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Assessment of ventricular dysfunctions in children with Type 1 Diabetes Mellitus (T1DM).

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Abstract

Introduction: Diabetes mellitus is associated with long-term damage, dysfunction and failure of various organs especially the eyes, kidneys, heart and blood vessels. Abnormalities of LV function primarily reflected a diastolic abnormality which was an early sign of diabetic cardiomyopathy and had been shown to precede systolic dysfunction in diabetic patients. Echocardiography can be used for the diagnosis of diabetic cardiomyopathy or diabetes-induced myocardial dysfunction. Moreover, tissue Doppler Imaging (TDI) had emerged as a new sensitive technique for the evaluation of diastolic function. Aim of the work was to detect early left ventricular dysfunctions in children with type 1 diabetes mellitus and their correlation with the glycemic control of these children.

Subjects and methods: This study included two groups, (Group I) included 46 children who were diagnosed as type 1 diabetic patients, and (Group II) which included 23 apparently healthy, age and sex matched children as a control group. They were subjected to thorough history taking, clinical examination, laboratory investigations including total serum cholesterol and triglycerides. Left ventricular functions were assessed by resting Trans Thoracic Echocardiography (TTE) and Tissue Doppler Imaging (TDI).

Results: There were significant higher diastolic indices by both TTE and TDI in type 1 diabetic children than the control group. Diagnosis of definite left ventricular diastolic dysfunction was detected in 5 (10.9%) diabetic children by TTE and in 7 (15%) diabetic children by TDI. Finally, there were insignificant associations between duration of the disease, hypoglycemic attacks, DKA, systolic and diastolic blood pressures, HbA1c% levels and different echocardiographic, tissue Doppler parameters.

Conclusion: Alteration of myocardial function induced by DM may begin earlier than was generally thought and these changes might be not correlated with duration of diabetes nor glycemic control. Children and adolescents with T1DM already have significant changes in myocardial diastolic function of the LV and seem to be at risk of developing further cardiac dysfunctions.

Keywords: Left ventricular dysfunctions, Type 1 diabetes mellitus children, Echocardiography tissue Doppler.

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Introduction

Chronic hyperglycemia of Diabetes Mellitus (DM) is associated with long-term damage, dysfunction and failure of various organs especially the eyes, kidneys, heart and blood vessels [1]. Although published work on diabetes and the heart relates mainly to type 2 diabetes, type 1 diabetes also imparts substantial risk for cardiovascular disease, despite its much younger age of onset. Indeed, the age-adjusted relative risk for cardiovascular disease in type 1 diabetes far exceeds that of type 2 diabetes mellitus [2]. Children and young adolescents rarely have insight on regarding their disease, and their diet accordingly, they are difficult to be controlled. Therefore, alteration of myocardial function induced by DM may begin earlier than is generally thought and these changes may be accelerated when glycemic control is poor [3]. In diabetic

patients without known cardiac disease, abnormalities of LV function primarily reflected a diastolic abnormality which has been described as an early sign of this diabetic heart muscle disease (diabetic cardiomyopathy) it was preceding systolic damage [4]. Echocardiography can be used for the diagnosis of diabetic cardiomyopathy or diabetes-induced myocardial dysfunction [5]. Tissue Doppler Imaging (TDI) has emerged as a new sensitive technique for the evaluation of diastolic function based on measurement of wall motion velocities a relatively preload-independent method [6,7].

Aim of the Work

Aim was to detect early left ventricular dysfunctions in children with type 1 diabetes mellitus and their correlation with the glycemic control of these children.

