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Left ventricular function in type 2 diabetics

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Abstract

Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease and many mechanisms, such as microvascular disease, autonomic dysfunction, metabolic disorders, and interstitial fibrosis, have been suggested as causative factors. However, the exact causes and mechanisms of diabetic cardiomyopathy remain unclear. Several studies have demonstrated evidence for preclinical left ventricular (LV) diastolic dysfunction in patients with diabetes mellitus (DM) independent of coronary disease or hypertension. The prevalence of diastolic dysfunction in asymptomatic patients with type 2 diabetes mellitus or its relation with other diabetic complications (nephropathy, retinopathy, and neuropathy) is not well defined and data are controversial. A case series study of ninety patients with type 2 diabetes mellitus was designed to determine the frequency of asymptomatic left ventricular diastolic dysfunction in type 2 diabetes patients and its relation to patients' duration, control of diabetes and other factors, the setting was at Diabetes Clinic, Echocardiography Unit and wards of Ibn Sina Teaching Hospital. During the period from the 1st of July to 31st of December 2011, eighty seven consecutive normotensive diabetic patients type 2 (mean age 51.35±8.21 years) and having no coronary artery disease on non invasive testing, were studied for assessment of left ventricular diastolic function using pulsed Doppler at the tip of mitral valve, the peak late (atrial) transmitral flow velocity (A wave), the peak early transmitral flow velocity (E wave),the (E wave) deceleration time and the ratio between (E wave) and (A wave) were assessed. Tissue Doppler was also used to assess the basal septal (medial) mitral valve annular velocities, the peak early basal annular velocity (E` wave ) and the peak late basal annular velocity (A` wave) in addition E/E` ratio was assessed, left ventricular diastolic function was classified as left ventricular diastolic dysfunction positive and left ventricular diastolic dysfunction negative, further classification in to normal, impaired relaxation and Pseudonormal groups was made, age gender duration of diabetes, atherogenic index, obesity were studied in relation to left ventricular diastolic dysfunction using Chi square and Fissures exact tests, T-tests and ANOVA were used to calculate means and to compare them.

وظيفة البطين الأيسر لدى مرضى السكر من النمط الثاني

الخلاصة

إن انتشار خلل البطين الانبساطي غير المصحوب باعراض لدى مرضى داءالسكر من النمط الثاني او علاقته مع مضاعفات داء السكر غير معّرف بصورة واضحة و ان اعتلال عضلة القلب السكري ومسبباته والاليات الدقيقة له لاتزال غير واضحة. الخلل العصبي اللاارادي، والاضطرابات الايضية قد تكون احد مسبباته . اجريت الدراسة لسبعة وثمانون مريضا (48رجل و 39امراة)بداء السكر من النمط الثاني بهدف استقصاء ترداد خلل البطين الأيسر الانبساطي لدى المرضى المصابين وليس لديهم أعراض وعلاقته مع عمر المرضى، مدة داء السكر. اما موقع اجراء الدراسة فكان وحدة تخطيط صدى القلب في العيادة الاستشارية وعيادة داء السكر وردهات مستشفى ابن سينا التعليمي في الموصل . ابتداء

