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Echocardiographic Data and B-Type Natriuretic Peptide in Children and Adolescents with Type I Diabetes Mellitus and Normal Ejection Fraction

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ABSTRACT

Background: Type I Diabetes Mellitus (T1DM) is one of the most common endocrine diseases in the world. It is also the dominant type of diabetes mellitus among children and adolescents that, if left uncontrolled, becomes a major risk factor for cardiovascular disorders and may cause clinical and subclinical cardiac dysfunction.
Objective: This study aimed to compare uncontrolled pediatric and adolescent patients and similar healthy people regarding cardiac function according to echocardiography and B-type Natriuretic Peptide (BNP).
Methods: This case-control study was carried out in the Outpatient Department of Nemazi tertiary hospital in Shiraz, Iran between June and September 2016. The study included 29 consecutive outpatient cases aged 5 - 18 years who had been diagnosed with T1DM for more than three years and had normal ejection fraction in M-mode echocardiography. The control group consisted of 29 age- and gender-matched healthy non-diabetic volunteers. Both cases and controls were selected by simple random sampling. The participants underwent clinical evaluation, including BNP assay and echocardiographic examination composed of two-dimensional echocardiography, M-mode echocardiography, pulsed Doppler imaging, and Tissue Doppler Imaging (TDI). P-value ≤ 0.05 was considered to be statistically significant.
Results: The results revealed a decline in cardiac function in TDI, which was related to the HbA1C level and duration of the disease. A significant difference was found between the cases and the controls regarding the left ventricular posterior wall, interventricular septal diameters in diastole, and E/A ratio of tricuspid valve (P = 0.047, P = 0.001, and P = 0.021, respectively). A significant difference was also observed between the two groups in terms of septal S′ and E′ parameters (P = 0.004 and P = 0.002, respectively). Moreover, diminished E/A ratio of tricuspid valve annulus was related to the increased duration of the disease. Even though left ventricular hypertrophy occurred in the patients, no significant increase was observed in BNP values.
Conclusion: The results indicated that M-mode, two-dimensional, pulsed Doppler, and TDI echocardiography might efficiently evaluate cardiac function in patients with preserved ejection fraction. However, BNP measurement might not be useful for screening of cardiac function.

1. Background

One of the most common endocrine diseases among children is Type I Diabetes Mellitus (T1DM), which is a chronic lifelong disorder and leads to multi-system involvement (1). T1DM is caused by insulin deficiency following the destruction of the insulin-producing pancreatic beta cells. T1DM is common in childhood (2-4), which is a major risk factor for cardiovascular diseases associated with some complications, the most common one of which being coronary artery disease followed by heart failure (5).

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Diabetic cardiomyopathy has been defined as primary myocardial disease, but the underlying mechanisms leading to diabetic cardiomyopathy are poorly understood (6, 7). Clinical research has shown the prevalence of systolic and diastolic cardiomyopathy regardless of coronary artery involvement, hypertension, and asymptomatic cardiac dysfunction that can occur among diabetic patients due to microvascular diseases, metabolic disorders, and autonomic dysfunction (8, 9). Diastolic dysfunction is one of the earliest signs of diabetic cardiomyopathy in adult patients, which mostly occurs before systolic dysfunction (10, 11). Abnormal heart function can also occur in the presence or absence of the clinical signs of heart failure or systolic dysfunction (12).

Although cardiovascular diseases are the most common cause of mortality amongst adults with diabetes mellitus, our knowledge concerning the effects of T1DM on cardiovascular outcomes among the youth is very limited (10-12). Insulin resistance and metabolic syndromes affect heart function independently of Body Mass Index (BMI), blood pressure, and age. Recent studies have suggested that cardiac dysfunction is not only due to continuous hyperglycemia, but is also correlated to insulin resistance condition (13-15). Tissue Doppler Imaging (TDI) seems to be an appropriate modality to assess cardiac function, especially during the diastolic phase (15).

B-type Natriuretic Peptide (BNP) is released by ventricles, especially hypertrophied ventricles, in both systolic heart failure and diastolic dysfunction (16). New heart failure guidelines have put emphasis on the early detection of the asymptomatic changes of cardiac function and recognition of its main risk factors (17).

2. Objectives

We hypothesized that there are some abnormal and asymptomatic cardiac parameters in children and adolescents with poorly controlled T1DM who have normal ejection fraction. Therefore, the present study aims to compare these patients and healthy controls regarding BNP values and some important cardiac parameters, especially diastolic function, based on echocardiography.

