Middle-East Journal of Scientific Research 23 (8): 1930-1940, 2015
ISSN 1990-9233

DOI: 10.5829/idosi.mejsr.2015.23.08.95176

Assessment of Diastolic Function and P-wave Dispersion and Their Relationship to Lipid Abnormalities and Microalbuminuria in Type 1 Diabetes Adolescents

[1]Amany Ibrahim, [1]Maha Mohsen Amin, [2]Yasser Hussein Kamel and [3]Fawzia Salim Hamad

[1]The Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU),
Faculty of Medicine, Cairo University, Cairo, Egypt
[2]The Pediatric Cardiology Department, Children's Hospital, Cairo University, Cairo, Egypt
[3]The General Pediatric Department, Children's Hospital, Cairo University, Cairo, Egypt

Abstract: The Objective of this work was to access diastolic functions and P-wave dispersion in Type 1 diabetic adolescents, to investigate the relation between P-wave dispersion and the diastolic functions & to correlate the results to other diabetic complications; lipid profile abnormalities and microalbuminuria. Case-control study included 50 pubertal adolescents with Type 1 diabetes of more than 5 years duration, with age ranging from 9.5-19 years matched to 30 healthy controls. All subjects were evaluated for their metabolic profile, lipid profile and albumin/creatinine ratio. Conventional echocardiography and 12 leads electrocardiography were performed. Results revealed that diastolic dysfunction of both ventricles and increased P-wave dispersion were found in Type 1 diabetic patients. Significant correlations were found between P-wave dispersion and each of left ventricular end diastolic diameter, A mitral and isovolumetric relaxation time. Significant positive correlation between low density lipoprotein level and albumin/creatinine ratio. In conclusions, Type 1 diabetes resulted in prolongation of P-wave dispersion, P-wave dispersion was correlated to left ventricular diastolic dysfunction therefore P-wave dispersion can help in identifying the high risk patients before progressing to overt heart failure. This study also proved that dyslipidemia played an essential role in the pathogenesis of diabetic nephropathy.

Key words: Diastolic dysfunction · Diabetic cardiomyopathy · Type 1 diabetes

INTRODUCTION

In clinical practice, there is a tendency to focus on microvascular risk in type 1 diabetes (T1D) and macrovascular complications in type 2 diabetes (T2D). In fact, micro- and macro-vascular complications are highly relevant to both T1D and T2D and balance should be done by exploring the often overlooked link between T1D and cardiac disease [1]. T1D increases the risk of cardiovascular disease (CVD) by more than 10 times, compared to general population [2-5]. The spectrum of diabetic heart disease involves progresses from normal heart to preclinical left ventricular (LV) diastolic and systolic dysfunction followed by overt echo evidence of LV dysfunction and finally symptomatic heart failure [6]. P-wave dispersion (PD) is an ECG index that measures the difference between the longest and the shortest P-wave duration recorded from multiple different ECG surface leads. The term dispersion in the context of P-wave indices describes atrial conduction and not the repolarization conveyed by T-wave dispersion [7]. It has a good predictive value for assessment the risk of having atrial fibrillation (AF) in various subclinical cardiac disorders. Insults such as chronically elevated atrial pressure, ischemia and metabolic stress lead to atrial remodeling marked by inflammation, fibrosis and poor cellular coupling. Thus, studies argued that the electrophysiological result of prolonged P-wave duration due to slowed conduction and PD can predict the occurrence of AF [8]. Accordingly, the aims of this study are to access diastolic functions and PD in T1D adolescents, to investigate the relation between PD and the diastolic functions & to correlate the results to other diabetic complications; specifically lipid profile abnormalities and microalbuminuria as an early manifestation of diabetic nephropathy.

Corresponding Author: Amany Ibrahim, The Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU), Faculty of Medicine, Cairo University, Cairo, Egypt. Tel: +20 1005547127, E-mail: amanyatt@yahoo.com.

MATERIALS AND METHODS

Patients: We studied 50 adolescents (28 males) with T1D attending the outpatient clinic of the Diabetes Endocrine and Metabolic Pediatric Unit (DEMPU) at Cairo University, New Children's Hospital, for regular follow-up, between November 2011 and December 2012, as well as, 30 age- and sex-matched healthy controls. T1D patients were diagnosed according to the ADA consensus guidelines [9] and suffered from diabetes for at least 5 years and pubertal from Tanner 2 stage onwards for both males and females. T1D Patients with known cardiac disease whether congenital or acquired, arrhythmias, hypertension or thyroid disorder were excluded. The control group was recruited from healthy adolescents attending the general pediatric clinics at the New Children's Hospital. The protocol was approved by the local research ethics committee of the pediatric department at Cairo University and all the participants or their guardians gave informed consent.

Methods: All patients and controls were subjected to full clinical examination, cardiac examination to detect any structural cardiac abnormality, blood pressure were compared to percentile curves for same age and sex. Patients lying on or higher than the 95th percentile for their height were considered hypertensive [10].

According to the protocol adopted at the DEMPU using percentile curves for Egyptian children and adolescents [11], anthropometric data including length, weight were reviewed. The height was measured by using a Harpenden stadiometer and recorded to the nearest 0.1cm and the weight was measured by using self-calibrating electronic SECA scale that records to the nearest 0.1 kg. BMI (body mass index) was calculated as weight in kg/height in m2]. Growth vision computer software provided by Novo Nordisk was employed to assess height SDS, weight SDS and BMI SDS. Pubertal assessment was done by rating breast development in girls [12] and genital development in boys [13] and also pubic and axillary development for boys.

