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Evaluation of Cardiac Dysfunction in Children and Adolescents with Type 1 Diabetes Mellitus

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Abstract

Background

This study was conducted to identify cardiac dysfunction and the relationship of hemoglobin A1c (HbA1c) levels and serum lipids to echocardiographic indices in children and adolescents with T1DM.

Materials and Methods: This case-control study was conducted on 100 cases including 50 children and adolescents aged 3-19 years old suffering T1DM for at least two years and 50 age- and sex-matched healthy subjects with the patients. This study was conducted in Shahrekord, Iran. All participants underwent TDI echocardiography and the levels of HbA1C and serum lipid were measured in diabetic patients. Then echocardio function of two groups were compared and the relation between these findings and HbA1C and lipids was evaluated. Data was analyzed using SPSS software (version 23.0).

Results: MPI, E/A, E'/A', E wave, A wave, IVRT, ET, EDV, LVIDd and LVIDs were significantly different between diabetes and control groups ($P<0.05$). However, EF, E/ E', IVCT, ESV and EF values showed no significant difference between diabetes and control groups ($P>0.05$). A significant, positive correlation was observed between E/E' and TG ($p=0.007$, $r= 0.37$). E/A showed positive correlation with HDL ($p=0.046$, $r=0.284$) and negative correlation with TG ($p = 0.048$, $r=-0.281$), and LDL ($P=0.012$, $r=-0.352$). E'/A' showed positive correlation with HDL ($p=0.033$, $r=0.302$), and negative correlation with TG ($p=0.014$, $r=-0.347$) in diabetic patients.

Conclusion

In diabetic patients, first, cardiac diastolic function decreases, resulting in a decrease in E′/A and E/A ratios as well as a decrease in myocardial performance index, which indicates systolic and diastolic function, and is recommended to be taken into account in the initial examination of the heart of diabetics and not to wait for late-onset systolic function change.

Key Words: Children, Diabetic cardiomyopathy, Diabetes mellitus, Echocardiograph.

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1- INTRODUCTION

Diabetes mellitus (DM) is a metabolic and multifaceted disorder characterized by hyperglycemia caused by insulin insufficiency or insulin resistance. Type I Diabetes mellitus (T1DM) is a heterozygous disease caused by autoimmune damage to pancreatic beta cells leading to insulin insufficiency (1). This disease is more commonly diagnosed in children and adolescents, accounting for 90% of diabetes cases in children and adolescents, less than half of which can be diagnosed before the age of 15 (2). Mortality and morbidity of DM are due to microvascular complications including retinopathy, nephropathy and neuropathy and/or macrovascular complications such as coronary artery disease, carotid artery and other large vessels whose diagnosis is increased with the onset of disease in childhood (3). Generally, people with diabetes are at high risk of cardiovascular disease and warning signs of cardiac complications are often not recognized due to poor screening measures (4). In fact, the major cause of diabetes-related mortality is cardiovascular disease that is 2-5 times more common in diabetics than in normal population (5, 6).

Hyperglycemia, high blood pressure, dyslipidemia and renal dysfunction are risk factors for cardiovascular complications in diabetic patients (7). Microvascular complications in diabetic patients are associated with an increase in mortality due to organ damage and increased risk of cardiovascular disease (4). Heart failure may occur due to impaired heart filling (diastolic dysfunction) or impaired contraction and emptying (systolic dysfunction). Although there are many studies on diastolic and systolic disorders in young adults with diabetes mellitus (8-10), evidence on children and adolescents with DM is scarce (11). In recent years, as a roughly independent preload method, Tissue Doppler Imaging (TDI) has been developed as a novel and sensitive technique for assessing diastolic function based on wall motility velocity measurement. Using TDI, general and regional diastolic ventricular dysfunction can be diagnosed in a variety of heart diseases (12). Considering that cardiovascular complications are among the predominant complications of diabetes, it is crucial to diagnose and control its complications especially when the disease is developed at younger ages. Additionally, due to the high mortality and morbidity as well as the high cost of treatment, it is essential to determine and monitor the myocardial diseases in diabetic patients prior to the development of signs and symptoms of heart failure. The aim of this study was to evaluate the cardiac dysfunction in children and adolescents suffering from Type 1 Diabetes Mellitus (T1DM).