من الفترة الاول من تموز 2011ولغاية 31 كانون الاول 2011 تم جمع سبعة وثمانون مريض ومريضة متوسط العمر(٥١,٣٥ سنة) والذين اخضعوا للدراسة لغرض تقييم وظيفة البطين الايسر بأستخدام الدوبلر النسيجي و الدوبلر النبضي على راس الصمام التاجي . وتم تصنيف وظيفة البطين الايسر الانبساطية الى ايجابية وسلبية ، وايضا تصنيف اخرالى (طبيعية، ارتخاء بطيني معاق ، طبيعية كاذبة)، لقد تمت مقارنة العمر ، مدة داء السكر ، ، مَنْسَبُ المَعَصِّد ، والسمنة مع خلل وظيفة ا لبطين الايسر الانبساطي بواسطة الفحوصات الاحصائية مربع كاي ، فشر، أما فحصا أنوفا و تيوكي، فقد استخدما عند الضرورة لتبيين العلاقة بين متوسطات العوامل المقارنة ضمن مجاميع وظيفة البطين الايسر الانبساطية من اصل سبعة وثمانون مريضا بداء السكر من النمط الثاني (48 ذكرا و ٣٩ انثى)،كان هنالك ٣٤ (٣٩,٥٪) مريضا(١٠منهم ذكور و ٢٤ اناث) يعانون من خلل وظيفي انبساطي في البطين الأيسر مع العلم بأن الوظيفة التقلصية للبطين الأيسر كانت طبيعية (p<٠,٠٠١)، وان الأناث المصابات بالخلل كن اكثر من الذكور بنسبة ٢,٤ :١ لقد لوحظ ان الخلل يزداد بصورة ملموسة بزيادة العمر (p=٠,٠١)،كذلك كانت الحال مع مدة داء السكر ، حيث يزاد الخلل بزيادة مدة داء السكر (p=٠,٠٠١)، ان عوامل الخطورة القلبية الوعائية من ارتفاع الدهون في الدم كانت ذات علاقة مباشرة بالخلل(p=٠,٠٠٦)، بيد ان السمنة لم تكن لها علاقة احصائية بالخلل(p=٠,٢79).

Introduction

Diabetes mellitus prevalence is rising all over the world, thereby becoming an increasingly powerful threat to global health. The World Health Organization projects that by the year 2025 more than 5% of the world population, i.e. 300 million people will suffer from diabetes [(1)]. Since diabetes is of great importance to the development of heart failure thus it has been considered as an independent risk factor for heart failure in the American College of Cardiology and the American Heart Association [(2)]. Evidence of diabetic cardiomyopathy was found in diabetic patients even in the absence of other co-morbidities [(3)]. Metabolic disturbances and insulin resistance, myocardial fibrosis, cardiac autonomic neuropathy are involved in mechanisms of diabetic cardiomyopathy[(4)]. Diastole is the portion of the cardiac cycle that begins with aortic closure and ends with mitral closure. In diastolic dysfunction, the abnormality in LV relaxation and/or compliance alters the onset, rate, and extent of LV pressure decline and filling during diastole. These changes create an abnormal relation between left ventricular pressure and volume so that higher filling pressures are needed to maintain normal LV end-diastolic volume and cardiac output [(5)]. It is widely accepted that the pathophysiology of heart failure in patients with decreased ejection fraction involves a predominant decrease in systolic function justifying the term "systolic heart failure". In contrast, the underlying pathophysiology of patients with heart failure with normal left ventricle systolic function (normal EF) involves a predominant abnormality in diastolic function, the diastolic heart failure [(6)]. During the last two decades, Doppler echocardiography has emerged as an important and easy method to perform noninvasive diagnosis, providing reliable data on diastolic performance [(7)]. Heart failure is defined as a pathophysiological state in which the heart fails to pump blood at a rate commensurate with metabolic requirements or to do so only from an elevated filling pressure. It is usually, but not always, caused by a defect in myocardial contraction. However, in some patients with heart failure a similar clinical syndrome is present but there is no detectable abnormality in myocardial contraction function[(8)]. Thus, heart failure, a clinical syndrome, may occur in the presence of either a normal or abnormal left ventricular EF. Boyer et al. detected altered left ventricular filling in 46% asymptomatic normotensive type 2 diabetic patients when screened by conventional Doppler, whilst newer techniques showed diastolic dysfunction in 75% of patients [(9)]. A more recent study in patients with type 2 diabetes free of any detectable cardiovascular disease found

that 47% of the subjects had diastolic dysfunction, of which 30% had the first stage dysfunction (impaired relaxation), and 17% had second stage dysfunction (pseudonormal filling), a more advanced abnormality of left ventricular relaxation and compliance, which otherwise would be classified as having a normal diastolic physiology [(10)]. These new techniques, especially tissue Doppler image and color M-mode, have provided information to overcome some technical limitations [(10)]. The aim of study is to determine the frequency of asymptomatic LVDD in type 2 DM patients and correlate LVDF with several clinical and biochemical parameters and to determine if left ventricular (LV) diastolic dysfunction worsens with duration of diabetes mellitus (DM) type2