Laboratory Investigations: Lipid profile was measured for patients and controls including serum triglycerides (TG), total cholesterol (TC) and high density lipoproteins (HDL) by enzymatic colorimetry using Olympus auto-analyzer AU 400 (Olympus Diagnostics, GmbH, Germany). Low density lipoprotein cholesterol (LDL) was calculated according to Friedewald's formula LDL = TC - HDL - TG/5 (mg/dl) [14]. Limits above the standard normal values were used as cut off in the present work; serum cholesterol > 200mg/dl, serum TG > 130 mg/dl, serum LDL >130 mg/dl, serum HDL < 40 mg/dl) [15]. Only for T1D patients, glycosylated hemoglobin (HbA1c) was done (it is routinely done twice a year using high performance liquid chromatography (HPLC) technique) [16]. For assessment of glycemic control the mean HbA1c was calculated over the last year prior to the study for each patient. Microalbuminuria was assayed using SERAPAK immuno-microalbumin Kit (Bayer Corporation, Benedict Ave, Tarry town, NY, USA). Persistent microalbuminuria was defined when two out of three early morning urine samples, 2 months apart showed urinary albumin/creatinine (alb/cr) ratio of 30-300 µg/mg. Possible factors affecting urinary albumin excretion as exercise, fever and posture were excluded [17]. T1D patients were further subdivided into two groups: Normo-albuminuric and micro-albuminuric according to absence or presence of microalbuminuria in their urine samples.

Electrocardiogram (ECG) and Echocardiography: A standard 12 lead-ECG was done to show the PD. The onset of P-wave was defined as the junction between the isoelectric line and the start of P-wave deflection while the offset of the P-wave was defined as the junction between the end of the P-wave deflection and the isoelectric line. PD is defined as the difference between the minimum (P-min) & maximum (P-max) P-wave duration calculated from any derivation of 12-lead ECG (PD=Pmax-Pmin). Echocardiography was also done to detect left atrium (LA) diameter and left ventricular end diastolic diameter (LVEDD) according to the American Society of Echocardiography Criteria [18]. Evaluation of diastolic function of both right ventricle (RV) and LV were assessed according to the recent consensus guidelines on diastolic function evaluation [19]. The LV diastolic function, transmitral diastolic flow, Doppler tracing was imaged in the apical four-chamber view by using pulsed wave Doppler with sample volume sited at the tip of the mitral leaflets. The mitral early diastolic velocity (E-wave), mitral late diastolic velocity (A-wave), the mitral early diastolic velocity/ mitral late diastolic velocity (E/A ratio mitral) and isovolumetric relaxation time (IVRT) (time from the end of systolic ventricular outflow to mitral valve opening) were measured accordingly. The RV diastolic function was measured similar to LV regarding but the

sample volume of Doppler was symmetrically set at the tricuspid valve instead of mitral valve. Doppler patterns of diastolic function include normal diastolic function, impaired relaxation, pseudo-normal filling and restriction mainly based on the E/A ratio. Various abnormalities in diastolic function, e.g. prolonged IVRT, delayed mitral valve opening and impairment in rapid diastolic filling, increased atrial contribution of LV filling, reduced E/A mitral ratio are characteristics findings [20].

Statistical Methods: SPSS (version 15) was used for analysis of data. Data was summarized as mean and SD. T- test was used for analysis of 2 independent variables. One way ANOVA was used for analysis of more than 2 independent variables. Pearson's correlation was also done. P-value is significant if < 0.05.

RESULTS

The comparison of clinical, anthropometric, laboratory and echocardiographic data among the study groups are shown in Table 1. No significant difference was found between diabetic patients (n= 50) and control (n = 30) as regards age indicating that both groups are comparable. T1D patients were significantly shorter (height SDS) than controls. T1D patients had significantly higher HbA1c, TC and LDL than controls, but no significant difference was found between both groups as regards HDL and TG. E mitral, E/A ratio mitral, E tricuspid and A tricuspid were significantly lower in the T1D patients than the controls. However, IVRT, LVEDD, IVRTTR and PD were significantly higher in T1D patients than the controls.

When correlating the P-wave characteristics (P-max, P-min, PD) with the echocardiographic data, only a significant negative correlation was found between PD and both of A mitral and IVRT and a significant positive correlation was detected between PD and LVEDD (Table 2).

A correlation between P-wave and echocardiography data of T1D patients in relation to lipid profile, alb/cr ratio, diabetes duration, insulin dose, HbA1c and BMI SDS was done and revealed no significant correlations between lipid profile in relation to disease duration, insulin dose, HbA1c and BMI. A significant negative correlation was found between the disease duration and E mitral and E/A ratio mitral. A significant positive correlation was detected between the disease duration and IVRT. A significant positive correlation was found between BMI SDS and both of P-max and P-min. A significant positive correlation was found between the LDL level and the alb/cr ratio (Table 3).

When comparing normo-albuminuric diabetic patients with micro-albuminuric diabetics; micro-albuminuric diabetics had significantly higher TC and LDL than normo-albuminuric diabetic patients (Table 4).

LA diameter was found significantly higher in Tanner stage 4 (2.53±0.13) than both of Tanner stage 2 (2.44± 0.16) and Tanner stage 3 (2.52±0.13) with a p-value of (0.003) (Figure 1).