3. Patients and Methods

3.1. Study Participants

This case-control study was carried out in the Outpatient Department of Nemazi tertiary hospital, Shiraz, Iran between June and September 2016. The study was conducted on 29 consecutive outpatient cases aged 5 - 18 years who were diagnosed with T1DM. T1DM was diagnosed based on the World Health Organization's (WHO) guidelines (18). The control group also consisted of 29 healthy non-diabetic volunteers who were comparable to diabetic patients in terms of age and gender distribution. The pediatric patients with T1DM whose disease was diagnosed for more than three years, had normal ejection fraction according to M-mode echocardiography, had normal electrocardiography, had uncontrolled diabetes as shown by glycosylated hemoglobin (HbA1C), and were on insulin injection were enrolled into the research. History taking and physical examination were done for all patients to detect any other disorders that could exclude them from the study. The exclusion criteria were any coronary artery diseases and ischemia, cardiac arrhythmias, ejection fraction lower than 60% based on M-mode echocardiography, structural heart disease, hypertension (blood pressure ≥ 95th percentile), anemia, and macrovascular or microvascular complications such as nephropathy.

3.2. Study Protocol

At first, detailed physical examination was documented for all patients in the case and control groups. Age, weight, height, disease duration, BMI, and BNP values were determined, as well. To define uncontrolled diabetes, the average of annual HbA1C values in the last two years was used, and mean HbA1C levels equal to or higher than 9% were selected as the threshold for uncontrolled diabetes for those who were more prone to developing heart and vascular complications (19). In the next step, a normal resting standard 12 lead electrocardiogram was obtained. Afterwards, transthoracic M-mode, two-dimensional, and color Doppler echocardiography with an echocardiographic system (Vivid 3 General Electric) were performed to assess heart function and to rule out other structural heart diseases. Echocardiography was done by one expert pediatric cardiologist, and three-four cardiac cycles were analyzed to get the best phase for better evaluation and decreasing intraoperative variability. Echocardiographic parameters were recorded in the standard apical four chamber view. Moreover, pulsed Doppler sample was obtained within the inflow area of the left and right ventricles just below the valves annulus near the valves tip and parallel to the presumed axis of blood flow. To minimize the potential effects of transducer angulations, Doppler sampling was aligned in different planes until maximum diastolic flow velocities were recorded, the sector angle was less than 30°, and frame rate was 150-230/s. Furthermore, the sample size was adjusted as small as possible to produce stronger spectral Doppler recording (20, 21). TDI data were also obtained at the cardiac base in the apical four-chamber view from three different locations; i.e., the lateral mitral annulus, the inter-ventricular septum at the annular plane, and the lateral tricuspid annulus.

In this study, most echocardiographic criteria were assessed and compared within and between the patient and healthy groups in order to determine the significant parameters. In order to assess the effect of T1DM duration and HBA1C level on the cardiac parameters, the patients were stratified into two subgroups in terms of the disease duration and HBA1c level and the statistically significant echocardiographic data were evaluated among these subgroups. The HBA1C level subgroups consisted of ≤ 10% and > 10%, and the disease duration subgroups consisted of ≤ 5 years and > 5 years.

This investigation was conducted based on the principles outlined in the Declaration of Helsinki, and the protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1394.S30). Indeed, written informed consents were obtained from all participants or their parents/guardians.

3.3. Statistical Analysis

Clinical data have been presented as mean and Standard Deviation (SD). The data were entered into the SPSS software, version 19 and were analyzed using one-way ANOVA and independent t-test for parametric variables and Kruskal-Wallis and Mann-Whitney tests for non-parametric ones. $P \leq 0.05$ was considered to be statistically significant.

4. Results

The patients group consisted of 14 males and 15 females with the mean age of 12.5 ± 2.7 years, mean weight of 42.62 ± 13.68 kg, and mean BMI of 19.99 ± 2.82 kg/m2. The control group also consisted of 13 males and 16 females with the mean age of 11.2 ± 3.1 years, mean weight of 41.14 ± 9.69 kg, and mean BMI of 19.99 ± 2.82 kg/m2. The two groups were similar regarding age, weight, sex, and BMI.

Laboratory results showed that the average HbA1C level within the past two years was 10.13 ± 0.96% (min = 9.50, max = 14.20) in the case group, representing poor disease control.

The two groups' echocardiographic data, including M-mode, two-dimensional, and Doppler echocardiography, have been shown in Table 1. In addition, their TDI parameters have been presented in Table 2.

According to Table 1, the case and healthy groups were significantly different with respect to the Left Ventricular Posterior Wall Thickness (LVPW) diameter, Interventricular Septal (IVS) diameter, and E/A ratio of the tricuspid valve as well as S-wave velocity of the pulmonary vein.

