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Inas Abdul-Sattar Saad
Department of Pediatric,
Cairo University,
Cairo, Egypt

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Effect of Glycemic Control on the Progress of Left Ventricular Hypertrophy and Diastolic Dysfunction in Children with Type I Diabetes Mellitus

[1]Inas Abdul-Sattar Saad and [2]Tarek Salah Ibrahim

The present research evaluated the progression of left ventricular structural and functional changes in children and adolescent patients with type I DM and the effect of glycemic control on these changes. A Prospective, case-controlled, observational study was carried out in tertiary referral hospital in Holly Makkah-KSA including 135 young patients with type I DM recruited from the endocrinology clinic and were followed up in the hospital cardiac center unit. Patients were divided into 2 groups: group composed of 46 patients with type I DM and left ventricular hypertrophy (LVH+ve group) compared to another group, composed of 89 patients with type I DM but had a normal left ventricular echocardiographic parameters (LVH -ve group). All the studied patients were subjected to full history taking, clinical and cardiac examination. Electrocardiogram, laboratory tests for glycosylated hemoglobin, lipid profile, albuminuria and careful ecocardiographic examination were done. All patients were followed up and participated in a program for glycemic control. Echocardiographic follow-up was done thoroughly again for patients who had left ventricular hypertrophy (LVH) after two years. Our results showed that echocardiographic parameters after 2 years follow up showed statistically significant difference regarding cardiac structural and functional parameters in favor for the patients in group who achieved glycemic control. Also comparing echocardiographic parameters of those patients who achieved glycemic control to their baseline results showed that mean value of interventricular septal dimension (IVSd) decreased from 1.12cm to 1.03 ($p = 0.04$), posterior wall dimension (PWd) decreased from 1.07-0.97 ($p = 0.05$) however diastolic dysfunction represented by isovolumic relaxation time (IVRT) and E/A did not show a statistically significant change. Patients who did not achieve glycemic control showed worsening of their echocardiographic parameters: IVSd increased significantly ($p = 0.01$), E/A ratio showed a significant decrease ($p = 0.006$) and IVRT significantly increased ($p = 0.04$). We concluded that good glycemic control in diabetic patients could improve some structural parameters of the heart while failure to achieve glycemic control leads to deterioration in functional and structural parameters of the heart. Follow up and early detection of myocardial structural and functional changes 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.

Key words: DM, type I diabetes, diastolic cardiac dysfunction, glycemic control, children

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[1]Department of Pediatric, Cairo University, Cairo, Egypt
[2]Department of Child Health, National Research Center, Cairo, Egypt

INTRODUCTION

Diabetes has now reached epidemic proportions, affecting an estimated 110 million people worldwide. Around 12-20% of these patients are of type I DM (Epshteyn *et al*., 2003). The more frequent incidence of heart failure in diabetics even in the absence of ischemic or valvular heart disease, leads to the presumption that diabetes mellitus unfavorably affects the heart muscle by its complications (Berkova *et al*., 2003). Devereux *et al*. (2000) concluded that patients with diabetes had greater left ventricular wall thickness than non-diabetic individuals. Also Hairayama *et al*. (2001) 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) (1991) that demonstrated poor prognosis of heart failure in diabetic patients. A high prevalence of diastolic dysfunction with preserved systolic function was observed in asymptomatic type 1 diabetic patients (Karamitsos *et al*., 2006). This diastolic abnormality appears related to interstitial collagen deposition and LV hypertrophy that appear in the absence of hypertension (Fang *et al*., 2004). 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 (Fang *et al*., 2004). The relationship between myocardial hypertrophy and diastolic dysfunction and glycemic control is still a matter of debate (Cosson and Kevorkian, 2003). Cardiac catheterization, is the gold standard in assessing myocardial dysfunction as it appears to be a sensitive method for evaluating the manifestation and course of early diastolic cardiomyopathy as it can assess simultaneously volumes and pressures (Schannwell *et al*., 2002). Radionuclide angiography and Cine magnetic resonance imaging is an alternative sensitive approach (Iltis *et al*., 2004). Over the last two decades, Doppler echocardiography has emerged as an important and easy, non-invasive diagnostic tool providing reliable data on diastolic performance of the heart (Cosson and Kevorkian, 2003). In young patients information correlating type I DM with changes in left ventricular structure and function, are lacking.

The aim of the present study was to evaluate the progression of left ventricular structural and functional changes in children and adolescent patients with type I DM and the effect of glycemic control on these changes.

MATERIALS AND METHODS

A prospective, case-controlled, observational study was carried out in Al-Nour Specialist Hospital (tertiary referal hospital Holly Makkah-KSA).