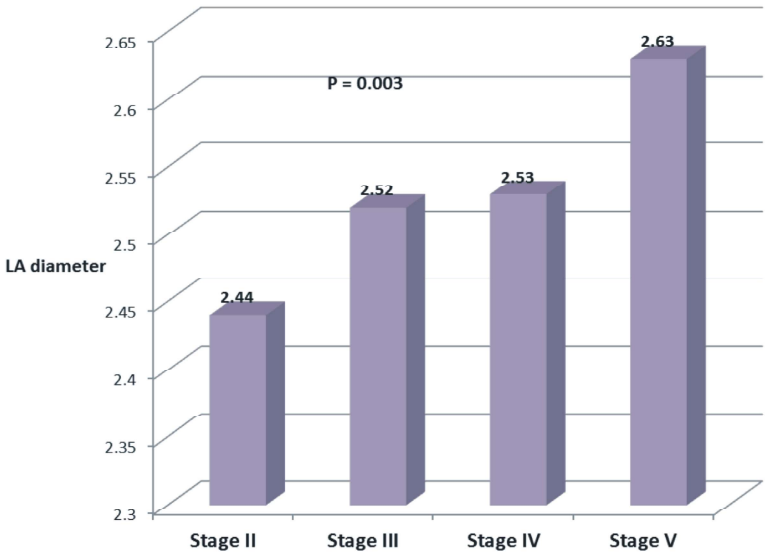

Fig. 1: Comparison between LA diameters in T1D patients in relation to pubertal staging.
LA: left atrial diameter (measured in centimeters), T1D: type 1 diabetes, P-value is significant if < 0.05.

Table 1: Comparison between demographic data, anthropometric data, laboratory data, echocardiographic data and p-wave characteristics of T1D patients and controls

	Patients (n=50)		Controls (n=30)		
Variables	Mean	SD	Mean	SD	P-value
Age (years)	14.50	2.39	13.48	2.31	0.07
Weight (kg)	49.96	14.31	46.91	11.91	0.3
Weight (SDS)	-0.03	1.56	0.53	1.22	0.08
Height (cm)	151.80	11.89	149.85	9.37	0.4
Height (SDS)	-1.29	1.61	-0.27	0.94	0.002
BMI (kg/m2)	21.37	4.14	20.36	3.50	0.3
BMI (SDS)	0.57	1.08	0.40	1.67	0.6
HbA1 (%)	8.68	2.14	5.36	0.68	0.0001
TC (mg/dl)	161.33	34.77	100.4	19.7	0.0001
LDL (mg/dl)	100.53	33	63.07	19.36	0.0001
HDL (mg/dl)	47.63	10.77	52.43	11.11	0.06
TG (mg/dl)	77.61	31.93	69.23	27.44	0.2
E mitral (m/sec)	0.52	0.09	0.79	0.17	0.0001
A mitral (m/sec)	0.5	0.12	0.47	0.11	0.1
E/A ratio mitral	1.12	0.45	1.62	0.3	0.0001
IVRT (msec)	78.94	11.56	67.07	9.06	0.0001
LA (cm)	2.56	0.14	2.52	0.32	0.4
LVEDD (cm)	4.61	0.21	4.37	0.41	0.001
E tricuspid (m/sec)	0.6	0.07	0.66	0.07	0.0001
A tricuspid (m/sec)	0.39	0.09	0.49	0.13	0.0001
E/A ratio tricuspid	1.57	0.27	1.44	0.4	0.1
IVRTTR (msec)	68.84	1.3	66	9.5	0.04
P-max (msec)	0.1	0.01	0.1	0.02	0.1
P-min (msec)	0.04	0.01	0.04	0.01	0.2
P D	0.07	0.02	0.06	0.01	0.005

Data are given mean±SD, T1D: type 1 diabetes, BMI: body mass index, SDS: standard deviation score, HbA1c: glycosylated hemoglobin, LDL: low density lipoprotein, HDL: high density lipoprotein, TC: total cholesterol, E mitral: mitral early diastolic velocity wave, A mitral: mitral late diastolic velocity wave, E tricuspid: tricuspid early diastolic velocity wave, A tricuspid: tricuspid late diastolic velocity wave,, P-max: maximum p-wave, P-min: minimum p-wave, PD = p-wave dispersion, IVRT: isovolumetric relaxation time, IVRTTR: isovolumetric relaxation time of tricuspid, LA: left atrium, LVEDD: left ventricle end diastolic diameter, Kg: kilogram, mg: milligram, m: meter, cm: centimeter, mm: millimeter, sec: second, msec: millisecond. P-value is significant if < 0.05.

Table 2: Correlation between P-wave characteristics and echocardiographic data in T1D patients.

Variables	Correlation coefficient	P-max	P-min	PD
E mitral (m/sec)	r	0.23	-0.07	0.25
	P- value	0.12	0.62	0.08
A mitral (m/sec)	r	-0.23	0.15	-0.32*
	P- value	0.12	0.3	0.03
E/A ratio mitral	r	0.22	-0.11	0.28
	P- value	0.13	0.46	0.06
IVRT (msec)	r	-0.27	0.18	-0.38*
	P- value	0.06	0.22	0.01
LA (cm)	r	0.07	-0.02	0.07
	P- value	0.64	0.91	0.63
LVEDD (cm)	r	0.21	-0.14	0.3*
	P- value	0.15	0.34	0.04
E tricuspid (m/sec)	r	-0.05	-0.01	-0.03
	P- value	0.71	0.93	0.82
A tricuspid (m/sec)	r	-0.09	-0.02	-0.06
	P- value	0.53	0.88	0.70
E/A ratio tricuspid	r	0.07	-0.03	0.08
	P- value	0.65	0.83	0.58
IVRTTR (msec)	r	-0.03	-0.06	0.02
	P- value	0.82	0.70	0.90

T1D: type 1 diabetes, E mitral: mitral early diastolic velocity wave, A mitral: mitral late diastolic velocity wave, E tricuspid: tricuspid early diastolic velocity wave, A tricuspid: tricuspid late diastolic velocity wave, P-max: maximum p-wave, P-min: minimum p-wave, PD = p-wave dispersion, IVRT: isovolumetric relaxation time, IVRTTR: isovolumetric relaxation time of tricuspid, LA: left atrium, LVEDD: left ventricle end diastolic diameter, m: meter, cm: centimeter, mm: millimeter, sec: second, msec: millisecond. P-value is significant if < 0.05.

