Effect of glycemic control on the progress of left ventricular hypertrophy and diastolic dysfunction in children with type I diabetes mellitus

Tip 1 diyabetes mellituslu çocuklarda sol ventikül hipertrofisi ve diyastolik disfonksiyonun ilerlemesine glisemik kontrolün etkisi

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ABSTRACT

Objective: To evaluate progression of left ventricular (LV) structural and functional changes in patients with type 1 diabetes and effect of glycemic control on these changes.

Methods: A prospective, longitudinal study consisted of 48 patients who were originally studied. At two years follow-up, 44 patients were reevaluated, 35 patients from the original study were reevaluated after another 2 years for the 3rd time using the same protocol. The control group comprised 30 age-and sex-matched healthy volunteers. All studied patients were subjected to full history taking, clinical and cardiac examination. M-mode echocardiography was done, blood samples were taken and examined for HbA1c and urine samples were tested for the presence of albuminuria. ANOVA for repeated measurements, t-test for dependent and independent variables, and Mann-Whitney U test were used for statistical analyses.

Results: Seven (14.6%) of our patients had LV hypertrophy, 23 (47.9%) patients had diastolic dysfunction and ten patients only achieve improvement in glycemic control. Duration of diabetes was significantly higher in patients with LV hypertrophy (LVH) ($p<0.05$). Patients with no improvement in glycemic control had a significant increase in interventricular septum (IVS) and left ventricular posterior wall (LVPW) in the third examination ($p<0.05$ for both).

Conclusion: Prevalence of LVH and diastolic dysfunction among diabetic patients is high. Glycemic control in diabetic patients could not improve LVH or diastolic dysfunction. On the other hand, failure to achieve glycemic control leads to deterioration in structural parameters.
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Key words: Glycemic control, echocardiography, progression, insulin-dependent diabetes mellitus, left ventricular hypertrophy, diastolic dysfunction

ÖZET

Amaç: Diyabetik hastalarda sol ventrikülün yapısal ve işlevsel değişikliklerinin ilerlemesi ve tip 1 diyabetin etkisi ile bu değişikliklere glisemik kontrolün etkisini değerlendirmek.

Yöntemler: Bu prospektif, longitüdinal çalışma başlangıçta 48 hastadan oluşmaktaydı. İki yıllık takip sırasında, 44 hasta tekrar değerlendirildi, orijinal çalışmadan 35 hasta sonraki 2 yılda aynı protokoller kullanılarak tekrar değerlendirildi. Kontrol grubu cinsiyet ve yaş uyumlu 30 sağlıklı gönüllüden oluşmaktaydı. Çalışılan tüm hastalar, tam öyküleri alınıp, klinik ve kardiyak incelemeye tabi tutuldu. M-mode ekokardiyografi yapıldı, kan örnekleri alındı, HbA1c için değerlendirildi ve idrar örnekleri albüminüri varlığı için test edildi. İstatiksel analizde, tekrarlayan ölçümler için ANOVA, bağımlı-bağımsız değişkenler için t-test ve Mann-Whitney U testi kullanıldı.

Bulgular: Hastalarımızın 7'sinde (%14.6) sol ventrikül hipertrofisi (SVH) vardı, 23 (%47.9) hasta da diyastolik disfonksiyon vardı ve yalnızca 10 hastada glisemik kontrolde iyileşme sağlandı. Diyabet süresi SVH olan hastalarda önemli derecede daha yüksekti ($p<0.05$). Glisemik kontrolde iyileşme olmayan hastaların üçüncü kontrollerinde, interventriküler septum ve sol ventriküler posteriyor duvarında önemli bir artış vardı ($p<0.05$).

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Sonuç: Sol ventrikül hipertrofisi ve diyastolik disfonksiyonun prevalansı diyabetik hastalar arasında fazladır. Diyabetik hastalarda glisemik kontrol SVH ve diyastolik disfonksiyonu iyileştiremedi. Diğer taraftan, glisemik kontrolü sağlamada başarısızlık yapısal parametrelerde bozulmaya yol açar. *(Anadolu Kardiyol Derg 2012; 12: 498-507)*
Anahtar kelimeler: Glisemik kontrol, ekokardiyografi, ilerleme, insüline bağlı diyabetes mellitus, sol ventrikül hipertrofisi, diyastolik disfonksiyon

Introduction

Although complications of diabetes mellitus (DM) may involve almost all organs, little attention has been paid to studies of heart function. However, the more frequent incidence of heart failure in diabetics even in the absence of any heart disease, leads to the presumption that DM unfavorably affects the heart muscle by its complications (1). Devereux et al. (2) concluded that patients with diabetes had greater left ventricular wall thickness than non-diabetic individuals. Also Hirayama et al. (3) showed that left ventricular hypertrophy (LVH) in diabetic patients is an ominous prognostic sign and an independent risk factor for cardiac events. This could explain previous report from The SOLVD (Studies of Left Ventricular Dysfunction) (4), which demonstrated poor prognosis of heart failure in diabetic patients.