Results

From result eighty seven type2 DM patients, 39females(45.3%) and 48 males (55.17%) were involved in the current study. 34 (39.5%) patients (10 males and 24 females) were found to have diastolic dysfunction with normal systolic function ($p<0.001$). The LVDD in females was higher than males, female: male ratio was 2.4: 1. Left ventricular diastolic dysfunction is significantly increased with increasing age ($p=0.01$). There was a correlation between left ventricular diastolic dysfunction and the duration of diabetes ($P=0.001$), Cardiovascular risk factors like hyperlipidaemia was found to be significantly related to left ventricular diastolic dysfunction ($P=0.006$); while obesity didn't show a statistically significant correlation to left ventricular diastolic dysfunction ($p=0.279$).

Conclusions

The left ventricular diastolic dysfunction was frequent in type 2diabetes mellitus and pseudo normal filling pattern was found in type 2 diabetes patients, thus type 2 diabetes could be an independent predictor of asymptomatic left ventricular diastolic dysfunction. Significant correlations of left ventricular diastolic dysfunction with diabetes duration, age, female gender and hyperlipidaemia were documented, whereas none statistically significant relation was observed between left ventricular diastolic dysfunction and obesity.

Patients and methods

During the period from the 1st of July to 31st of December 2011, eighty seven consecutive normotensive type 2diabetic patients 39females (54.7%) and 48males(55.17%) mean age 51.35±8.21 years were studied for assessment of LVDF the setting was at Diabetes Clinic, Echocardiography Unit and wards of Ibn Sina Teaching Hospital.

Exclusion criteria

hypertension, ischemic heart disease (detected by history and examination, surface electrocardiogram, exercise testing, or left ventricular wall abnormalities in echocardiographic examination), cardiac arrhythmias, congenital or acquired valvular heart disease, chronic renal failure, age greater than 60 years, insulin therapy, and poor echocardiographic window.

Collection of data

All patients undergo to proper history and clinical examination. The measurements of weight, height, fasting blood glucose, total serum cholesterol, HDL, and serum creatinine and urea were performed in all cases. The duration of diabetes and medical treatment were carefully collected, atherogenic index and calculation of BMI were done.

Echocardiographic examination

By using pulsed Doppler the patients were examined and according to the American society of echocardiography guidelines, (ALOKA SSD-1700 DYNA VIEW II) at the tip of mitral valve, the peak early transmitral flow velocity (E wave), the peak late (atrial) transmitral flow velocity (A wave), the (E wave) deceleration time and the ratio between (E wave) and (A wave) were registered. The tissue Doppler was used to assess the basal medial mitral valve annular velocities, the peak early basal annular velocity (E` wave) and the peak late basal annular velocity(A` wave) in addition to E/E` ratio were assessed , E/A<1, E DT >220 ms, E`/A`<1, E`<8, E/E`<8 were considered as criteria for diagnosing impaired relaxation, while the pseudonormalised patients that can`t be caught by transmitral flow Doppler alone were unmasked by combining the flow Doppler criteria together with tissue Doppler criteria thus, E/A>1, E DT<220 ms, E`/A`<1 , E`<8, E/E`>8 were the criteria for the pseudonormal LV filling pattern, the E` is reduced in diastolic dysfunction and not affected by preload thus patients with normal transmitral flow E/A ratio and reduced E` and E`/A` ratio are said to be pseudonormal that is a more advanced stage of LVDD than impaired relaxation, EF and FS were used to report the systolic function hence EF≥50% and FS≥ 30% were considered indicators of normal systolic function [(11)]. The LVDF was divided in to two groups (LVDD positive and LVDD negative), another classification was used also in which LVDF was classified in to (normal, impaired relaxation, pseudonormal). Age groups were classified in to two groups: (40 - 49 years) and (50- 60years), then compared to LVDF with calculation of the mean age for the LVDF groups. The duration of DM was grouped as ≤10 years and >10 years, then compared to LVDD, with the mean duration being assessed for the LVDF groups. The risk of hyperlipidaemia was assessed by estimating the atherogenic index (a ratio of total serum cholesterol to HDL), so risky if >5 and low risk if <5[(12)]. Obesity evaluated by BMI that may be the best metric indicator when assessing changes of adiposity derived from the standard formula (weight in kg /height in m^2), the patient was considered to be obese if BMI was ≥30 (kg/m^2[(13)].