Table 3: Correlation between P-wave characteristics and echocardiography of T1D patients in relation to lipid profile, alb/cr ratio, disease duration, insulin dose, HbA1C and BMI SDS

Variables	Correlation coefficient	TC	LDL	HDL	TG	Alb/cr	Disease Duration (years)	Insulin dose (u/ kg/d)	HBA1c (%)	BMI (SDS)
E mitral (m/sec)	r	-0.15	-0.2	0.00	-0.2	- 0.07	-0.38	-0.01	-0.18	0.00
	P-value	0.31	0.17	0.99	0.17	0.62	0.01	0.94	0.22	0.98
A mitral (m/sec)	r	0.09	0.15	-0.12	0.08	- 0.01	0.27	-0.11	0.19	0.11
	P-value	0.56	0.32	0.4	0.58	0.93	0.06	0.44	0.2	0.47
E/A ratio mitral	r	-0.11	-0.17	0.1	-0.13	-0.03	-0.29	0.14	-0.23	-0.05
	P-value	0.47	0.25	0.48	0.36	0.81	0.04	0.32	0.11	0.72
IVRT (ms)	r	0.12	0.2	-0.02	0.15	0.1	0.39	0.13	0.18	0.07
	P-value	0.41	0.18	0.87	0.30	0.49	0.0001	0.38	0.22	0.64
LA (cm)	r	-0.04	-0.06	-0.14	-0.11	0.00	0.09	-0.04	0.18	-0.13
	P-value	0.78	0.66	0.35	0.43	0.98	0.54	0.77	0.22	0.39
LVEDD (cm)	r	-0.07	-0.1	-0.12	0.01	0.00	0.07	-0.02	-0.06	-0.08
	P-value	0.62	0.5	0.4	0.95	0.99	0.64	0.9	0.7	0.56
E tricuspid (m/sec)	r	-0.03	-0.04	0.00	-0.36	0.18	-0.14	0.09	0.16	-0.04
	P-value	0.84	0.79	0.99	0.01	0.20	0.34	0.55	0.27	0.8
A tricuspid (m/sec)	r	0.01	-0.04	0.01	-0.24	0.18	-0.05	0.09	0.16	-0.05
	P-value	0.92	0.76	0.93	0.10	0.22	0.72	0.52	0.28	0.74
E/A ratio tricuspid	r	-0.06	0.04	-0.02	0.00	-0.08	0.00	-0.04	-0.09	0.04
	P-value	0.69	0.8	0.9	0.98	0.59	1.00	0.8	0.54	0.79
IVRTTR (msec)	r	-0.11	-0.04	-0.08	-0.04	0.09	0.14	0.08	0.01	0.12
	P-value	0.44	0.77	0.6	0.8	0.53	0.34	0.57	0.94	0.4
P-max (msec)	r	0.12	0.14	-0.01	0.01	0.14	-0.14	-0.06	-0.06	0.29
	P-value	0.43	0.35	0.94	0.96	0.36	0.34	0.68	0.69	0.04
P-min (msec)	r	-0.03	0.03	-0.07	0.02	0.13	0.02	0.13	0.04	0.36
	P-value	0.82	0.82	0.61	0.88	0.4	0.9	0.36	0.79	0.01
PD	r	0.12	0.09	0.05	-0.01	0.01	-0.13	-0.17	-0.08	-0.06
	P-value	0.4	0.56	0.72	0.93	0.96	0.37	0.26	0.58	0.67
Alb/ Cr ratio	r	0.16	0.32	0.05	0.17	-	0.12	0.19	0.17	0.03
	P-value	0.28	0.02	0.76	0.23	--	0.14	0.19	0.24	0.85

T1D: type 1 diabetes, BMI: body mass index, SDS: standard deviation score, HbA1c: glycosylated hemoglobin, Alb/ Cr ratio= albumin/ creatinine ratio measured in μg albumin/g creatinine, LDL: low density lipoprotein, HDL: high density lipoprotein, TC: total cholesterol, E mitral: mitral early diastolic velocity wave, A mitral: mitral late diastolic velocity wave, E tricuspid: tricuspid early diastolic velocity wave, A tricuspid: tricuspid late diastolic velocity wave,, P-max: maximum p-wave, P-min: minimum p-wave, PD = p-wave dispersion, IVRT: isovolumetric relaxation time, IVRTTR: isovolumetric relaxation time of tricuspid, LA: left atrium, LVEDD: left ventricle end diastolic diameter, Kg: kilogram, mg: milligram, m: meter, cm: centimeter, mm: millimeter, sec: second, msec: millisecond. P-value is significant if < 0.05.

Table 4: Comparison between normo-albuminuric and micro-albuminuic T1D patients regarding demographic, anthropometric, laboratory, echocardiography data and P-wave characteristics

	Normo-albuminuric (n=36)		Micro-albuminuric (n=14)		
Variables	Mean	SD	Mean	SD	P-value
Age (years)	14.55	2.35	14.36	2.58	0.8
Disease Duration (years)	7.81	2.89	8.71	2.92	0.3
Insulin dose (u/kg/d)	1.06	0.35	1.13	0.33	0.5
Weight (SDS)	-0.01	1.68	-0.09	1.27	0.9
BMI (kg/m2)	21.36	4.61	21.40	2.76	0.9
BMI (SDS)	0.52	1.17	0.69	0.86	0.6
HbA1c (%)	8.37	2.00	9.47	2.28	0.1
TC (mg/dl)	153.34	32.35	181.29	33.58	0.01
LDL (mg/dl)	91.78	28.56	122.43	34.13	0.002
HDL (mg/dl)	47.34	10.97	48.36	10.62	0.8
TG (mg/dl)	72.86	31.69	89.50	30.42	0.1
E mitral (m/sec)	0.52	0.09	0.50	0.09	0.4
A mitral (m/sec)	0.50	0.12	0.52	0.12	0.6