Study group and design: Hundred and thirty five young patients with type 1DM were recruited from the endocrinology clinic from July 2001 to July 2004 and enrolled in the present study, examined in the pediatric cardiology unit and followed up for two years. Age of our patients ranged from 4-16 years with a mean of 10.76±5.23 years. Female to male ratio was around 2:3.

All the studied patients were subjected to full history taking and Careful clinical and cardiac examination in the pediatric cardiology clinic. Blood samples were taken and examined for glycosylated hemoglobin and lipid profile. Urine samples were tested for the presence of albuminuria. Standard 12-lead ECG using Agilent digital ECG, was done for all patients. All data were collected at the start of the study (baseline).

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: vived 7 Pro, GE Vingmed ultrasound AS-N190, Horton-Norway equipped with 3 and 7 MHZ transducers). Simultaneous electrocardiogram (standard lead II) and videotape recording were used. Left ventricular end diastolic dimensions, left ventricular end systolic dimensions in addition to interventricular septum and posterior wall thickness dimensions in diastole and systole were measured by standard M-mode guided by two-dimensional echocardiography. Left ventricular systolic function represented by Ejection Fraction (EF) and Fractional Shortening (FS), diastolic function represented by Isovolumetric Relaxation Time (IRT) and Mitral inflow velocity ratio (E/A) were obtained digitally. Left ventricular hypertrophy was defined as wall thickness of Inter-Ventricular Septum (IVS) or Posterior Wall (PW) or both > 2 SD above normal) and diastolic dysfunction (defined as prolonged isovlumic relaxation time ≥ 90 milliseconds or decreased E/A mitral inflow ≤ 1) (Snider *et al*., 2002).

Patients were divided into 2 groups: group composed of 46 patients with type I DM and Left ventricular hypertrophy (LVH +ve group) compared to another group composed of 89 patients with type I DM but had a normal left ventricular echocardiographic parameters (LVH-ve group).

Follow-up: All patients were followed up in the pediatric endocrinology clinic and participated in a program for glycemic control. Glycemic control improvement was defined as >1% absolute decrease of glycosylated hemoglobin (HA1c). Patients who had LVH were followed up thoroughly after two years to reassess left ventricular echocardiography parameters and 3 patients missed the follow-up.

Statistical analysis: Statistical analysis was done using unpaired t-test, Fisher's Exact test, chi-square test and Wilcoxon's Rank Sum test as appropriate. A probability (p) of less than 0.05 was accepted as statistically significant. Data are expressed as mean±SD, unless stated otherwise

RESULTS

Present research carried out 135 patients with type I DM, their age ranged from 5.6 to 14 years with a mean of 9.5±4.8 years, male to female ratio was 2:3. Forty six patient of the study group (34%) had left ventricular hypertrophy with diastolic dysfunction while the rest of patients had normal echocardiographic findings.

By observing Table 1 it is apparent that there was no statistically significant difference between the two groups regarding left ventricular systolic function, serum lipids, duration of illness (since the discovery of diabetes mellitus), albuminuria, body dimensions and blood pressure.

We investigated the two groups of patients trying to compare their level of HbA1c, though there was a trend for patients with LVH to have the level of HbA1c to be higher than those without LVH, but this trend was not significant statistically (p-value = 0.056) and the same could be applied to corrected QT interval. The mean level of HbA1c in patients with positive LVH was 10.3±2.7 and those without hypertrophy their mean HbA1c level was 9.6±2.8 and this indicated that both groups had unsatisfactory glycemic control.

After a follow-up period ranged from 1.8-2.2 years in the endocrinology clinic with trial to get better glycemic control for patients with +ve LVH, three cases lost follow-up. In the follow-up: from 43 cases who had LVH, 20 patients (46.5%) achieved improvement in their glycemic control (glycemic control +ve group) and the remaining 23 patients (53.5%) failed to achieve control (glycemic control -ve group). Table 2 show the comparison between both groups regarding progress of the echocardiographic LV changes parameters and apparently there was statistically significant difference between both groups in favor for the patients who achieved better glycemic control.