Statistical Analysis

All variables were expressed as numbers and percentages and were compared using Chi square test or Fisher's exact test when appropriate. The mean value was calculated ± SD for all variables by T-test, and means for some variables with in LVDF groups were compared by ANOVA test as needed. The overall analysis was conducted using SPSS version 11, a p-value < 0.05 was considered statistically significant.

Results

Eighty seven normotensive type 2 diabetic patients, 48 (55.17%) males and 39 (45.35%) females (mean age 51.35±8.21 years), and having no CAD on non invasive testing were studied for assessment of LVDF. Clinical and biochemical data in addition to echocardiographic data were expressed inform of mean±SD in tables (1), all the patients were having normal systolic function as means of both EF and FS. Among 87 (100%) patients, only 34(39.5%) were having diastolic dysfunction with a higher frequency among females 24(61.5%) than males 10 (21.3%) and in a ratio of 2.4:1.

Table (1): Clinical, biochemical data and echocardiographic presented as mean ± SD

VARIABLES	MEAN ± SD
Age (years)	51.35±8.21
HR (bpm)	77.79± 9.77
FBS (mmol/L)	10.1±3.57
DM duration (years)	6.19±4.43
BMI (kg/m^2)	29.33±5.07
Systolic blood pressure (mmHg)	124.42±1.22
Diastolic blood pressure (mmHg)	82.05±6.82
Atherogenic index	4.97±1.24
Blood urea (mmol/L)	5.36±1.34
Serum creatinine (umol/L)	76.10±11.75
LVESD (mm)	27.4±2.57
LVEDD (mm)	42.54±3.36
EF (%)	72.86±5.28
IVS (mm)	10.10±1.75
FS (%)	35.54±4.29
LPW (mm)	10.26±1.81
LA (mm)	29.57±6.07
E (cm/s)	68.51±11.19
AR (mm)	28.77±5.52
A (cm/s)	59.79±10.50
E/A	1.20±0.33
E`(cm/s)	11.97±4.06
E DT (ms)	221.06±27.90
A`(cm/s)	10.85±1.81
E`/A`	1.11±0.36
E/E`	6.23±1.79

data presented as mean ± SD

The LVDD was found to be increased as much as the mean duration of DM increased ($p<0.001$), table (2).

Table (2): Duration of type 2 DM compared to LVDF(E/E`)(Percentage calculated within the duration groups).

DM DURATION (YEARS)	LVDD NEGATIVE N (%)	LVDD POSITIVE N (%)	TOTAL N (%)	P-VALUE
Mean±SD	4.22±2.81	9.17±4.82	87(100%)	<0.001
≤10	50(67.6%)	24(32.4%)	74 (100%)	0.001
>10	3(23.07%)	10(76.923%)	13(100%)	
Total N (%)	53(60.91%)	34(39.5%)	87(100%)	

Age was classified in to two groups, and then compared to LVDF, the frequency of impaired relaxation LVDD was found to be increased with increasing age, meanwhile pseudonormal LVDD was also found to be more frequent as age progresses. This correlation was significant at (p=0.01), table (3).