Table 4: Continued

	Normo-albuminuric (n=36)		Micro-albuminuric (n=14)		
Variables	Mean	SD	Mean	SD	P-value
E/A mitral	1.15	0.46	1.04	0.45	0.4
IVRT (msec)	77.83	11.36	81.79	12.01	0.3
LA (cm)	2.56	0.13	2.57	0.17	0.8
LVEDD (cm)	4.62	0.18	4.59	0.27	0.6
E tricuspid (m/sec)	0.60	0.07	0.61	0.07	0.8
A tricuspid (m/sec)	0.38	0.09	0.42	0.10	0.2
E/ A tricuspid	1.60	0.26	1.48	0.27	0.2
IVRTTR (msec)	68.78	1.46	69.00	0.78	0.6
P-max (msec)	0.10	0.01	0.11	0.01	0.1
P-min (msec)	0.04	0.01	0.04	0.02	0.6
PD	0.07	0.01	0.07	0.02	0.4

Data are given mean±SD, T1D: type 1 diabetes, BMI: body mass index, SDS: standard deviation score, HbA1c: glycosylated hemoglobin, Alb/Cr ratio: albumin/ creatinine ratio measured in μg albumin/g creatinine, LDL: low density lipoprotein, HDL: high density lipoprotein, TC: total cholesterol, E mitral: mitral early diastolic velocity wave, A mitral: mitral late diastolic velocity wave, E tricuspid: tricuspid early diastolic velocity wave, A tricuspid: tricuspid late diastolic velocity wave, P-max: maximum p-wave, P-min: minimum p-wave, PD: p-wave dispersion, IVRT: isovolumetric relaxation time, IVRTTR: isovolumetric relaxation time of tricuspid, LA: left atrium, LVEDD: left ventricle end diastolic diameter, Kg: kilogram, U/Kg/d: unit per kilogram per day, mg: milligram, m: meter, cm: centimeter, mm: millimeter, sec: second, msec: millisecond. P-value is significant if < 0.05.

DISCUSSION

Main findings in our study were PD was found to be significantly prolonged in T1D compared to controls and was related to left ventricular diastolic dysfunction (LVDD). PD is an important non-invasive ECG marker indicating heterogeneity of intra-atrial conduction. Prolonged PD is very well known electrophysiological marker for the prediction of AF [21-23], making cardiac rhythm disorders liable to occur in patients with T1D. AF should be regarded as a marker of adverse outcome promoting aggressive management of possible risk factors [23].

In majority of studies, LVDD is demonstrated in diabetic patients with intact systolic function. Since diastolic function usually declines before systolic and this precedes clinical signs, therefore, diagnosis of diastolic dysfunction is very important for early diagnosis, follow up, treatment and prognosis of heart failure in diabetic patients [20]. Our study showed a significant difference regarding diastolic function of the ventricles namely decrease in their mitral E/A ratio (one of the abnormalities denoting LVDD) but not in tricuspid E/A ratio (RV function is still relatively intact), this is a well-known finding which is consistent with previous conventional Doppler studies in T1D population that showed abnormal diabetic filling pattern (relaxation abnormality) [24, 25]. Very limited studies exist for RV diastolic function in T1D diabetic population, because of its complex geometric shape, also the RV has contributes to the overall cardiac function affecting both the course and prognosis in patients with heart failure [26, 27]. We detected significant increase in IVRT & IVRTTR that denotes early myopathic diastolic function affecting both RV & LV. Affection of both ventricles is expected as they are anatomically united by their common blood supply, muscle fiber anatomy, inter-ventricular septum and pericardium [28]. Previous reports showed no difference between diabetic and control regarding the E/A ratio for either LV or RV by conventional Doppler, but with Tissue Doppler Imaging (TDI) it showed late atrial filling, decreased E/A ratio of the lateral segment of RV [29, 30]. In a previous study, systolic & diastolic function in diabetic patient were compared to controls, systolic dysfunction was found in all diabetics, however, LV& RV diastolic dysfunction was diagnosed in 25% of diabetic with higher peak A & lower E/A ratio [6]. Similarly, diastolic alterations (E/A ratio mitral, IVRT & E-wave deceleration time) were detected in the diabetic group [31]. RV diastolic dysfunction was detected in non-uniform (T1D & T2D) diabetic cohort using TDI, although conventional Doppler failed to show any difference in E/A ratio among diabetic and healthy subject [32].

When correlating the PD to diastolic function, a significant negative correlation with the A-mitral, IVRT and significant positive one with LVEDD. Increased LVEDD may be the result of sustained chronic tachycardia or one of the echo findings for diastolic dysfunction in diabetics as sustained chronic tachycardia diminishes the number of microtubules in the cardiac myocyte which contribute to myocardial dysfunction due to depletion of high energy phosphate [33].

In our study, no correlation was found between diabetes duration and PD, while a positive correlation existed between diabetes duration and IVRT and a negative one with E/A ratio mitral denoting that micro-vascular disease may share in the development of decreased LV compliance making diabetic population at risk of developing progressive heart failure. It was reported that diastolic dysfunction occurred 8 years after the onset of diabetes which is earlier than systolic dysfunction occurring after 18 years [34]. Koken and colleagues found no correlation with the diabetes duration but the mean duration in their study was 5.1 years [35]. In another study, it was concluded that there is an association between diabetes duration and LVDD and demonstrated that a duration ≥ 4 years has the strongest association with LVDD [36].