TDI revealed significant differences between the two groups regarding septal S´ and E´ parameters, but not concerning the lateral mitral and tricuspid annulus (Table 2).

In order to assess the effect of HBA1C level on the cardiac parameters, the patients were stratified into two HBA1C subgroups as mentioned in the "Methods" section. HbA1C levels ≤ 10% and > 10% were detected in 20 (69%) and 9 patients (31%), respectively. Then, ANOVA was used to evaluate the differences between the two subgroups concerning the significant echocardiographic parameters (Tables 1 and 2). The results showed that increased HbA1C levels were accompanied with increased Interventricular Septal Dimension in diastole (IVDd) and decreased E/A ratio of tricuspid valve (Table 3).

Considering the duration of T1DM, the patients were classified into two subgroups as follows: ≤ 5 years (20

Table 1. M-mode and Doppler Echocardiographic Results in the Patient and Control Groups (Mean ± SD)

Variables	Patients	Control Group	P-value
LVIDd (mm)	41.43 ± 4.59	39.43 ± 5.09	0.130
LVIDs (mm)	22.33 ± 3.72	23.13 ± 5.40	0.520
LVPWs (mm)	12.55 ± 2.25	11.23 ± 2.59	0.047
LVPWd (mm)	6.72 ± 1.21	6.05 ± 1.68	0.094
IVSd (mm)	7.36 ± 1.51	6.16 ± 1.06	0.001
Mitral valve – E (cm/s)	85.67 ± 19.02	102.10 ± 21.72	0.141
Mitral valve – A (cm/s)	59.06 ± 10.04	57.78 ± 13.33	0.932
E/A ratio mitral valve	1.44 ± 0.35	1.75 ± 0.46	0.092
Mitral valve EDT (msec)	175 ± 67.88	138.33 ± 30.33	0.230
Tricuspid valve – E (cm/s)	60.35 ± 11.47	79.25 ± 21.21	0.012
Tricuspid valve – A (cm/s)	52.42 ± 12.71	42.21 ± 10.02	0.001
E/A ratio tricuspid valve	1.15 ± 2.13	1.88 ± 1.95	0.021
SWPV (cm/s)	48.39 ± 11.65	57.51 ± 13.63	0.007
DWPV (cm/s)	56.66 ± 12.65	51.92 ± 10.42	0.135

Abbreviations: LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension systole; LVPWs, left ventricular posterior wall thickness systole; LVPWd, left ventricular posterior wall thickness in diastole; IVSDd, interventricular septal diameter at the end of diastole; Mitral and tricuspid valve E, peak E velocity in mitral and tricuspid valves; Mitral and tricuspid valve A, peak A velocity in mitral and tricuspid valves; E/A, ratio of peak E to peak A; EDT, E-wave deceleration time of mitral valve; SWPV, S wave velocity of the right upper pulmonary vein; DWPV, D wave velocity of the right upper pulmonary vein

Table 2. Tissue Doppler Echocardiographic Variables in the Patient and Control Groups (Mean ± SD)

Variables		Patients	Control Group	P-value
Mitral valve (cm/s)	S´	12.67 ± 1.63	13.44 ± 2.69	0.130
	E´	11.65 ± 3.21	11.89 ± 4.23	0.734
	A´	11.44 ± 4.16	11.50 ± 3.87	0.910
	E´/A´	1.02 ± 1.2	1.03 ± 1.6	0.53
Tricuspid valve (cm/s)	S´	11.10 ± 1.71	10.35 ± 1.94	0.200
	E´	11.37 ± 6.57	14.96 ± 6.32	0.112
	A´	9.31 ± 5.99	12.50 ± 6.66	0.161
	E´/A´	1.16 ± 2.2	1.19 ± 2.3	0.09
Septum (cm/s)	S´	7.96 ± 1.29	9.24 ± 1.82	0.004
	E´	8.06 ± 2.29	9.71 ± 1.97	0.002
	A´	5.92 ± 1.49	6.82 ± 1.72	0.640
	E´/A´	1.52 ± 1.54	1.78 ± 1.3	0.19

Abbreviations: S, peak systolic annular velocity; E´, peak early diastolic annular velocity; A´, peak late diastolic annular velocity

Table 3. Analysis of Variance of Statistically Significant Echocardiographic Data among HbA1C and Disease Duration Subgroups