In diabetic patients without known cardiac disease, abnormalities of LV function primarily reflect a diastolic abnormality which has been described as an early sign of this diabetic heart muscle disease (diabetic cardiomyopathy) preceding systolic damage (5). This diastolic abnormality appears related to interstitial collagen deposition and LV hypertrophy that appear in the absence of hypertension (6). There is evidence that metabolic disturbances, myocardial fibrosis, small vessel disease, cardiac autonomic neuropathy, and insulin resistance may all contribute to the development of diabetic cardiomyopathy (6). The relationship between myocardial hypertrophy and diastolic dysfunction and glycemic control is still a matter of debate (5).

There is growing evidence to support the existence of diabetic cardiomyopathy as a distinct clinical entity that may lead to heart failure independent of coronary artery disease or hypertension. Although there is a general agreement that left ventricular (LV) diastolic dysfunction may be present in diabetic patients, recent studies using tissue Doppler imaging (TDI) also support the presence of subtle systolic abnormalities in the longitudinal axis (7).

In young patients information correlating type I DM with changes in left ventricular structure and function, is lacking.

This is why; we aimed to evaluate the impact of type 1 diabetes on cardiac structure and function. In addition, to evaluate the progression of left ventricular structural and functional changes in children with type I DM and the effect of glycemic control on these changes.

Methods

Study design

It is a prospective longitudinal observational study done after obtaining approval from the ethical committee. Written informed consent was obtained from all patients, their parents and controls after full discussion about the aim of the study.

Patients

The study included 48 patients with type 1 DM among those attending to the endocrine clinic. The control group consisted of 30 ages and sex matched healthy normal volunteers.

The exclusion criteria were as follows:

1. Patients during acute diabetic complications e.g. diabetic ketoacidosis (DKA) or hypoglycemia
2. Patients suffering from cardiac diseases e.g. congenital, rheumatic heart, left ventricular dysfunction or hypertension
3. Patients suffering from chronic renal failure and electrolyte imbalance
4. Patients receiving drugs for cardiovascular disease
5. Patients with duration of type 1 diabetes less than 5 years
6. Patients age < 10 and > 18 years old.

Study protocol

Study group consisted of 48 patients who were followed up. At two years follow- up, 44 patients were reevaluated. Four patients from the original study could not be located. Thirty-five patients from the original study were reevaluated after another 2 years for the 3rd time using the same protocol. The control group comprised 30 age- and sex- matched healthy volunteers. They were evaluated only at the beginning of the study by the same protocol.

Clinical evaluation

All the studied patients were subjected to:

1. Full history taking, careful clinical and cardiac examination
2. Blood pressure was measured three times after 5-minute rest in the sitting position on both upper limbs with the use of automatic manometer (Omron M4 Plus, Omron Healthcare Europe, Hoofddorp, Netherlands). The mean value of the second and the third measurement was calculated. The measurements taken on the dominant limb were analyzed.

Echocardiography

Imaging and Doppler echocardiogram were performed using standardized protocol with M-mode, 2-dimensional, pulsed, continuous- wave and color-flow Doppler capabilities using General Electric medical echocardiographic machine (model: Vivid 7 Pro, GE Vingmed ultrasound AS-NI90, Horton-Norway

equipped with 3&7 MHZ transducers). Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) interventricular septum (IVS) and LV posterior wall thickness (LVPW) dimensions in diastole, aorta and pulmonary artery dimensions, right ventricular dimension were measured by standard M-mode guided by two-dimensional echocardiography. Left ventricular systolic function represented by ejection fraction (EF) and fractional shortening (FS) were obtained digitally. The following Doppler echocardiography parameters of LV diastolic and RV systolic performance were evaluated: peak mitral flow velocities during early (E) and late diastole (A), their ratio (E/a), early diastolic mitral flow acceleration time (ETacc), late diastolic mitral flow time (AT), IVRT - isovolumic relaxation time, peak pulmonary flow velocity (PFV), acceleration and deceleration times of PFV.

LVH was defined as wall thickness of IVS or LVPW or both > 2 SDS above normal (8) and diastolic dysfunction was defined as prolonged IVRT >90 milliseconds or abnormal E/A ratio ($\leq$1 or $\geq$2.5).

Left ventricular mass (LVM) was calculated with the anatomically validated formula of Devereux (9):

LVM=0.8_[1.04_(IVSd+PWLVd+LVIDd)^3-LVIDd^3]+0.6 (g)

The LVM index (LVMI) adjusts for body size and is taken as LVM (g) divided by body weight (kg). LVH was considered present at LVMI >3 g/kg.

Laboratory investigation

Simultaneously all patients underwent the following tests:

1. Glycosylated hemoglobin (HbA1c) was done every 3 months by DCA 2000 (Bayer AG, Leverkusen, Germany), based on specific inhibition of latex immunoagglutination using kits provided by Helena Laboratories, Beaumont, TX, USA (10). The mean value was calculated per year.
2. Screening for microalbuminuria: It was assessed in fresh morning urine samples by measuring albumin/creatinine ratio by enzyme linked immunosorbent assay (ELISA).

Follow-up

All patients were followed up in the endocrinology clinic, and participated in a program for glycemic control (It included diabetes education by dietitian, self-blood glucose monitoring twice / day and exercise daily). Glycemic control improvement was defined as >1% absolute decrease of HbA1c. All patients were followed- up after two years, then after another 2 years to be evaluated clinically and by echocardiography (for assessment of left ventricular structural and functional parameters).