Our study showed no correlation of BMI SDS or HbA1c, on PD or Echocardiographic parameters. Despite the fact that hyperglycemia will lead to accumulation of advanced glycation end product in the myocardium [37], similarly another study showed no correlation of HbA1c to echocardiographic finding [29] but it was shown that the extent and frequency of diastolic dysfunction was proportional to the HbA1c level [38]. In a recent study, PD was significantly higher in the diabetic patients with HbA1c >7.5% compared to control and this was also found in patients that were followed up >1 year [39]. The discrepancy in studies regarding HbA1c may be explained that the hyperglycemia is the core of the problem but not the sole element which affects the cardiac functions or can be explained that we considered the HbA1c in short term (only one year prior to the study) not long term HbA1c. Unlike our study, IVRT was correlated positively with BMI. The chronological age and disease duration were identified as predictive factors for mitral A-wave [31].

We detected that the LA diameter increased with progression of pubertal stage and this is of importance as LA dilatation reflects long term increased filling pressure [40, 41]. It was reported also that female children showed signs of significant diastolic filling abnormality than in male diabetic patients [42].

No long term studies are established to link between dyslipidemia (increased TC, high LDL, low HDL & high TG) in T1D children with subsequent CVD [43]. But lipid abnormalities have been linked to the development & prognosis of micro- and macro-vascular complications in adolescents with T1D [44, 45]. Comparing T1D patients to control we found a significant difference regarding TC & LDL making diabetic group at risk of aggravation of the atherosclerosis process and at risk for coronary artery disease. No statistical significant difference in HDL & TG among diabetic and control, the normal HDL in the diabetic population indicate that HDL metabolism remain undisturbed in T1D as HDL is produced in the liver and intestine, similar findings were reported by Chaturvedi and colleagues [46]. Moreover another study even showed that HDL was significantly higher in diabetic when compared to control group [47]. The increased HDL level in T1D patients signifies that this HDL may be dysfunctional in combating the adverse pro-inflammatory and pro-atherogenic effect of oxidized LDL. The dysfunctional HDL would make T1D subjects more vulnerable to oxidative vascular damage despite higher absolute levels of HDL [48].

Considering the studies which suggest that dyslipidemia is also involved in the development of microvascular complications, correlation of lipid profile with alb/cr ratio was done and it showed significant positive correlation with LDL and when comparing the diabetic group regarding the presence or absence of micro-albuminuria, we detected a significant difference in TC & LDL. This shows a potential role of dyslipidemia in the pathogenesis of diabetic nephropathy. Similarly, in a study exploring the prevalence of lipid abnormality and their relationship with microalbuminuria in T1D patients; a significant increase in females more than males as regard TC, LDL & HDL was shown. Alb/cr ratio was related to both TC & LDL cholesterol [45]. Other studies demonstrated that raised lipid levels are involved in the pathogenesis and progression of renal disease and treatment of dyslipidemia can reduce albumin excretion [49]. In the Steno study, micro-albuminuric subjects were found to have higher TC levels than normo-albuminuric ones [50], another study demonstrated that micro-albuminuric T1D patients had significantly higher mean TC and TG levels [51] and this was similar to our study as regards to TC but against ours as regard TG as our study showed no correlation with the TG. It is logical to postulate that endothelial dysfunction in the myocardium leads to increased ventricular scarring and stiffness as microalbuminuria is a marker of endothelial dysfunction in the glomerulus which is an arteriole [52]. Therefore, correlation was done between alb/cr ratio and p-wave characteristics & echocardiographic finding and comparison done between both normo-albuminuric & micro-albuminuric groups; we found no correlation to any of them. Contrary to our study, it was shown that renal dysfunction was related to LV systolic and diastolic dysfunction and PD is independently associated with rapid renal decline [42]. Renal dysfunction was postulated

to have impact on LV mass, septal thickness, systolic function, diastolic compliance and also decreased myocardial performance was associated with albuminuria in diabetic patients [53].

Our study had the following limitations; it was conducted in a single center (DEMPU) although it is a big one (following up more than 8000 T1D patients) and included only a small number of patients. Also, analysis of the prognostic value of PD wasn't performed. However, the correlation between PD and AF has been shown in the previous studies.

CONCLUSION

T1D can result in prolongation of PD that can be diagnosed on ECG even when the patients are asymptomatic. Since PD correlates with echo findings specific to LVDD namely (A mitral, IVRT and LVEDD) therefore it may be helpful in identifying the high risk patients for LVDD. It is also proved that dyslipidemia played an essential role in the pathogenesis of diabetic nephropathy.

ACKNOWLEDGMENT

We thank all subjects and parents who participated in our study. We would like to express our appreciation to our colleagues and nurses at DEMPU who facilitated this work.