	ANOVA amongst the HbA1C Level Subgroups		ANOVA amongst the Disease Duration Subgroups	
Variables	**F-test**	**P-value**	**F-test**	**P-value**
IVSDd	3.72	0.038	0.27	0.602
LVPWs	0.49	0.453	0.16	0.683
Tricuspid E	0.629	0.541	4.16	0.050
Tricuspid A	2.23	0.130	4.03	0.047
Tricuspid E/A	3.45	0.041	4.21	0.043
Tissue Septum E´	2.20	0.136	0.42	0.521
Tissue Septum S´	1.22	0.312	0.63	0.362
SWPV	2.23	0.131	1.83	0.187

Abbreviations: LVPWs, left ventricular posterior wall thickness in systole; Tricuspid E, peak E velocity in tricuspid valve; Tricuspid A, peak A velocity in tricuspid valve; SWPV, S wave velocity of pulmonary vein; tissue septum S´, peak systolic annular velocity; tissue septum E´, peak early diastolic annular velocity; IVSDd, interventricular septum diameter at the end of diastole

patients, 69%) and > 5 years (nine patients, 31%). ANOVA was used to evaluate the significant differences between the two subgroups concerning echocardiographic variables. The results revealed a decline in the E/A ratio of tricuspid valve with increase in disease duration (Table 3).

BNP values were checked in the patient and control groups. The mean BNP was 45.3 ± 32.25 pg/mL in the patients and 36.29 ± 30.70 pg/mL in the controls, but the difference was not statistically significant (P = 0.292).

5. Discussion

The study findings revealed some pre-clinical functional abnormalities, especially diastolic data and hypertrophy of the left ventricular walls, in pediatric and adolescent patients. Nonetheless, these results could not fulfill the criteria of diastolic dysfunction. The results also indicated lower E, A, and E/A ratio of the tricuspid valve among the patients. Besides, mitral valve E/A was lower amongst the patients although the difference was not statically significant (P = 0.092).

Nikhil M Dikshit et al. showed lowered mitral and tricuspid E/A and peak A velocities in these patients as the sensitive indices of diastolic ventricular function. They stated that diastolic dysfunction in T1DM was an early marker of diabetic cardiomyopathy (22). In another research, diastolic dysfunction was assessed using TDI and the results demonstrated that 23% of the patients had diastolic dysfunction. They disclosed that decreased mitral inflow E/A ratio and diastolic dysfunction were associated with the subsequent development of heart failure (23).

The current study findings showed a significant decrease in septal E´ and S´, which was in line with the results of a previous research (21). Some other studies also reported this echocardiographic abnormality in patients as an early sign of diabetic cardiomyopathy (24-27).

The present study results indicated a significant correlation between tricuspid E/A (Table 2) and HbA1C level and T1DM duration subgroups. Another study revealed cardiac dysfunction in 64% of adult patients, and it was significantly associated with uncontrolled diabetes assessed based on the HbA1C level. Indeed, the prevalence of cardiac dysfunction increased with longer duration of diabetes in the patients. It should also be noted that diastolic dysfunction had appeared before systolic involvement in the patients (26). In the same vein, Siddiq Ibrahim Khalil et al. reported that 58% of the patients with diabetes mellitus suffered from diastolic dysfunction. They stated that cardiac dysfunction was significantly associated with the disease duration and patient's age (24).

In the current study, BNP values were within the normal range in both control and patient groups, and no significant difference was observed between the two groups in this regard. Hence, cardiac dysfunction could not be determined by means of BNP assessment. Similarly, another study explored the usefulness of BNP for screening the left ventricular diastolic dysfunction in patients with type II diabetes without structural heart disorders. The results revealed that BNP levels could not be used to detect mild cardiac dysfunction in this subset of patients (25). Another study compared BNP and TDI concerning their usefulness in detection of diastolic dysfunction in diabetic patients and the patients who were diagnosed with abnormal left ventricular diastolic function and had normal BNP concentrations (27, 28). The present study results also showed left ventricular hypertrophy in the patients, which was in agreement with some other studies and might be due to metabolic abnormalities (29, 30).

5.1. Conclusion

The present study aimed to evaluate cardiac dysfunction in the children with T1DM and demonstrated that echocardiographic cardiac abnormalities could develop in these patients without any prior symptoms or evidences of cardiac dysfunction. Thus, a thorough echocardiographic study should be performed in diabetic children during their follow-up, and the necessity of treatment should be considered based on their conditions. The results also indicated that BNP measurement was not significantly useful for screening cardiac dysfunction among children, but TDI effectively showed the earlier evidence of cardiac dysfunction in these patients.

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Authors' Contribution

Study concept and design: M.E. and H.M.; analysis and interpretation of data: M.E. and R.N.; drafting of the manuscript: M.E. and H.A.; critical revision of the manuscript for important intellectual content: M.E. and H.M. and H.A.; statistical analysis: R.N.

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The authors have no financial interests related to the material in the manuscript.

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