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 15.0 (Chicago, Illinois, USA). T-test for independent and dependent variables was done and non-parametric (Mann-Whitney U) test was done when data was not symmetrically distributed. ANOVA for repeated measurements for comparison of continuous variables in patients with diabetes was also done followed by posthoc analysis (Tukey's test) by using GraphPad Prism version 5 for Windows software (Graphad software, San Diego, California USA). Pearson's correlation analysis was also done. Stepwise multiple regression analysis was also performed to find an association of LVEDD and LVESD with duration of disease, systolic and diastolic blood pressures, variables with p value <0.05 in simple Pearson's correlation analysis.

Results

The study included 48 patients with type 1 diabetes, 20 (41.7%) male and 28 (58.3%) female patients; their mean age was 12.6±3.4 years (range 10-18 years), mean duration of disease -5.5±3.5 years (5-14 years), body mass index (BMI)-25.1±4.3 kg/m^2 (18.2-38.2 kg/m^2), mean HbA1c-8.6±1.6% (8.5-12.3%) and mean insulin dose was 1.3±0.8 IU/kg (0.5-2.3 IU/kg). Seven (14.6%) of our patients had LVH, 23 (47.9%) patients had diastolic dysfunction and ten patients only achieve improvement in glycemic control (as not all patients follow the instruction of glycemic control program).

No significant difference was found in age and BMI between patients and controls. Echocardiographic cardiac dimension in diabetic patients and controls is shown in Table 1. Correlation between duration of disease, systolic and diastolic blood pressures with echocardiographic parameters of patients included in the study in the first examination is presented in Table 2. Systolic blood pressure was the only parameter related to LVEDD (β=0.2, 95% CI: 0.1-0.3, p=0.002), while, diastolic blood pressure was the only parameter related to LVESD (β=0.2, 95% CI: 0.04-0.3, p=0.01) by stepwise multiple regression analysis in the diabetic patients (Table 3).

No significant correlations were found between echocardiographic measurements and BMI, HbA1c or insulin dose. Albumin/creatinine ratio had only a significant correlation with IVS (r=0.4, p=0.02) and LVMI (r=0.4, p=0.04).

Comparison between echocardiographic cardiac dimensions in diabetic patients in the 1st, 2nd and 3rd examination is shown in Table 4. Duration of diabetes was significantly higher in patients with LV hypertrophy (p<0.05) (Table 5). Patients who achieved improvement in glycemic control had a significant difference in E/A ratio (p<0.05) (Table 6). Patients with improvement in glycemic control had no significant differences in IVS, LVPW, LVMI, FS, EF, E/A ratio or IVRT values (Table 7). Patients with no improvement in glycemic control had a significant increase in IVS and LVPW. On the other hand, there was a significant decrease in ETacc and IVRT in the third examination when compared to first examination (p<0.05) (Table 7).

Discussion

In our study, IVS, LVPW and LVMI (LV hypertrophy) were significantly higher in the 1st, 2nd and 3rd examination of diabetic

Table 1. Comparison of echocardiographic cardiac dimensions in patients with type 1 diabetes and controls

Variables	First examination (n=48)	Second examination (n=44)	Third examination (n=35)	Controls (n=30)	*p 1st&controls	*p 2nd&controls	*p 3rd&controls
LA, mm	26.0±3.8	26.3±3.5	27.8±3.5	22.3±6.2	0.005	0.002	0.0001
Ao, mm	21.7±2.0	23.4±2.9	23.7±3.0	20.5±3.3	0.07	0.0001	0.0001
RV, mm	16.0±3.1	15.7±2.4	17.1±3.1	14.6±4.5	0.2	0.2	0.009
PA, mm	19.4±3.0	20.6±3.0	20.7±2.8	16.4±2.2	0.0001	0.0001	0.0001
IVS, mm	6.5±1.7	7.1±1.2	7.3±1.8	5.3±0.9	0.0001	0.0001	0.007
LVPW, mm	6.1±1.4	6.8±1.2	7.3±1.8	5.0±1.0	0.0001	0.0001	0.0001
LVEDD, mm	40.4±5.8	41.3±5.9	42.0±4.0	38.5±5.0	0.2	0.04	0.001
LVESD, mm	26.3±4.7	26.8±5.1	26.6±3.6	25.5±4.5	0.5	0.3	0.3
SV, mL	49.9±23.7 42.0 (21.0-136.0)	53.2±23.1 47.0 (17.0-136.0)	56.1±17.1 53.0 (22.0-115.0)	39.8±13.5 24.0 21.0-64.0)	0.04	0.008	0.0001
EF, %	66.5±14.5	68.1±12.7	72.4±5.8	70.0±6.9	0.2	0.5	0.2
FS, %	35.8±7.4	36.1±4.6	37.1±4.1	33.2±4.5	0.1	0.2	0.2
E, cm/sec	82.2±13.5*	79.4±12.6	82.9±24.6*	192.9±43.1	0.0001	0.0001	0.0001
A, cm/sec	48.8±9.6*	52.8±12.9	51.8±12.0*	121.6±36.2	0.0001	0.0001	0.0001
E/A ratio	1.7±0.4	1.6±0.4	1.7±0.6	2.1±3.0	0.4	0.3	0.2
ETacc, msec	299.5±136.5 268 (138.0-660.0)	221.4±98.1 199 (16.0-491.0)	81.0±11.9 80 (56.0-104.0)	83.6±13.4 83.0 (58.0-114.0)	0.0001	0.0001	0.0001
AT, msec	121.1±61.6	126.2±51.6	110.5±28.4	44.7±11.1	0.0001	0.0001	0.0001
IVRT, msec	93.6±18.7	91.9±18.3	74.6±14.5	77.5±13.4	0.0001	0.001	0.0001
PFV, cm/sec	101.4±14.1	100.6±13.8	98.7±15.1	93.7±11.7	0.02	0.04	0.4
Acceleration of PFV, msec	95.6±18.3	93.1±32.7	91.4±20.3	85.6±17.6	0.03	0.3	0.1
Deceleration of PFV, msec	193.8±35.1	190.9±30.1	186.3±38.1	171.2±66.3	0.09	0.1	0.1
LVMI, g/kg	2.7±1.4 2.6 (0.7-7.7)	2.5±0.5 2.2 (0.8-4.5)	2.1±0.7 2.0 (0.9-3.3)	1.4±0.2 1.5 (1.0-1.9)	0.0001	0.0001	0.0001