Subjects and Methods

This study included 69 children and was done in Minia University children hospital during the period from October 2011 to October 2012, after approval of the ethical committee of Faculty of Medicine, Minia University. An informed consent from each child's care giver before enrollment in to the study was done. Accordingly, the studied children were classified into two groups: Group I: included (46) children who were already diagnosed as type 1 diabetic child according to the standard ADA criteria 2017. Their age ranged from 10-18 years with a mean ± 14.6 ± 2.1, they were 14 (30.4%) females and 32 (69.6%) males, the mean age of onset of diabetes mellitus ranged from 4-12 years with a mean of 8.4 ± 1.9, their duration of diabetes mellitus ranged from 5 to 10 years with a mean of 6.1 ± 1.4, insulin dosage ranged from 0.3 to 2.4 IU/Kg/day with a mean of 1.1 ± 0.8. Positive family history of diabetes mellitus was found in 24 (52.2%) diabetic children while it was negative in 22 (47.8%) children and had disease duration more than 5 years. Regarding glycemic control according to the level of HbA1c%, 27 (58.7%) of the diabetic children had good glycemic control while 19 (41.3%) of them had poor glycemic control, history of neurological complications was positive in 13 (28%) of them, history of diabetic ketoacidosis attacks was positive in 15 (32.6%), while history of hypoglycemic attacks was positive in 29 (63%). Group II: included (23) apparently healthy, age and sex matched children as a control group, they were sibling of the diabetic group. Exclusion criteria: Children with congenital heart diseases, valvular heart diseases, serious diseases such as; renal disease or moderate to severe asthma and those used medication known to affect cardiac functions such as digitalis, angiotensin converting enzyme inhibitor, or B-blocker. The studied cases were subjected to the following; thorough history taking, clinical examination and laboratory investigations including HbA1c%, total cholesterol and triglycerides by using semi-automatic micro flow cell Photometer, chemistry analyzer model AE–600N Erma Japan. Resting Transthoracic Echocardiography (TTE) was performed for patients and controls by using general electric (Vivid 3 Dimension, GE Vingmed Ultrasound AS N-3190 Horten, Norway) equipped with 2.5-3.5 MHz transducers and pulsed wave tissue Doppler imaging program. The recordings and measurements were obtained in accordance with the Recommendations for Chamber Quantification [8]. To assess systolic function using M-mode Images under guidance of two dimensional (2D) echocardiography and obtained in the standard views (parasternal and apical views) will include the following measurements: Ejection fraction by M-mode image and ejection fraction by biplane Simpson rule (in 4 and 2 chamber views) [9]. Assessment of left ventricular diastolic function by using Conventional pulsed-wave Doppler echocardiography by measuring the following: the peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio and E wave Deceleration Time (DT). Pediatric references for diastolic Doppler indices for determination of diastolic dysfunction (Table 1) [10].

According to the normal cut-off values adopted from the guidelines of American Society of Echocardiography Recommendations for the Evaluation of Left Ventricular Diastolic Function using 2 D Echocardiography [11]:

Grade I (impaired relaxation) was defined as deceleration time>200 ms, isovolemic relaxation time>100 ms, E/A<1.

Grade II (Pseudo normalization) was defined as deceleration time 160-200 ms, isovolumic relaxation time 60-100 ms, E/A>2.

Grade III (Restrictive filling) was defined as deceleration time<160 ms, Isovolumic relaxation time<60 ms, E/A ratio>2.

Finally, tissue Doppler imaging (TDI) was performed in the apical views (four chamber, two chamber, and long axis). The following TDI variables were evaluated peak

Table 1. *Pediatric references for diastolic Doppler indices for determination of diastolic dysfunction*

Factor	3-8 years		2-9 years		13-17 years	
	Mean	1 SD	Mean	1 SD	Mean	1 SD
E velocity (cm/s)	92	14	86	15	88	14
A velocity (cm/s)	42	11	41	9	39	8
Deceleration time (ms)	145	18	157	19	172	22
LV IVRT (ms)	62	10	67	10	74	13

systolic (Sm), peak early diastolic (Em) and peak late diastolic (Am) myocardial velocities. E/Em (E/e′) will be calculated. For each parameter three cardiac cycles were averaged. Similarly pediatric references for TDI variables were used [12]. All measurements were analyzed by one observer who was blinded to all patients' data.

Statistical Methodology [13]

Data entry and analysis were all done with I.B.M. compatible computer using software called SPSS for windows version [13]. Graphics were done by Excel. The data were coded and verified prior to data entry. Quantitative data were presented by mean and standard deviation, while qualitative data were presented by frequency distribution. Chi square test was used to compare between more than one proportion. Student t-test was used to compare two means. Correlation was used to relate two numerical variables. A statistically significant level was considered when p value was less than 0.05. Pearson Correlation analysis was used to assess the strength of association between two variables. The correlation coefficient, denoted symbolically r), defines the strength and direction of the linear relationship between two variables).