Table (3): Age in relation to LVDF (Percentage calculated within the age groups).

AGE (YEARS)	LVDF			TOTAL N(%)	P-VALUE
	NORMAL N(%)	LVDD			
		Impaired Relaxation N(%)	Pseudonormal N(%)		
40 - 50	**25(78.1%)**	**5(15.6%)**	**2(6.3%)**	**32(100%)**	**0.01**
		7(21.9%)			
51- 60	**28(50.9%)**	**22(40.7%)**	**5(9.3%)**	**55(100%)**	
		27(49.09%)			
Total N (%)	**53(60.5%)**	**27(31.4%)**	**7(8.1%)**	**87(100%)**	
		34(39.5%)			

When the enrolled cardiovascular risk factors were compared to the LVDF, risk of hyperlipidaemia demonstrated by atherogenic index were found to be significantly associated to LVDD (p=0.01) respectively, while obesity failed to do so (p=0.279), table (4).

Table (4): Cardiovascular risk factors in relation to LVDF (Percentage calculated within the groups).

CARDIOVASCULAR RISK FACTORS		LVDD NEGATIVE N (%)	LVDD POSITIVE N (%)	TOTAL N (%)	P-VALUE
Obesity	BMI≥ 30	17(53.2%)	15(46.8)	32(100%)	0.279 (NS)*
	BMI< 30	36(66.6%)	19(35.1%	54(100%)	
Atherogenic index	≥ 5	21(66.6%)	24(33.3%	45(100%)	0.01
	<5	32(76.1%)	10(24.3%)	42(100%)	

*NS: Not significant.

Discussion

Several studies have demonstrated evidence for preclinical left ventricular (LV) diastolic dysfunction in patients with diabetes mellitus (DM) independent of coronary disease or hypertension[14]. An important finding of the present study was the presence of asymptomatic LVDD in 39.5% of type 2 diabetic patients, 31.4% having impaired relaxation and 8.1% having pseudonormal LV filling pattern, whereas systolic function was preserved in all patients. These results indicate that type 2 diabetes could be an independent predictor of asymptomatic LVDD a finding consistent with Gani, et al [15] and that LVDD may be a separate expression of early diabetic heart disease like diabetic cardiomyopathy with diabetes and is rarely clinically apparent unless associated with myocardial ischaemia[16].The present observation of this frequency of LVDD in type 2 diabetics is consistent with several recent studies , Poirier, et al has, noted diastolic dysfunction (impaired relaxation) in 32% of normotensive diabetics that is greatly goes with the present finding[17] . Zabalgoitia, et al[10] found impaired relaxation in 30% of normotensive patients with well controlled diabetes, although the frequency of pseudonormal filling pattern in their study was 17%, these differences in the frequency of LVDD may be attributed to ethnicity and selectivity of patients i.e. when the patients enrolled in the study were having hypertension or ischemic heart disease etc. We can forecast a higher frequency of LVDD probably due to multi factorial effect while when the data are selective its reasonable that LVDD frequency will be lower. As against the high prevalence of diastolic dysfunction noted in the present study, however LV systolic function was within normal limits supporting the existence of a primary diabetic cardiomyopathy of

predominantly diastolic nature. Diastolic dysfunction may occur early in diabetes [18], It was observed that the subjects having diastolic dysfunction were more prevalent within the age group of 50 years and above. Patients below the age of 50 years were more likely to have normal diastolic function. This goes with the results of the Rotterdam study [19]. The reported LVDD among our patients was related to the duration of the diabetes, and this agree with the results of Yujeong Kimthis et al study[20] which show significant correlation between duration of diabetes mellitus (DM) and left ventricular (LV) diastolic function. Hyperlipidaemia have been found to be statistically significant in correlation to LVDD, whereas valuable number of hyperlipidemic patients were suffering from asymptomatic LVDD; meanwhile obesity was not significantly correlated to LVDD. These findings are consistent with Gani, et al. [15], who described the same results.

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