ventricular septal thickening among diabetic group compared to control group, other studies like Ghada El Shahed et al,[8] Kamile Gul et al,[37] and Febe E. et al [70] show no significant septal thickening in diabetic patients while other studies show that IVSd is higher in diabetic group like Suys BE et al.[46]

Regarding LVEDd, there was no significant difference between diabetic and control group. This is in agreement with Ghada El Shahed et al,[8] Rowland TW et al,[71] and Kimball T. et al,[72] who found that stroke volume significantly increased in diabetic patients while Airakinsen et al,[73] found that stroke volume is significantly decreased in diabetic patients with severe complications. Also this study reveals that EF shows no significant difference between both groups, this agrees with Elshahed et al,[8] KamileGul et al,[37] and Febe E. et al.[70]

This study reveals that there is significant decrease in E/A ratio among diabetic group compared to control group, this may be explained by that in diabetes, there is an increase in apoptosis which lead to fibrosis & connective tissue proliferation, so more collagen is deposited in a diffuse distribution, this causes increased ventricular stiffening and decreased compliance.[75,76] These structural changes lead to increased wall stress, increased oxygen demand, ischemia, and left ventricular diastolic dysfunction.[4] This result was consistent with J.Charvat et al,[29] GulhanYusel et al,[77] and Sotonye T. et al.[78]

This study also compared the echocardiographic parameters between male and female diabetic patients, results are statistically not significant regarding E/A and E / É ratio, while mean EF was significantly lower in male patients than female patients without reaching systolic dysfunction, also there was significant increase in septal thickness in males compared to females.

This study also compared the prevalence of diastolic dysfunction between both types of diabetes, as 78% of patients with type2 diabetes have diastolic dysfunction compared to 22% in type2, which is highly significant difference.

Also this study compared the echocardiographic parameters between both types of diabetic patients, this showed that mean E/A ratio was lower significantly in patients with type2 diabetes compared with those with type1 patients, and as E/A ratio is an indicator of diastolic dysfunction ,so this difference seems to be associated with type 2 DM (significant diastolic impairment occurs with this group of patient since they are older, & the age is considered as a risk factor for diastolic dysfunction,[79] also this group usually presented after long time from diabetic onset, so may have associated microangiopathy and other complications even at time of diagnosis, which has important impact on physiopathogenesis of diastolic dysfunction.[56,80] Actually we did not find available studies that compared these variables between both types of diabetes as most studies involve one of the diabetic types, not both.

The relation between diabetic duration and prevalence of diastolic dysfunction was also studied, as there was no statistically significant relation between duration of diabetes and diastolic dysfunction and also the impact of this duration on echocardiographic parameters was studied with no significant impact on any of them. This was consistent with other studies like and Elshahed et al, [8] and Bonito PD et al,[81] while it disagrees with Patil et al study.[35]

This study also reveals that 21 patients (95%) of diabetic group who have diastolic dysfunction, have grade1 diastolic dysfunction, and only1 patient (5%)has grade2 diastolic dysfunction, and as tissue Doppler imaging best benefit is to reveal the pseudonormal pattern(grade2)diastolic dysfunction, this may explain why our study was not consistent with other previous studies in that the tissue Doppler parameters do not have high significance in detecting diastolic dysfunction in diabetic group. Also the discrepancy can be explained by the basis of lack of uniformity in patient inclusion and exclusion criteria between studies in terms of glycemic control, diabetic duration, presence or absence of diabetic complications, gender, BMI, and age.

Finally we think that any level of hyperglycemia is sufficient to initiate changes in the cardiovascular system and that the long-term glycemic control probably can determine the rate of progression of these changes .

Recommendation:

A prospective follow-up of patients with regular echocardiographies could help to clarify the mechanism(s) and to identify the parameters that are predictive for the development of a diabetic cardiomyopathy.

Conclusion:

There is high prevalence of DD in diabetic patients and the Prevalence of DD was higher in type 2 diabetes, compared to type 1 diabetes.

Increasing age associated with an increase in prevalence of DD while

Gender has no significant impact on DD prevalence.

DM duration has no significant impact on DD prevalence as well as DD grading.

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