2- MATERIALS AND METHODS

2-1. Study design and population

In this case-control study, a total of 50 children and adolescents aged 3-19 years old with T1DM (cases group) for at least two years, referred to the endocrine clinic of Shahrekord University of Medical Sciences (SKUMS), Iran, were enrolled.

2-2. Methods

The control group consisted of 50 healthy children and adolescents frequently matched by sex and age with the case group, and neither suffering from chronic disease nor having history of taking drugs producing or affecting cardiovascular complications. Using a study that reported Tei index in the same patient groups (x1= 0.43± 0.08), (x2= 0.47± 0.07), alpha = 0.05 with 0.75 power, minimum sample size required 50 in each group (13). Sample size was calculated using Stata software by the formula used for calculating means samples. Cases were selected through a census over a six-month

period in endocrine clinic of SKUMS. Simultaneously with the selection of cases, controls were randomly selected using simple random sampling by random number table in children and adolescents admission list from the clinics of SKUMS.

2-3. Anthropometric measurements

First, data including age, sex, time of onset of diabetes, daily intake of insulin, and history of drug consumption were collected. After the patient's demographic data was collected and physical examination was performed, the height, weight and BMI of the patients were measured. After medical history recording and physical examination, the height and weight of the patients were measured by a pediatric endocrinologist with a scale (Seca, Germany), weight and height to the nearest 0.1 cm for height and 0.1 kg for weight. Patients' height was measured using a standard wall height gauge, with the legs, knees, hips, shoulders and back along the spine perpendicular and straight lines and arms freely on either side.

Patients' blood pressure was measured using a barometer with a cuff fitted to the patient's arm after 15 minutes of relaxation. The control group consisted of 50 healthy children and adolescents referred to the clinic for examination matched by sex and age with the patients group and neither suffering from chronic disease nor having history of taking drugs producing or affecting cardiovascular complications. The results of three HbA1C tests over one year were collected from patients' medical records to determine the degree of diabetes management. The mean HbA1C was calculated and recorded in the questionnaire including demographic data, echocardiography data, and tests for all participants.

2-4. Laboratory measurements

Then, 4-ml blood samples of brachial vein were taken to measure Fasting Blood Sugar (FBS), High triglyceride (TG), cholesterol, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein LDL levels. Samples were taken at 8:00 am after overnight fasting and before the injection of insulin. Random microalbumin and creatinine of urine were also investigated. FBS was measured by enzymatic, calorimetric and single-point measurements by photometric method at a wavelength of 546 nm using Pars Azmoon kit (Iran). In this procedure, the hydrogen peroxide released from glucose formed Kinonimin after reacting with phenol and 4-amino-antipyrin in the presence of the peroxidase enzyme. The amount of produced kinonimin has a direct correlation with glucose level. To measure TG with Pars Azmoon, Iran kit, glycerol was first isolated from fatty acids using lipoprotein lipase, and then the released hydrogen peroxide from glycerol reacted with 4-amino-antipyrin and phenol in the presence of the peroxidase enzyme and formed kinonimin. The amount of produced kinonimin has a direct correlation with TG.

To measure cholesterol using a Pars Azmoon kit (Iran), hydrogen peroxide produced as a result of hydrolysis and oxidation of cholesterol, reacted with phenol and 4-amino-antipyrin in the vicinity of the peroxidase enzyme, formed kinonimin. The amount of kinonimin was measured photometrically at 546 nm, which has positive correlation with the amount of cholesterol. HDL and LDL levels were determined by photometric methods without the need for any centrifugation. In this method, antibodies eliminate the human lipoproteins except the targeted lipoprotein and only the concentration of the specific lipoprotein is calculated using an enzymatic dye reaction. FBS, TG, cholesterol, HDL, and LDL tests were measured using a calorimetric method. The obtained data were documented in the questionnaire. Patients were divided into 3 groups based

on their mean HbA1C during the last year: 6-7.5, 7.6-9.9, and over 10 (13).