Data are presented as mean± SD and median (range) values
*t - test for independent variables and Mann-Whitney U test
A - peak mitral flow velocity during late diastole, Ao - aorta dimension, AT - late diastolic mitral flow time, E - peak mitral flow velocity during early diastole, EF - ejection fraction, ETacc - early diastolic mitral flow acceleration time, FS - fractional shortening, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LA - left atrium dimension, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPW - left ventricular posterior wall thickness, PA - pulmonary artery dimension, PF - pulmonary flow, PFV - peak pulmonary flow velocity, RV - right ventricular dimension, SV - stroke volume

patients, LVEDD (LV dilatation) was higher in 2nd and 3rd examination, and lastly IVRT (LV diastolic dysfunction) was significantly higher in the 1st and 2nd examination than those in controls. On the other hand, EF and FS (LV systolic function) showed no significant difference. Seven (14.6%) of our patients had left ventricular hypertrophy, 23 (47.9%) patients had diastolic dysfunction and ten patients only achieved improvement in glycemic control. Comparing the 3 examinations of diabetic patients, ETacc was significantly different on the 3 examination, and IVRT was significantly lower on the 3rd examination than the 1st and 2nd examinations. This means that follow- up of patients and early detection of cardiac abnormalities help in prevention of the natural progression of cardiac affection and facilitate improvement of cardiac function.

Previous studies showed that type1 DM might be associated with LV diastolic dysfunction in the presence of normal EF, suggesting that in type 1 DM, LV diastolic dysfunction may be the earliest marker of diabetic cardiomyopathy. LV diastolic dysfunction is an independent predictor of untoward cardiac outcome (11, 12).

The term diabetic cardiomyopathy has been proposed to denote the presence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular or hypertensive heart disease (5). Adult diabetic patients without clinical heart

Table 2. Correlation between duration of disease, systolic and diastolic blood pressure with echocardiographic parameters of patients included in the study in the first examination

Variables	Correlation coefficient	Duration of disease, years	Systolic blood pressure, mmHg	Diastolic blood pressure, mmHg
LA, mm	r	0.6	0.3	0.2
	p	0.0001	0.07	0.4
AO, mm	r	0.3	0.3	0.5
	p	0.05	0.06	0.06
RV, mm	r	0.3	0.4	0.3
	p	0.04	0.6	0.06
PA, mm	r	0.5	0.3	0.2
	p	0.002	0.08	0.2
IVS, mm	r	0.3	0.4	0.4
	p	0.04	0.2	0.02
LVPW, mm	r	0.05	0.1	0.2
	p	0.8	0.6	0.2
LVEDD, mm	r	0.4	0.5	0.5
	p	0.03	0.002	0.004
LVESD, mm	r	0.4	0.4	0.4
	p	0.02	0.01	0.01
SV, mm	r	0.4	0.6	0.5
	p	0.03	0.0001	0.002
E, cm/sec	r	-0.02	-0.1	0.2
	p	0.9	0.8	0.4
A, cm/sec	r	0.1	0.1	0.2
	p	0.7	0.6	0.4
E/A ratio	r	-0.1	-0.1	0.02
	p	0.4	0.6	0.9
IVRT, msec	r	0.1	0.2	0.3
	p	0.7	0.2	0.1
LVMI, g/kg	r	-0.1	0.06	0.1
	p	0.7	0.7	0.5

Pearson correlation analysis
A - peak mitral flow during late diastole, Ao - aorta dimension, E - peak mitral flow during early diastole, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LA - left atrium dimension, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPWS - left ventricular posterior wall thickness, PA - pulmonary artery dimension, RV - right ventricular dimension, SV - stroke volume

failure were reported to have hypertrophic, non-compliant left ventricles. Early determination of myocardial manifestations of DM is of major importance, since myocardial involvement considerably influences the prognosis of diabetic patients (5). Boyer et al. (13) found left ventricular diastolic dysfunction in 63% of his study group (adult patients) and concluded that the prevalence of left ventricular diastolic dysfunction in asymptomatic diabetic patients is much higher than previously suspected. In addition, Stakos et al. (14) stated that type 1 DM is associated with cardiovascular abnormalities and early detection and treatment of these abnormalities may help to prevent the natural progression of the disease.