Results

Comparison between Type 1 Diabetes Mellitus (T1DM) and the control group as regarding some standard echocardiographic parameters showed that they had significant higher (E wave) and (A wave) readings and lower (DT) than the control group where ($P \leq 0.001$) for all (Table 2). Regarding some tissue Doppler imaging parameters, comparison between T1DM and the control showed that T1DM had significant higher Septal Am, lateral (Em), (Am) and (Sm) readings than the control group where ($P<0.05$). Moreover, they had significant higher septal and lateral (E⁄Em) ratios than the control group where ($P <0.001$) for both Tables 3 and 4. Table 4 showed that 2D echocardiography sensitivity was (75%), versus (69.2%) of tissue Doppler imaging. On the other hand, tissue Doppler imaging was more specific than 2D echocardiography (97%) versus (73.7%). Finally AUC of 2D echocardiography was (65%) versus (70%) of tissue Doppler imaging. Concerning different correlations, there was a significant fair negative correlation between age of the diabetic children and E/A ratio where (r=-0.3 and P=0.03), also there was

Table 2. *Comparison between type 1 diabetic children (Group I) and the control group (Group II) as regarding some standard echocardiographic parameters*

2D echocardiography	Group I	Group II	T	P value
	Mean ± SD	Mean ± SD		
LVEDD (cm)	4.2 ± 0.6	4.3 ± 0.4	0.6	0.5
LVESD (cm)	2.6 ± 0.4	2.6 ± 0.3	0.1	0.9
EF (%)	67.2 ± 5.1	64.7 ± 5.7	1.8	0.07
FS (%)	37.3 ± 4	36.3 ± 5.4	0.9	0.4
E wave (cm/s)	104.5 ± 23.1	64.4 ± 10.4	7.9	<0.001*
A wave (cm/s)	73.5 ± 14.8	52.4 ± 8.9	6.3	<0.001*
E/A ratio	1.43 ± 0.3	1.3 ± 0.2	1.9	0.05
DT(ms)	134.1 ± 33.1	172.3 ± 8.3	5.4	<0.001*
IVRT (ms)	95.2 ± 18.6	86.9 ± 14.9	1.9	0.07

*Significant

LVEDD: Left Ventricular End Diastolic Diameter; LVESD: Left Ventricular End Systolic Diameter; EF: Ejection Fraction; FS: Fraction Shortening; E: Peak early Doppler diastolic flow velocity; A: Peak late Doppler diastolic flow velocity; E: Wave Deceleration Time; IVRT: IsoVolumetric Relaxation Time; ms: milliseconds; cm: centimeters

Table 3*. Comparison between type 1 diabetic children and the control group as regarding some tissue Doppler imaging parameters*

Tissue Doppler parameters	Group I	Group II	T	P value
	Mean ± SD	Mean ± SD		
Septal Em (cm/s)	15.4 ± 3.9	13.7 ± 2.5	1.9	0.06
Septal Am (cm/s)	9.2 ± 2.4	7.7 ± 1.1	2.8	0.007*
Septal Sm (cm/s)	9.8 ± 7.6	7.9 ± 1.3	1.2	0.2
Lateral Em (cm/s)	17.2 ± 4.3	13.1 ± 2	4.4	<0.001*
Lateral Am (cm/s)	9.6 ± 3.2	7.6 ± 1	2.9	0.005*
Lateral Sm(cm/s)	9.9 ± 2.6	7.9 ± 1.3	3.5	0.001*
E⁄Em septal	6.9 ± 1.6	4.7 ± 0.4	6.7	<0.001*
E⁄Em lateral	6.4 ± 1.7	4.9 ± 0.4	4	<0.001*

*Significant

Em: Peak early diastolic myocardial velocity; Am: Peak late diastolic myocardial velocity; Sm: Peak systolic myocardial velocity; E: Peak early Doppler diastolic flow velocity

a significant fair negative correlation between insulin dose and EF% where (r=-0.3 and P=0.02) (Table 5). Moreover, cholesterol and triglycerides had significant fair positive correlations with EF% where (r=0.3, P=0.04 and r=0.36, P=0.02), respectively. On the other hand, triglycerides had a significant fair negative association with E/ A ratio where (r=-0.4 and P=0.003) (Table 6).

Discussion

The presence of cardiac abnormalities in young patients with T1DM was controversial. The use of non-invasive methods such as conventional echocardiography and tissue Doppler echocardiography, the results of which correlated favorably with other invasive techniques which had enabled us to study asymptomatic groups with no need of more invasive methods [14]. The aim of our study was to detect early left ventricular dysfunctions in children with type 1 diabetes mellitus and their correlation with glycemic control of these children.