2-5. Doppler and Tissue Doppler imaging measurements

Doppler echocardiography was performed using Philips 2-4 MHZ transducer. All patients were investigated in left lateral position. Several Doppler and 2D planes were used. Ventricular dimensions were measured based on the American Society of Echocardiography guideline. Maximal initial filling speed (E), and delay (A) were obtained through the flow velocity of the atrio-ventricular valve. Then, the ratio of maximum velocity of the early to late the mitral valve (E/A) was measured.

Based on the TDI and pulse-view (PW) activation, the tissue Doppler function was recorded on the same device, and the heart muscle wall velocity was recorded at the base of the septum. During the systole, when the impulse moves toward the apex of the heart, a steady positive motion (S wave) is recorded. During diastole, when the impulse moves to the heart base, two severe negative movements are recorded, one in the initial phase of the diastole (E 'or Em wave) and the other one in the late phase of the diastole (A' or Am wave); their maximum speed was recorded.

Also, the E/E' ratio, which indicates the ratio of the primary flow of the valve to the wall diastolic wave, and the ratio of E'/A' were calculated. These ratios are in fact the criteria for measuring diastolic cardiac function. It should be noted that IVCT was calculated from the end of the diastolic wave (A') to the onset of the wave S, and IVRT from the end of the wave S to the onset of the primary diastolic wave E' as well as ET from the initiation to the end of the wave S. MPI is an echocardiographic time interval that includes both systolic and diastolic distances, and creates a combined index of total ventricular function. MPI was calculated using the (IVCT + IVRT)/ET formula. In addition to the above information, SV, EDV, ESV and EF were also measured by echocardiography. Noticeably, in this study EF and IVCT were considered as criteria for cardiac systolic function and IVRT, E/A, E/E' and E'/A' ratios were considered as the standard diastolic function of the heart. Also, MPI is considered as a general measure of myocardial function in both systolic and diastolic systems.

2-6. Ethical consideration

Written consent to participate in the study was obtained from all participants and their parents (ID code: IR.SKUMS.REC.1396.219).

2-7. Inclusion and exclusion criteria

The inclusion criteria were patients with T1DM receiving insulin therapy, duration of T1DM being over 2 years, not suffering from other severe illnesses affecting the cardiac function, not using cardiac function modifying drugs, not having definitively diagnosed heart disease, not having hypertension and microvascular complications of diabetes.

2-8. Data Analyses

All continuous values are expressed as mean ± standard deviation (SD), and categorical variables are presented as percentage. Kolmogorov-Smirnov test was used to evaluate data distribution. The t-test was employed to compare differences in means of continuous variables between two groups. Chi-square and Pearson correlation coefficient were used to compare the relationship between qualitative and quantitative variables respectively. Data were analyzed by Stata software (Stata Corp. 2018. Stata Statistical Software: Release 15.1 College Station, TX: Stata Corp LP). P- value of less than 0.05 was considered as significant.

3- RESULTS

The study population included 50 children having T1DM and 50 healthy children. Of the patients, 42% (n=21) were males and 58% (n=29) were females and in control group 48% (n=24) were males and 52% (n=26) were females. The control group was matched for sex and age with studied group and were healthy. The mean duration of diabetes mellitus in the case group was 4.88±2.16 years. The mean ratio of urinary microalbumin to creatinine was 14.69 ± 6.16, which was in the normal level in all 50 patients and none had microalbuminuria. According to **Table.1**, there was no significant difference in age, BMI and diastolic blood pressure between the two studied groups, but the systolic blood pressure was significantly higher in the diabetic group compared to the control group ($p<0.05$). To compare the echocardiographic findings of two studied groups, the independent t-test was used and the obtained results are listed in **Table.2**. The mean MPI, E/A, E'/A', E wave, A wave, IVRT, ET, EDV, LVIDd and LVIDs showed significant difference between diabetic and control groups ($p< 0.05$), but the mean EF, E/E', IVCT, ESV and HF showed no significant difference between the diabetic and control groups ($p> 0.05$).