Table 3. Stepwise multiple regression analysis of left ventricular dimensions in relation to duration of disease, systolic and diastolic blood pressure of diabetic patients

Variables	B	95% confidence interval	p
*LVEDD			
Constant	18.4	5.2-31.6	0.008*
Diastolic blood pressure, mmHg	0.2	0.1-0.3	0.002*
**LVESD			
Constant	14.4	5.2-23.7	0.003*
Systolic blood pressure, mmHg	0.2	0.04-0.3	0.01*

*R^2=0.26, SEM: 5.09 , dependent variables: LVEDD
**R^2=0.19, SEM: 4.29, dependent variables: LVESD
R^2: Coefficient of determination
SEM - standard error of mean
Independent variables-duration of disease, systolic and diastolic blood pressure
LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension

Duration of diabetes had a positive significant correlation with LA (r=0.6, p=0.0001), Ao (r=0.3, p=0.05), PA (r=0.5, p=0.0001), IVS (r=0.3,=0.04), LVEDD (r=0.4, p=0.03), LVESD (r=0.4, p=0.02) and SV (r=0.4, p=0.03) measured at the first time. On the other hand, no significant correlations were found between echocardiographic measurements and HbA1c or insulin dose. Albumin/creatinine ratio had only a significant correlation with IVS (r=0.4, p=0.02) and LVMI (r=0.4, p=0.04).

This coincides with the result of Gül et al. (15), who found a strong correlation between impairment of diastolic parameters and DM duration and diabetic complications, and no correlation between glycemic control and diastolic dysfunction. On the other hand, Kim et al. (16) found mild progression of LV systolic and diastolic functions from normal to dysfunction according to the duration of DM and LV diastolic function showed a significant and inverse correlation with HbA1c.

In the contrary, Saad et al. (17) reported that there was no statistically significant difference between diabetic patients suffering from LV hypertrophy with diastolic dysfunction and those not having such changes regarding left ventricular systolic function, serum lipids profile, duration of illness, albuminuria, body dimensions and blood pressure. This was comparable to results in the study conducted by Suys et al. (18), regarding LV wall thickness, involving adolescents with type I DM compared with the control. LVH has been demonstrated to predict cardiovascular related mortality in adults with DM (19). Similarly also, Giunti et al. (20) concluded that diastolic abnormalities are common in patients with type I DM and are not related to the duration of the disease. However, Adel et al. (21) stated that abnormal LV diastolic function in patients with mean type 1 DM duration of 8.2

Table 4 . Changes in left ventricular function during follow-up in diabetic patients

Variables	First examination (n=35)	Second examination (n=35)	Third examination (n=35)	*F	*p
LA, mm	26.1±3.8[a]	26.4±3.3[ab]	27.8±3.5[b]	4.6	0.01
Ao, mm	21.7±2.1[a]	23.3±2.9[b]	23.7±3.4[b]	8.4	0.0007
RV, mm	15.6±2.7[a]	15.7±2.4[b]	17.1±.2[b]	3.6	0.03
PA, mm	19.5±3.1	20.4±3.1	20.7±2.8	2.0	0.1
IVS, mm	6.7±1.8	7.3±1.2	7.3±1.8	1.9	0.2
LVPW, mm	6.1±1.5	6.8±1.2	7.3±1.8	1.9	0.2
LVEDD, mm	40.3±6.0	41.2±5.7	42.0±4.0	2.4	0.1
LVESD, mm	26.2±4.8	26.7±5.1	26.6±3.6	0.3	0.7
SV, mL	49.9±23.7 42.0 (21.0-136.0)	53.2±23.1 47.0 (17.0-136.0)	56.1±17.1 53.0 (22.0-115.0)	2.6	0.09
EF, %	65.7±15.6	67.5±13.6	72.4±5.8	3.1	0.06
FS, %	36.3±7.8	36.0±4.5	37.1±4.1	0.3	0.7
E, cm/sec	81. 3±13.7	80.2±12.8	82.9±24.6	0.2	0.8
A, cm/sec	48.9±9.8	51.9±12.1	51.8±12.0	0.7	0.5
E/A ratio	1.7±0.5	1.6±0.4	1.7±0.6	0.4	0.7
ETacc, msec	299.5±136.5[a] 268 (138.0-660.0)	221.4±98.1[b] 199 (16.0-491.0)	81.0±11.9[c] 80 (56.0-104.0)	35.6	0.0001
AT, msec	124.7±66.0	120.9±53.0	110.5±28.4	0.9	0.4
IVRT, msec	92.1±16.3[a]	92.6±19.4[a]	74.6±14.5[b]	12.1	0.0001
PFV, cm/sec	100.6±15.2	101.1±13.6	98.7±15.1	0.3	0.8
Acceleration of PFV, msec	94.0±18.1	95.1±35.5	91.4±20.3	0.2	0.8
Deceleration of PFV, msec	189.6±33.5	190.1±31.1	186.3±38.1	0.2	0.9
LVMI, g/kg	2.7±1.4 2.6 (0.7-7.7)	2.5±0.5 2.2 (0.8-4.5)	2.1±0.7 2.0 (0.9-3.3)	1.1	0.3

Data are presented as mean± SD and median (range) values
*ANOVA for repeated measurements [a,b,c] - p<0.05, posthoc Tukey test for the difference
A - peak mitral flow velocity during late diastole, Ao - aorta dimension, AT - late diastolic mitral flow time, E - peak mitral flow velocity during early diastole, EF - ejection fraction, ETacc - early diastolic mitral flow acceleration time, FS - fractional shortening, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LA - left atrium dimension, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPW - left ventricular posterior wall thickness, PA - pulmonary artery dimension, PF- pulmonary flow, PFV - peak pulmonary flow velocity, RV - right ventricular dimension, SV - stroke volume

years was correlated with glycemic control, free and total carnitine, and low- and high-density lipoprotein cholesterol levels and this could not be elicited in patients with mean type 1 DM duration 3.5 years.