As regard the results of the current study, we found significant higher diastolic indices by both TTE and TDI in T1DM children than the control group which was indicated by significant higher E and A waves' velocity values by TTE, significant higher septal Am, lateral Em, Am velocities by TDI and significant higher septal and lateral E/Em ratios. On the other hand, there was insignificant difference between the type 1 diabetic children and the control groups as regard the systolic function indicated by EF%. LV diastolic dysfunction in patients with DM may be caused by increased LV diastolic stiffness, deposition of advanced glycation end products, and cardiac fibrosis, all as a consequence of DM [15]. Many studies agreed with our findings in detection of diastolic dysfunction in type 1 diabetic children such

Table 4. *Comparison between 2D echocardiography and tissue Doppler imaging as regarding detection of early changes in the diastolic function*

	2D Echocardiography	Tissue Doppler Imaging
Sensitivity	75%	69.20%
Specificity	73.70%	97%
Area Under the Curve (AUC)	65%	70%

Table 5. *Correlations between echocardiographic, tissue Doppler imaging parameters and different clinical variables*

Clinical Variable		2D Echocardiography			Tissue Doppler Imaging			
		EF%	E/A ratio	DT(ms)	Septal Em (cm/s)	Lateral Em (cm/s)	Septal E/ Em	Lateral E/ Em
Age (year)	r	0.2	-0.3	-0.5	-0.07	0.2	0.05	0.05
	P	0.2	0.03*	0.7	0.6	0.2	0.7	0.8
Duration of diabetes (year)	r	0.1	-0.2	-0.2	0.2	0.004	-0.1	0.003
	P	0.4	0.3	0.2	0.3	0.9	0.4	0.9
Insulin dose (IU/Kg)	r	-0.3	0.2	0.02	0.06	-0.01	0.07	0.005
	P	0.02*	0.2	0.9	0.7	0.5	0.6	0.9
Hypoglycemic attacks No/year	r	-0.06	0.03	-0.1	-0.02	0.1	0.2	0.06
	P	0.7	0.9	0.5	0.9	0.4	0.2	0.7
DKA (No/year)	r	0.001	-0.2	-0.3	-0.04	0.12	-0.04	-0.05
	P	0.9	0.2	0.05	0.8	0.4	0.8	0.7
Systolic blood pressure(mm Hg)	r	0.07	-0.05	0.01	0.01	0.06	0.04	0.003
	P	0.6	0.7	0.9	0.9	0.7	0.8	0.9
Diastolic blood pressure (mm Hg)	r	0.08	0.03	0.085	-0.09	-0.06	0.3	0.2
	P	0.6	0.9	0.6	0.6	0.7	0.1	0.2

Grades of r: 0.00 to 0.24 (weak or no association) 0.25 to 0.49 (fair association), 0.50 to 0.74 (moderate association), 0.75+ (strong association)

Table 6. *Correlations between echocardiographic, tissue Doppler imaging parameters and laboratory variables*

Laboratory variable		2D Echocardiography			Tissue Doppler Imaging			
		EF%	E/A ratio	DT (ms)	Septal Em (cm/s)	Lateral Em (cm/s)	Septal E/ Em	Lateral E/ Em
HbA1c%	R	-0.03	0.1	0.2	0.04	0.1	0.1	-0.02
	P	0.8	0.5	0.2	0.8	0.5	0.3	0.9
Cholesterol (mg/ dl)	R	0.3	-0.2	-0.04	-0.07	-0.01	0.1	-0.003
	P	0.04*	0.2	0.8	0.6	0.9	0.5	0.9
Triglycerides (mg/dl)	R	0.36	-0.4	0.03	-0.08	-0.03	-0.09	-0.1
	P	0.02*	0.003*	0.8	0.6	0.9	0.5	0.4

* Significant

as Schannwell et al. [16], Di Bonito et al. [17], Stakos et al. [18], Elshahed et al. [14] and Salem et al. [19], where they suggested that T1DM might be associated with LV diastolic dysfunction in the presence of normal EF%. In contrast with our results, there were several studies that did not support diastolic dysfunction among type 1 diabetics such as Di Cori et al. [20], El-Banna et al. [21] and Kim [3]. This discrepancy might be due to the basis of lack of uniformity in patient inclusion and exclusion criteria such as glycemic control, DM duration, age and the use of different echocardiographic techniques that are not equally sensitive in detecting diastolic impairment.