Table-1: Comparison of demographic indicators in two groups of diabetes and control.

Variables	Mean± Standard Deviation		P- value
Age (year)	Diabetic	12.1±3.8	0.3156
	Control	11.4±2.8	
BMI (kg/m2)	Diabetic	18.6±2.9	0.5642
	Control	18.3±2.1	
SBP (mmHg)	Diabetic	106.9±8	0.0307
	Control	102.9±10	
DBP (mmHg)	Diabetic	68±6.7	0.5277
	Control	67±8.8	

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table-2: Comparison of measured variables in TDI echocardiography in two groups of diabetes and control.

Variables	Mean± Standard Deviation		P- value
	Diabetic	Control	
E wave	87.5±14.1	95.6±17.08	0.012
A wave	56.9±11.5	51.06±11.3	0.012
A′ wave	6.9±1.5	6.2±1.6	0.30
E/E′	7.5±1.6	7.4±1.4	0.8094
E′/A′	1.7±0.5	2.1±0.5	0.001
E/A	1.5±0.4	1.9±0.4	0.001
IVRT	55.4±13.1	49.2±8.6	0.006
IVCT	53.7±9.09	51.5±6.6	0.175
ET	260.04±19.6	273.6±23.2	0.002
MPI	0.41±0.06	0.36±0.03	0.001
HR	92.02±12.4	88.1±10.9	0.098
EF	65.4±6.7	64.4±4.4	0.2473
ESV	24.06±17.4	26.8±8.2	0.301
EDV	63.6±19.3	74.8±19.9	0.005
LVIDd	3.7±0.5	4.08±0.4	0.001
LVIDs	2.4±0.4	2.7±0.7	0.012

E: early diastolic wave; A: late (atrial) diastolic wave; A': late diastolic wave(by tissue Doppler); E':early diastolic wave(by tissue Doppler); IVRT: isovolemic relaxation time; IVCT: isovolemic contraction time; ET: ejection tim; MPI: myocardial performance index; HR: heart rate; EF: ejection fraction; ESV: end systolion volume; EDV: end diastolic volume; LVIDd: left ventricular diastolic iternal diamention; LVIDs: left ventricular systolic iternal diameter.

To investigate the relationship between echocardiography factors with Chol, TG, HDL, LDL, HbA1C and duration of disease in diabetic patients, Pearson correlation test was used (**Table.3**). Based on the results, the significant positive correlation was observed between E/E' with serum TG level (p = 0.0072, r=0.37). E'/A' ratio showed significantly negative correlation with TG level (p = 0.014, r=-0.347), and significantly positive correlation with HDL (p = 0.033). E/A ratio had a significant correlation with TG levels (p = 0.048, r=-0.281), LDL (p = 0.012, r=-0.352), and HDL (p = 0.046, r=0.284), though this relationship was inverse for the LDL and TG with E/A ratio. The analysis of the echocardiographic indices of MPI, EF, E/E′ with three subclasses of HbA1C is shown in **Table.4**. The results of this categorization outlined that despite all the differences between indices of MPI (P = 0.063), EF (p = 0.453) and E/E′ ratio (p = 0.229) in the three groups of HbA1C, none of these differences were statistically significant (p>0.05).

Table-3: Pearson correlation coefficient regarding measured parameters in echocardiography with serum lipids and duration of diabetes.