Weinrauch et al. (22), postulated that renal dysfunction has an impact on LV mass, septal thickness, systolic function and diastolic compliance as intensive diabetes control is applied over 12 months. Other authors stated that decreased myocardial performance was associated with albuminuria in diabetic patients (23). In the contrary, Saad et al. (17) and Galicka-Latala et al. (24) investigating the association of left ventricular wall hypertrophy and diastolic dysfunction with urinary albumin excretion in diabetic patients, they found no statistically significant correlation between them.

In our patients, systolic and diastolic blood pressures had a significant positive correlation with LVEDD and LVESD. On the other hand, diastolic blood pressure had a significant positive correlation with IVS thickness, systolic blood pressure was the only parameter related to LVEDD (β=0.2, 95% CI: 0.1 -0.3, p=0.002), while, diastolic blood pressure was the only parameter related to LVESD (β=0.2, 95% CI: 0.04 - 0.3, p=0.01) by stepwise multiple regression analysis in the diabetic patients. This result is in agreement with the findings of Fox et al. (25), who stated that body mass index, surface area and blood pressure influence left ventricular mass and geometry.

Table 5. Comparison of demographic data, clinical and echocardiographic variables in diabetic patients in relation to left ventricular hypertrophy in the first examination

Variables	No LV hypertrophy (n=41)	LV hypertrophy (n=7)	*p
Age of patients, years	12.4±3.6	13.1±3.3	0.6
Duration of disease, years	5.1±3.5	8.0±2.5	0.04
Age of onset of disease, years	7.2±2.8	5.1±2.7	0.1
Systolic blood pressure, mmHg	106.7±14.6	104.2±11.6	0.7
Diastolic blood pressure, mmHg	69.8±12.2	73.3±9.8	0.5
Insulin dose, IU/kg	1.2±0.5	1.8±2.0	0.2
HbA1c, %	8.5±1.5	9.5±0.8	0.2
Albumin/creatinine ratio	17.1±2.5	24.4±23.4	0.6
IVS, mm	6.1±1.2	8.8±1.9	0.0001
LVPW, mm	6.0±1.4	6.5±1.4	0.4
LVEDD, mm	40.9±6.3	38.3±2.5	0.3
LVESD, mm	26.6±5.0	24.6±3.0	0.4
SV, mL	52.2±25.9 45.5 21.0-136.0)	42.0±7.6 41.0 (33.0-56.0)	0.4
EF, %	65.1±15.4	74.4±5.2	0.06
FS, %	35.9±8.1	36.2±4.0	0.9
E/A ratio	1.7±0.4	2.0±0.7	0.1
ETacc, msec	294.1±141.4 23.0 (138.0-660.0)	289.0±121.3 299.0 (145.0-44.5)	0.9
AT, msec	118.4±61.9	129.5±69.6	0.7
IVRT, msec	91.6±18.5	95.3±10.6	0.6
PFV, cm/sec	99.9±13.9	108.2±14.5	0.2
Acceleration of PFV, msec	97.2±17.1	89.2±25.0	0.3
Deceleration of PFV, msec	194.1±34.7	183.7±34.8	0.5
LVMI, g/kg	2.3±1.0 2.4 (0.7-4.0)	3.2±1.2 3.1 (1.4-4.5)	0.1

Data are presented as mean± SD and median (range) values
*t-test for independent variables and Mann-Whitney U test
A - peak mitral flow velocity during late diastole, AT - late diastolic mitral flow time, E - peak mitral flow velocity during early diastole, EF - ejection fraction, ETacc - early diastolic mitral flow acceleration time, FS - fractional shortening, HbA1c - glycosylated hemoglobin, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPW - left ventricular posterior wall thickness, PF - pulmonary flow, PFV - peak pulmonary flow velocity, SV - stroke volume

Duration of diabetes was significantly higher in our patients with LVH. In the present study, though there was a trend for patients with LVH to have the level of HbAlc to be higher (9.5±0.8%) than those without LVH (8.5±1.5%), but this trend was not significant statistically. Other authors also reported that there is no correlation between HbA1c and the development of cardiovascular changes in children and adolescents with type I DM, which is similar to results of the current study (21, 26). In the same previous study, Giunti et al. (21), reported that left ventricular systolic function was comparable in both diabetics and controls which was the same result obtained in our study.