Concerning tissue Doppler imaging parameters, T1DM had significant higher septal Am, lateral (Em), (Am) and (Sm) readings and higher septal and lateral (E⁄Em) ratios than the control group. Zile et al. [22] proposed that the combination of transmitral flow velocity with mitral annular velocity (E/Em) integrated with transmitral pressure and myocardial relaxation. It had been proven useful in the assessment of LV filling pressure. The increase in the LV early filling E and the decrease in TDI Em resulted in a higher E/Em in our diabetics which reflecting a higher LV filling pressure, defective relaxation. This was in agreement with Salem et al. [19]. This was suggested to be due to hyperglycemia which induces changes in LV diastolic function, especially decreased compliance and relaxation. The influence of hyperglycemia on LV function suggested that hyperglycemia may decrease the expression of sarco (endo) plasmic reticulum Ca2-ATPase (SERCA2a) and the SERCA2a-to-phospholamban ratio23. Diagnosis of definite left ventricular diastolic dysfunction was detected in 5 (10.9%) diabetic children by TTE versus 7 (15%) diabetic children by TDI. This diastolic dysfunction suggested to be caused by increased LV diastolic stiffness, deposition of advanced glycation end products, and cardiac fibrosis, all as a consequence of diabetes mellitus. According to diabetic control, 3 poorly glycemic control diabetic children had diastolic dysfunction by 2 D echocardiography versus 2 with good glycemic control. On the other hand, tissue Doppler imaging detected 7 diabetic children with diastolic dysfunction; 5 of them with Poor glycemic control. Our study found that 2D echocardiography sensetivity was (75%) versus (69.2%) of tissue Doppler imaging in detection of early diastolic function changes while tissue Doppler imaging was more specific than 2D echocardiography, where its specificity was (97%), versus 73.7% of 2D echocardiography [23].

Concerning the correlations between Echocardiographic, tissue Doppler parameters with different clinical and laboratory variables, there were a significant fair negative correlation between age of the diabetic children and E/A ratio where (r=-0.3 and P=0.03), this finding was in agreement with Schwingshndl et al. [24] and in contrast to El shahed et al. [14]. Moreover, there were insignificant associations between duration of illness and different echocardiographic, tissue Doppler parameters where (P>0.05) for all. This was in agreement with Giunti et al. [25] and Salem et al. [19] studies .In contrast with this result, the studies of Suys et al. [26], Gul et al. [27] who found a strong correlation between impairment of diastolic parameters and DM duration. Moreover, Adel et al. [28], and Kim [3] found mild progression of LV systolic and diastolic functions from normal to dysfunction according to the duration of diabetes mellitus.

There were insignificant associations between HbA1c% levels and different echocardiographic, tissue Doppler parameters where (P>0.05) for all. This was in agreement with Gul et al. [27] who found insignificant correlation between echocardiographic parameters and HbA1c%. In contrary, Shishehbor et al. [29], Adel et al. [28], and Kim [3] found inverse correlation between HbA1c% and diastolic function. Also Grandi et al. [30] concluded that, in patients with type 1 diabetes, a close relation was found between glycemic control and LV diastolic function, which improves when glycemic control improves.

Finally,serum cholesterol levels had a significant fair positive association with EF%. On the other hand, serum triglycerides levels had significant fair association with EF% and a significant fair negative association with E⁄A ratio (Table 7). This was in agreement with Adel et al. [28]. This was suggested to be due to that diabetes mellitus was characterized by reduced glucose and lactate metabolism and enhanced fatty acid (FA) metabolism [31]. Despite an increase in FA use in diabetic hearts, it was likely that FA uptake exceeds oxidation rates in the heart, thereby resulting in lipid accumulation in the myocardium that may promote lipotoxicity [32]. Lipid intermediates such as ceramide might promote apoptosis of cardiomyocytes, thus representing another mechanism that might lead to cardiac dysfunction [33].

Conclusion

Alteration of myocardial function induced by DM may begin earlier than was generally thought and these changes might be not correlated with duration of diabetes nor glycemic control. Children and adolescents with T1DM already have significant changes in myocardial diastolic function of the LV and seem to be at risk of developing further cardiac dysfunctions.

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