Variables	HbA1C (%)	Cholesterol (mg/dl)	TG (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	duration of diabetes (year)
MPI	R = -0.2651 R = 0.0628	R = -0.25 R = 0.07	R = 0.04 R = 0.749	R = -0.27 R = 0.0523	R = 0.18 R = 0.2078	R = -0.0224 R = 0.877
EF	R = 0.14 R = 0.3198	R = -0.22 R = 0.112	R = 0.023 R = 0.8695	R = -0.13 R = 0.3646	R = -0.18 R = 0.2015	R = -0.17 R = 0.237
E/E′	R = 0.0406 R = 0.796	R = 0.14 R = 0.323	R = 0.37 R = 0.0072*	R = 0.08 R = 0.558	R = -0.11 R = 0.43	R = -0.07 R = 0.586
E′/A′	R = -0.28 R = 0.845	R = -0.009 R = 0.948	R = -0.347 R = 0.014	R = -0.18 R = 0.901	R = 0.302 R = 0.033	R = 0.915 R = 0.095
E/A	R = 0.011 R = 0.937	R = -0.206 R = 0.152	R = -0.281 R = 0.048	R = -0.352 R = 0.012	R = 0.284 R = 0.046	R = 0.246 R = 0.085

TG: triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table-4: Relationship between measured parameters in echocardiography with HbA1C.

Variables		Good (6-7.5)	Intermediate (7.6-9.9)	Poor ≥ 10	Total
E/E′	Normal	4	8	2	14
	Non-normal	4	21	11	36
MPI	Normal	0	13	5	18
	Non-normal	8	16	8	32
EF	Normal	6	26	12	44
	Non-normal	2	3	1	6

MPI: myocardial Performance Index; E: early diastolic wave; E': early diastolic wave (by tissue Doppler); EF: Ejection Fraction.

4- DISCUSSION

The present study was conducted on 50 diabetic children and 50 healthy children matched for age, BMI and DBP. In this study, the parameters obtained by TDI echocardiography were compared in two control and case groups and based on the independent t-test, the mean MPI, E/A, E'/A', E wave, A wave, IVRT, ET, EDV, LVIDs, and LVIDs were significantly different between two groups of diabetic and control (p<0.05), but EF, E/E', IVCT, ESV and HF showed no significant difference (p>0.05). It should be noted that in this study, EF and IVCT were considered as criteria for cardiac systolic function and IVRT, E/A, E/E' and E'/A' as

criteria for cardiac diastolic function. The major finding in our study was that the left ventricular diastolic dysfunction can be detected even in the presence of normal systolic function of this ventricle in people with T1DM by TDI. Most of previous studies have investigated impairment of cardiac myocardial function in adults, while studies on children are limited. In 2014, in a study conducted in Egypt by Khattab and Soliman on 30 children with T1DM and 20 healthy controls, the mean MPI, E/A, E'/A', IVRT, A wave and E waves were significantly different between the case and control groups (14).

These results were inconsistent with the results of the present study. In another study performed on 48 children with T1DM, and 30 healthy controls, EF was not significantly different between the patients and the control groups, but the waves E and A showed significant difference between patient and control groups, which are in agreement with our results (15). It is stated in the previous studies that diastolic dysfunction has been observed in people with DM, even in the presence of normal EF. In fact, it can be argued that diastolic dysfunction is one of the first signs of diabetic cardiomyopathy and the presence of diastolic dysfunction in the affected subjects with DM alone is a risk factor for heart failure, which affects patient prognosis (15). In a study conducted in Turkey in 2016 on 84 children and adolescents with diabetes mellitus and 32 healthy individuals, the mean E/E' and EF ratio had no significant difference between two groups; but the mean E/A ratio was 1.6 in the case group and 1.79 in the control group, which was statistically significant (16). This result was in line with the result of our study. Furthermore, the above cited study suggested that impaired cardiac diastolic function in children and adolescents with T1DM was diagnosed by Doppler echocardiography in the previous studies, but the E/E′ ratio showed no significant difference between patient and control group. Also, several studies have reported that the relationship between the determinants of cardiac dysfunction in TDI is controversial and contrasts with the increase in blood glucose levels in children with T1DM (16). A study by Salem et al. in Egypt on 40 children with T1DM and 20 healthy children, the mean of MPI and E/A and E'/A' were significantly different between the two groups (17). These findings were similar to those obtained in our study. It is also noted that early stages of myocardial dysfunction in people with diabetes, even in case of the normal heart function, can be identified and diagnosed by the echocardiography (17). A study conducted in Greece by Vazeou et al., on 42 children with T1DM and 43 control children showed that in absence of microangiopathy in the patient group, there was no significant difference between cardiac systolic and diastolic function between the patient and control groups. However, this difference was significant when patients with microangiopathy were selected. In this study, the mean age of patients was 18.4 and the mean duration of diabetes mellitus was 9.9 years (18).