Table 6. Comparison of demographic, clinical and echocardiographic variables in diabetic patients in relation to glycemic control (between first &third examination)

Variables	No glycemic control	Glycemic control	*p
Age of patients, years	12.5±3.7	12.3±3.3	0.9
Duration of disease, years	5.3±.1	6.8±4.5	0.3
Age of onset of disease, years	7.2±2.9	5.5±2.7	0.1
Systolic blood pressure, mmHg	106.6±14.8	102.8±9.4	0.5
Diastolic blood pressure, mmHg	70.2±12.0	69.4±11.6	0.9
Insulin dose, IU/kg	1.3±1.0	1.2±0.3	0.5
Albumin/creatinine ratio	18.6±4.9	17.2±19.4	0.9
IVS, mm	6.3±1.6	7.3±2.0	0.2
LVPW, mm	6.0±1.4	6.5±1.3	0.3
LVEDD, mm	41.2±6.2	39.3±4.5	0.4
LVESD, mm	26.7±5.2	26.0±2.4	0.7
SV, mL	53.0±25.1 44.0 (27.0-136.0)	45.3±19.6 40.0 (21.0-87.0)	0.4
EF, %	66.3±15.4	65.9±13.6	0.9
FS, %	36.6±8.2	33.6±5.1	0.3
E/A ratio	1.8±0.5	1.6±0.2	0.04*
ETacc, msec	298.4±136.0 268.0 (176.0-660.0)	292.5±151.9 268.0 (138.0-491.0)	0.9
AT, msec	114.7±59.6	141.8±73.5	0.3
IVRT, msec	92.2±18.4	88.6±10.8	0.6
Flow, cm/sec	100.1±13.8	104.0±16.3	0.5
Acceleration, msec	94.6±19.8	97.6±16.2	0.7
Deceleration, msec	190.5±32.4	198.3±43.7	0.6
LVMI, g/kg	2.6±1.0 2.6 (0.9-4.3)	2.5±1.2 2.4 (1.1-4.5)	0.3

Data are presented as mean± SD and median (range) values
*t- test for independent variables and Mann-Whitney U test
A - peak mitral flow velocity during late diastole, AT - late diastolic mitral flow time, E - peak mitral flow velocity during early diastole, EF - ejection fraction, ETacc - early diastolic mitral flow acceleration time, FS - fractional shortening, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPW - left ventricular posterior wall thickness, PF - pulmonary flow, PFV - peak pulmonary flow velocity, SV - stroke volume

In our study, patients who achieved improvement in glycemic control had a significant lower E/A ratio than those who could not achieve improvement in glycemic control. At the 3rd exami-

Table 7. Comparison of demographic, clinical and echocardiographic variables between 1st and 3rd examinations in diabetic patients with and without improvement in glycemic control

Variables	Improved glycemic control			No improved glycemic control		
	First examination	Third examination	*p	First examination	Third examination	*p
Systolic blood pressure, mmHg	103.6±10.7	120.0±20.0	0.04	106.3±15.1	114.6±10.8	0.005
Diastolic blood pressure, mmHg	72.1±11.9	82.9±11.1	0.01	69.8±11.6	77.3±11.2	0.003
Insulin dose, IU/kg	1.1±0.5	0.8±0.4	0.1	1.3±1.0	1.1±0.4	0.4
Albumin/creatinine ratio	21.1±20.5	27.6±33.3	0.7	7.9±9.7	19.8±25.2	0.1
IVS, mm	7.3±2.0	7.6±1.7	0.6	6.3±1.6	7.4±1.8	0.02
LVPW, mm	6.5±1.3	6.6±1.2	0.8	6.0±1.4	7.5±1.6	0.0001
LVEDD, mm	39.3±4.5	42.8±4.9	0.04	41.2±6.2	42.7±4.6	0.1
LVESD, mm	26.0±2.4	26.9±3.7	0.5	26.7±5.2	27.2±3.8	0.6
SV, mL	45.3±19.6 40.0 (21.0-87.0)	57.2±17.9 56.0 (36.0-92.0)	0.04	53.0±25.1 44.0 (27.0-136.0)	58.6±20.1 52.1 (36.0-115.0)	0.1
EF, %	65.9±13.6	73.7±4.6	0.1	66.3±15.4	71.9±6.1	0.1
FS, %	33.6±5.1	37.6±4.7	0.1	36.6±8.2	36.6±4.1	0.9
E/A ratio	1.6±0.2	1.5±0.3	0.8	1.8±0.5	1.8±0.7	0.9
ETacc, msec	298.4±136.0 268.0 (176.0-660.0)	78.7±17.1 88.0 (56-104)	0.01	298.4±136.0 268.0 (176.0-660.0)	80.7±12.2 80.0 (56.0-104.0)	0.0001
AT, msec	141.8±73.5	111.0±34.3	0.2	114.7±59.6	112.8±24.5	0.9
IVRT, msec	88.6±10.8	68.5±23.2	0.1	92.2±18.4	77.4±9.4	0.001
PFV, cm/sec	104.0±16.3	104.5±16.3	0.9	100.1±13.8	97.7±15.2	0.6
Acceleration of PFV, msec	97.6±16.2	90.5±26.3	0.4	94.6±19.8	93.2±18.1	0.8
Deceleration of PFV, msec	198.3±43.7	187.0±20.9	0.5	190.5±32.4	191.3±41.0	0.9
LVMI, g/kg	2.5±1.2 2.4 (1.1-4.5)	2.0±0.5 1.9 (0.9-2.7)	0.1	2.6±1.0 2.6 (0.9-4.3)	2.3±0.7 2.3 (0.9-3.3)	0.4