REFERENCES

1. Retnakaran, R. and B. Zinman, 2008. Type 1 diabetes, Hyperglycemia and the heart. The lancet, 371: 1790-99.
2. Deckert, T., J.E. Poulsen and M. Larsen, 1978. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death and complications. Diabetologia, 14: 363-70.
3. Dorman, J.S., R.E. Laporte, L.H. Kuller, K.J. Cruickshanks, T.J. Orchard, D.K. Wagener, D.J. Becker, D.E. Cavender and A.L. Drash, 1984. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: Mortality results. Diabetes, 33: 271-76.
4. Krolewski, A.S., E.J. Kosinski, J.H. Warram, O.S. Leland, E.J. Busick, A.C. Asmal, L.I. Rand, A.R. Christlieb, R.F. Bradley and C.R. Kahn, 1987. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am. J. Cardiol., 59: 750-55.
5. Orchard, T.J., T. Costacou, A. Kretowski and R.W. Nesto, 2006. Type 1 diabetes and coronary artery disease. Diabetes Care, 29: 2528-38.
6. Salem M., S. El Behery, A. Adly, D. Khalil and E. El Hadidi, 2009. Early predictors of myocardial disease in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes, 10: 513-21.
7. Kose S., K. Aytemir, I. Can, A. Iyisoy, A. Kilic, B. Amasyali, H. Kursaklioglu, E. Isik, A. Oto and E. Demirtas, 2002. Seasonal variation of P wave dispersion in healthy subjects. J Electrocardiol, 35: 307-311.
8. Spach, M. S., 2007. Mounting evidence that fibrosis generates a major mechanism for atrial fibrillation. Circ Res, 101: 743-745.
9. American Diabetes Association, 2015. Classification and Diagnosis of Diabetes. Diabetes Care, 38: S8-S16.
10. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents, 2004. Pediatrics, 114: 555-576.
11. Ghali I., N. Salah, F. Hussien, M. Erfan, M. El-Ruby, I. Mazen, M. Sabry, M. Abd El-Razik, M. Saad, L. Hossney, S. Ismaail, S. Abd El-Dayem and the research group, 2008. Egyptian growth curves for infants, children and adolescents. Published in: in Crecere nel mondo. Satorio A, Buckler JMH and Marazzi N, Eds., Ferring Publisher, Milan, Italy.
12. Marshall, W.A. and J.M. Tanner, 1969. Variation in pattern of pubertal changes in girls. Arch Dis Child, 44: 291-303.
13. Marshall, W.A. and J.M. Tanner, 1970. Variation in pattern of pubertal changes in boys. Arch Dis Child, 45: 13-23.
14. Friedwald, W.T., R.I. Levy and D.S. Frederickson, 1972. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem, 18: 499-502.
15. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung and Blood Institute, 2008. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics, 128: S213-S256.
16. Goldstein, D.E., R.R. Little, H.M. Wiedmeyer, J.D. England and E.M. McKenzie, 1986. Glycated hemoglobin: Methodologies and clinical applications. Clin Chem, 32: B64-70.

17. de Boer, I.H., T.C. Rue, P.A. Cleary, J.M. Lachin, M.E. Molitch, M.W. Steffes, W. Sun, B. Zinman and J.D. Brunzell, 2011. Diabetes, Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, N. H. White, R. P. Danis, M. D. Davis, D. Hainsworth, L.D. Hubbard and D.M. Nathan, 2011. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med., 171: 412-420.
18. Schiller N.B., P.M. Shah, M. Crawford, A. DeMaria, R. Devereux, H. Feigenbaum, H. Gutgesell, N. Reichek, D.L. Sahn, Schnittger and research group, 1989. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on standards, Subcommittee on Quantitation of Two-dimentional Echocardiography. J. Am. Soc. Echocardiogr, 2: 358-367.
19. Nagueh, S.F., C.P. Appleton, T.C. Gillebert, P.N. Marino, J.K. Oh, O.A. Smiseth, A.D. Waggoner, F.A. Flachskampf, P.A. Pellikka and A. Evangelisa, 2009. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J. Echocardiogr, 10: 165-93.
20. Cosson, S. and J.P. Kevorkian, 2003. Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy? Diabetes Metab, 29: 455-66.
21. Ozer, N., B. Yavuz, I. Can, E. Atalar, S. Aksoyek, K. Ovunc, F. Ozmen and S. Kes, 2005. Doppler tissue evaluation of intra-atrial and interatrial electromechanical delay and comparison with Pwave dispersion in patients with mitral stenosis. J. Am. Soc. Echocardiog, 18: 945-948.
22. Yavuzkır, M., A. Öztürk, N. Dağlı, S. Koca, I. Karaca, M. Balin and A. Işik, 2007. Effect of ongoing inflammation in rheumatoid arthritis on P-wave dispersion. J. Int. Med. Res., 35: 796-802.
23. Nichols, G.A., K. Reinier and S.S. Chugh, 2009. Independent Contribution of Diabetes to Increased Prevalence and Incidence of Atrial Fibrillation. Diabetes Care, 32: 1851-56.
24. Zarich, S.W., B.E. Arbuckle, L.R. Cohen, M. Roberts and R.W. Nesto, 1988. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardio-graphy. J. Am. Coll. Cardiol., 12: 114-20.
25. Frazer, G.E., R. Luke, S. Thompson, H. Smith, S. Carter and N. Sharpe, 1995. Comparison of echocardiographic variables between type 1 diabetics and normal controls. Am. J. Cardiol., 75: 141-45.
26. Ghio, S., A. Gavazzi, C. Campana, C. Inserra, C. Klersy, R. Sebastiani, E. Arbustini, F. Recusani and L. Tavazzi, 2001. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J. Am. Coll. Cardiol, 37: 183-188.
27. Meluzin, J., L. Spinarova, L. Dusek, J. Toman, P. Hude and J. Krejčí, 2003. Prognostic importance of the right ventricular function assessed by Doppler tissue imaging. Eur J. Echocardiography, 4: 262-71.
28. Santamore, W.P. and L.J. Dell'Italia, 1998. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. Prog Cardiovasc. Dis., 40: 289-308.
29. Eishahed, G.S., M.I. Ahmed, N.S. El-Beblawy, H.M. Kamal, M.F. lsmaiel and O.A.S. Bin Zheidan, 2008. Evaluation of Right and Left Ventricular Systolic and Diastolic Function in Patients with Type I Diabetes Using Echocardiography and Tissue Doppler Imaging. Suez Canal Univ Med. J., 11: 65-74.
30. Karamitsos, T.D., H.I. Karvounis, E.G. Dalamanga, C.E. Papadopoulos, T.P. Didangellos, D.T. Karamitsos, G.E. Parharidis and G.E. Louridas, 2007. Early diastolic impairment of diabetic heart: the significance of right ventricle. Int. J. Cardiol, 114: 218-223.
31. Santos, C.D., A.M. Souza, R.M. Pereira, M.C. da Silva Boguszewski, S.N. França, C.G. Vieira, M. Furuta and L. de Lacerda Filho, 2012. Assessment of diastolic function in children and adolescents with type 1 diabetes mellitus - Are there early signs of diabetic cardiomyopathy? Arq Bras Endocrinol Metab., 56: 226-232.
32. Kosmala, W., W. Kucharski, M. Przewlocka-Kosmala and W. Mazurek, 2004. Comparison of left ventricular function by tissue Doppler imaging in patients with diabetes mellitus without systemic hypertension versus diabetes mellitus with systemic hypertension. Am. J. Cardiol., 94: 395-9.
33. Takahashi, M., H. Tsutsui, S. Kinugawa, K. Igarashi-Saito, S. Yamamoto, M. Yamamoto, H. Tagawa, K. Imanaka-Yoshida, K. Egashira and A. Takeshita, 1998. Role of microtubules in the contractile dysfunction of myocytes from tachycardia-induced dilated cardiomyopathy. J. Mol. Cell Cardiol., 30: 1047-1057.