However, in our study, the mean age of patients was 12.1 years and the mean duration of the disease was 4.88 years. This could explain the difference in the results of Vazeou et al.'s study and our study results (18). Considering that in our study none of the patients had micro and macrovascular diabetes complications and also considering the results of Vazeou et al.'s study (18), it can be said that the lack of significant difference in the EF and E/E′ indices between the two groups of patients and the control group is due to the absence of microangiopathy. In a study conducted by Zorofyan et al., in Tehran in 2014 on 37 adult type II diabetic patients with normal blood pressure and coronary artery and EF above 50% compared to 39 healthy

controls, the mean MPI and E/A showed a significant difference between these two groups, which was consistent with our study. Also, the mean E/E′ was 6.6 in patients and 6.01 in control group ($p<0.05$) (18). This finding was not in line with the results of our study, which can be because the population of patients in the above study was adult with type II diabetes (19).

In a collaborative study conducted between Japan and the United States on 60 adult diabetic patients and 25 healthy volunteers, the mean E/A ratio was significantly different between the two groups, but the mean EF showed no significant difference. This study suggested that EF is not an appropriate and sensitive indicator for the diagnosis of systolic subclinical disorders in diabetic patients (20), which is in line with our study. In Nakai et al. (20), the mean E/E′ was 12.9 in patients and 9.1 in healthy subjects, which had significant difference (20), and was incongruous with our study.

In other words, in the adult population E/E′ ratio in diabetic patients was significantly higher than in healthy adults, but in our study, there was no significant difference between the two healthy and patients' populations, which can be due to the lower age and shorter duration of diabetes as well as the absence of diabetic complications in the patients in our study.

In the present study, based on the Pearson correlation analysis in patients with T1DM, significant relationship was observed positively between E/E' ratio and TG and also between E/A with HDL, but negatively between TG and LDL. Also, E/A' showed significantly positive correlation with HDL, but significantly negative relationship with TG. In a study by Adal et al. in Turkey on diabetes mellitus in children and adolescents, it was reported that in those with an average diabetes mellitus duration of 8 years, there was a significant relationship between LDL, HDL, HbA1c and cardiac function, but these relationships were not significant in those with diabetes mellitus duration of 3.5 years (21). This can justify the results of our study as the mean duration of diabetes was 4.8 years in our study. Studies have reported that the pathogenesis of diabetic cardiomyopathy is multifactorial that can include microvascular involvement, changes in myocardial metabolism, and structural changes in myocardial infarction due to fibrosis. Evidence indicated that deposition of lipids in the myocardium leads to myocardial damage in the heart.

Insulin resistance increases the intake and withdrawal of fatty acids in the myocardium and the accumulation of TG in the myocardium. It seems that this accumulation is associated with mitochondrial dysfunction, which causes cellular damage, apoptosis, and ultimately replacement of fibrosis (22). The above mentioned evidence can justify the presence of significant relationship between E/A, E'/A' and E/E' with the serum TG level in our study. Studies have also suggested that the increasing risk of heart disease in people with diabetes may be related to controlling blood glucose levels. However, no significant relationship was reported between diastolic dysfunction and HbA1c in previous studies (14, 17, 23).

5- CONCLUSION

Based on the results, in diabetic patients, first cardiac diastolic function decreases, which results in a decrease in E′/A and E/A ratios, as well as a decrease in myocardial performance index, which indicates systolic and diastolic function, and is recommended to be taken into account in the initial examination of the heart of diabetics and not to wait for late-onset systolic function change, and the E / E1 ratio is directly related to serum TG elevation.

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7- CONFLICT OF INTEREST: None.

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