Data are presented as mean± SD and median (range) values
*t- test for independent variables and Mann-Whitney U test
A - peak mitral flow velocity during late diastole, Ao - aorta dimension, AT - late diastolic mitral flow time, E - peak mitral flow velocity during early diastole, EF - ejection fraction, ETacc - early diastolic mitral flow acceleration time, FS - fractional shortening, IVRT - isovolumic relaxation time, IVS - interventricular septum thickness, LA - left atrium dimension, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end-systolic dimension, LVMI - left ventricular mass index, LVPW - left ventricular posterior wall thickness, PA - pulmonary artery dimension, PF - pulmonary flow, PFV - peak pulmonary flow velocity, RV - right ventricular dimension, SV - stroke volume

nation, 10 (56.1%) of the diabetic patients achieved improvement in their glycemic control. Comparing echocardiographic parameters of 3rd examination of patients who achieved improvement in their glycemic control to their baseline results, mean value of LV wall thickness dimensions (IVSd, PWd and IVMI) and diastolic dysfunction represented by IVRT and E/A did not decrease significantly. A few prospective studies evaluated the relation between glycemic control and diastolic function, obtaining negative results: good glycemic control for 6 or 12 months was not accompanied by any improvement in diastolic function (27). In the contrary, Saad et al. (17) and Aepfelbacher et al. (28) showed that improved glycemic control in patients with type 1 DM is associated with regression of septal thickness and left ventricular mass without significant effect on systolic or diastolic function. Also Weinrauch et al. (29), in a study involving patients with type I DM showed improvement in measures of heart rate variation correlated with a decrease in LV mass and dimensions after 12 months follow-up and this paralleled glycemic control.

The largest (n=136), prospective, randomized, radionuclide study led to the conclusion that improvement of glycemic control over a period of two years with intensive treatment did not affect the LV diastolic function (30), that is similar to our results that showed no improvement of diastolic dysfunction. However, Fiorina et al. (31), demonstrated a reduction in the rate of progression of diastolic dysfunction, evaluated using radionuclide ventriculography, in every uremic patient with type 1 diabetics after kidney-pancreas transplantation that may be positively associated with glycemic control. Another study conducted on 15 type I diabetic subjects suggested that good diabetic control was associated with the improvement in LV function (32). Grandi et al. (27) concluded that, in normotensive patients with type 1

diabetes, a close relation was found between glycemic control and LV diastolic function, which improves when glycemic control improves. Therefore, diastolic dysfunction can be prevented or reversed, at least partly, by tight glycemic control. But it worth mentioning that they observed such changes only in the first 6 months of tight glycemic control and after 12 months LV function parameters did not change.

The apparently contradictory results of different studies regarding effect of glycemic control can partially be explained by the statement published by Fang et al. (6) that diabetic cardiomyopathy appears to consist of two major components: the first being a short-term, physiological adaptation to metabolic alterations and could be reversible; whereas the second represents degenerative changes for which the myocardium has only limited capacity for repair.

In our study, patients who did not achieve improvement in glycemic control had a significant increase in IVS and LVPW. On the other hand, there was a significant decrease in ETacc and IVRT in the third examination when compared to first examination. Chlumsky et al. (33) stated that decompensation (lack of glycemic control) in diabetic patients without late complications leads to deterioration of diastolic function of the left ventricle, which is reversible if compensation with glycemic control occurs early. Shivalkar et al. (34) presented data showed an increasing occurrence of subclinical cardiac dysfunction and cardiovascular risk markers with duration in type I diabetic patients compared with age-matched controls. Similarly, Chrapko et al. (35) in a gated single positron emission tomography study in asymptomatic type 1 DM patients showed that four years after the basal study there is an increase of left ventricular dimensions and volumes. Suys et al. (18) found that young adult diabetic patients already have significant changes in left ventricular dimensions and myocardial relaxation. In addition, Mizushige et al. (36) in an animal study conclude that diabetes induced in rats causes alteration in left ventricular diastolic function, and these alterations could be tracked longitudinally by echocardiography and showed deterioration over time in such rats. Dent et al. (37) suggested that the early manifestation of diastolic dysfunction in diabetic hearts may relate to uncoupling of the contractile apparatus (which drives early relaxation), without concomitant increases in chamber stiffness (which produces more late diastolic changes) and occurs later as diabetes progress without good control.

Study limitations

1. Number of patients is small and must be done in a large scale.
2. Follow up study is difficult as patients usually missed due to death or noncompliant patients.

Conclusion

We conclude that, LV hypertrophy and diastolic dysfunction among diabetic patients is high. Glycemic control in diabetic patients could not improve LVH or diastolic dysfunction. On the other hand, failure to achieve glycemic control leads to deterioration in structural parameters. However, follow-up and early detection of left ventricular functional deterioration in young patients with type I DM contribute to better knowledge of diabetic cardiomyopathy and may help to prevent the natural progression of the disease. The present study also reinforce the need for similar additional studies, searching to clarify the physiopathology, the ways of prevention and the treatment of such dysfunction in diabetic patients.

We suggest that to maintain nor mal ventricular function in patients with DM apart from the duration of DM, more aggressive control of blood glucose levels are needed and must be started as early as possible. Children and young adolescents rarely have insight on regarding their disease, and their diet is accordingly difficult to control. 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. We recommend that close observation should begin early and should include detection of diabetic cardiac alterations, as well as other diabetic complications.

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