34. Cosson, S. and J.P. Kevorkian, 2003. Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy? Diabetes Metab, 29: 455-66.
35. Köken, R., T. Demir, T.A. Sen, A.A. Kundak, O. Oztekin and F. Alpay, 2010. The relationship between P-wave dispersion and diastolic functions in diabetic children. Cardiol Young, 20: 133-7.
36. From, A.M., C.G. Scott and H.H. Chen, 2010. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. J. Am. Coll. Cardiol, 55: 300-305.
37. Candido, R., J.M. Forbes, M.C. Thomas, V. Thallas, R.G. Dean, W.C. Burns, C. Tikellis, R.H. Ritchie, S.M. Twigg, M.E. Cooper and L.M. Burrell, 2003. A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. Circ Res., 92: 785-92.
38. Devereux, R.B., M.J. Roman, M. Paranicas, M.J. O'Grady, E.T. Lee, T.K. Welty, R.R. Fabsitz, D. Robbins, E.R. Rhoades and B.V. Howard, 2000. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation, 101: 2271-6.
39. Uysal, F., E. Ozboyaci, O. Bostan, H. Saglam, E. Semizel and E. Cil, 2014. Evaluation of electrocardiographic parameters for early diagnosis of autonomic dysfunction in children and adolescents with type-1 diabetes mellitus. Pediatr Int, 56: 675-80.
40. Vasan, R.S., M.G. Larson, D. Levy, J.C. Evans and E.J. Benjamin, 1997. Distribution and categorization of echocardiograph measurements in relation to reference limits the Framingham heart study; formulation of a height- and sex- specific classification and its prospective validation. Circulation, 96: 1863-1873.
41. Lang, R.M., M. Bierig, R.B. Devereux, F.A. Flachskampf, E. Foster, P.A. Pellikka, M.H. Picard, M.J. Roman, J. Seward, J.S. Shanewise, S.D. Solomon, K.T. Spencer, M.S. Sutton, W.J. Stewart and Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification, 2005. A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr, 18: 1440-63.
42. Suys, B.E., N. Katier, R.P. Rooman, D. Matthys, L. Op De Beeck, M.V. Du Caju and D. De Wolf, 2004. Female children and adolescents with type 1 diabetes have more pronounced early echocardiographic signs of diabetic cardiomyopathy. Diabetes Care, 27: 1947-53.
43. Hong, Y.M., 2010. Atherosclerotic Cardiovascular Disease Beginning in Childhood. Korean Circ J., 40: 1-9.
44. Dahl-Jørgensen, K., J.R. Larsen and K.F. Hanssen, 2005. Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia, 48: 1445-53.
45. Marcovecchio, M.L., R.N. Dalton, A.T. Prevost, C.L. Acerini, T.G. Barrett, J.D. Cooper, J. Edge, A. Neil, J. Shield, B. Widmer, J.A. Todd and D.B. Dunger, 2009. Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with type 1 diabetes. Diabetes care, 32: 658-63.
46. Chaturvedi, N., J.H. Fuller, M.R. Taskinen and EURO DIAB PCS Group, 2001. Differing association of lipids and lipoprotein disturbances with macrovascular and microvascular complication of type 1 diabetes. Diabetes Care, 24: 2071-7.
47. AL-Naama, L.M., M. Kadhim and M.S. AL-Aboud, 2002. Lipid profile in children with insulin dependent diabetes mellitus. J. Pak Med Assoc., 52: 29-34.
48. Babar, G.S., H. Zidan, M.E. Widlansky, E. Das, R.G. Hoffmann, M. Daoud and R. Alemzadeh, 2011. Impaired Endothelial Function in Preadolescent Children With Type 1 Diabetes. Diabetes Care, 34: 681-5.
49. Bonnet, F. and M.E. Cooper, 2000. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes Metab, 26: 254-64.
50. Hovind, P., L. Tarnow, P. Rossing, B.R. Jensen, M. Graae, I. Torp, C. Binder and H.H. Parving, 2004. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ, 328(7448): 1105.
51. Metwalley, K.A., H.S. Farghaly and A.R. El-Saied, 2013. Assessment of serum levels of soluble CD40L in Egyptian children and adolescents with type 1 diabetes mellitus: Relationship to microalbuminuria and glycemic control. Indian J Endocrinol Metab, 17: 1024-9.

52. Bell, D.S., 1995. Diabetic cardiomyopathy. A unique entity or a complication of coronary artery disease? Diabetes Care, 18: 708-714.

53. Weinrauch, L.A., A. Burger, R.E. Gleason, A.T. Lee and J.A.D' Elia, 2005. Left ventricular mass reduction in type 1 diabetic patients with nephropathy. J. Clin. Hypertens, 7: 159-64.