Table 1: Comparing clinical, Lab and Echo findings of the two diabetic groups

Parameters	LVH +ve group	LVH-ve group	p-value
IVSd (cm)	1.118±0.147	0.799±0.158	<0.001
PWd (cm)	1.07±0.262	0.648±0.118	0.005
E/A	1.2±0.34	1.6±0.26	0.041
IVRT (ms)	82±4	60±6	0.032
FS (%)	32±37	31±23	0.97
EF (%)	67±52	63±44	0.91
HbA1c	10.3±2.7	8.6±2.8	0.056
TG (mg dL^{-1})	102.4±47.1	88.7±55.8	0.35
Colestrol (mg dL^{-1})	180±39.8	178±39.5	0.86
LDL (mg dL^{-1})	103±46	99.2±25.1	0.78
HDL (mg dL^{-1})	61.9±11.1	58.9±16.9	0.63
Urinary albumen (mg dL^{-1})	1.25±0.08	1.28±0.12	0.75
Duration (Years)	4.51±3.8	4.61±4.1	0.91
BMI	21.6±4.1	22.3±3.2	0.39
Waist (cm)	61.9±13.4	59.9±15.5	0.41
Systolic BP	100.1±10.7	97.7±1	0.27
Diastolic BP	67.1±4.7	67.9±5.8	0.59
QTc (ms)	408±26	342±42	0.052

TG: Triglycerides, C: cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, BMI: Body Mass Index, QTc: corrected QT interval, ms: millisecond mg dL^{-1}: milligram/decilitre

Table 2: Echocardiographic parameters in patients achieved improved glycemic control compared to those who did not

Parameters	Glycemic control +ve group	Glycemic control -ve group	p-value
HbA1c (gm dL^{-1})	8.3±0.9	10±1.3	0.01
IVSd (cm)	1.03±0.11	1.26±0.14	0.031
PWd (cm)	0.97±0.23	1.16±0.42	0.035
E/A	1.27±0.27	1.04±0.32	0.047
IVRT (m sec)	82±8	90±6	0.031

HbA1c: Glycosylated hemoglobin, IVSd: Interventricular septum dimension, PWd: Posterior Wall Dimension, E/A: Mitral inflow velocity ratio, IVRT: Isovolumetricic Relaxation Time

Table 3: The changes of cardiac parameters in patients achieved glycemic control after 2 years follow-up

Parameters	Baseline parameter	Follow up parameter	p-value
IVSd (cm)	1.12±0.19	1.03±0.23	0.04
PWd (cm)	1.07±0.31	0.97±0.4	0.05
E/A	1.31±0.21	1.27±0.16	0.27
IVRT (m sec)	80±6.9	82±7.3	0.19

IVSd: interventricular septum dimension PWd: posterior wall dimension, E/A: Mitral inflow velocity ratio IVRT: isovolumetric relaxation time

By comparing echocardiographic parameters of those patients who achieved improvement in their glycemic control to their baseline results mean value of IVSd decreased from 1.12 cm to 1.03 (p = 0.04), PWd decreased from 1.07 to 0.97 (p = 0.05) however and diastolic dysfunction represented by IVRT and E/A though changed in favor for improvement but this was not a statistically significant change (Table 3).

Figure 1 showed the worsening of echocardiographic parameters in patients who did not achieve improvement in glycemic control: IVSd showed a statistically significant increase (p = 0.01), E/A ratio showed a significant decrease (p = 0.006) and IVRT significantly increased (p = 0.04) in these patients after 2 years follow-up, whereas Pwd showed a trend to increase

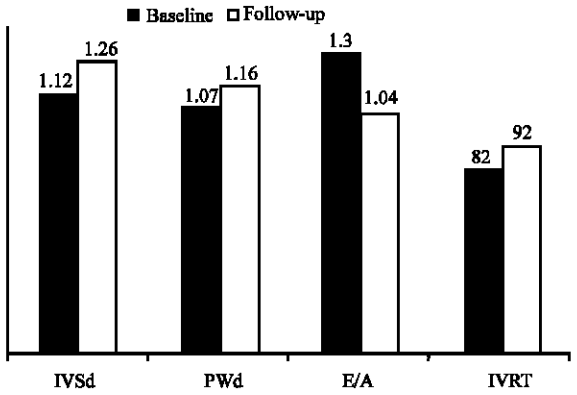

Fig. 1: Progress of cardiac parameters in glycemic control -ve patients

however this trend was not statistically significant (p value was 0.07). Systolic function represented by FS and EF was normal at baseline in both groups and did not change significantly in the follow-up.

DISCUSSION

Diabetes is a major risk factor for increased cardiovascular morbidity and mortality rates (Ebesthyne *et al*., 2003). 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 (Cosson and Kevorkian, 2003). Adult diabetic patients without clinical heart failure were reported to have hypertrophic, non-compliant left ventricles (Sato *et al*., 1999). Early determination of myocardial manifestations of DM is of major importance, since myocardial involvement considerably influences the prognosis of diabetic patients (Cosson and Kevorkian, 2003). Boyer *et al*. (2004) 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. Pertoni *et al*. (2005) concluded that there are often subclinical cardiac abnormalities in young diabetics resulting in impairment of diastolic function. Also, Stakos *et al*. (2005) 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. Echocardiography is one of the fastest growing procedures in cardiology and considered the cornerstone of diagnostic evaluation in patients with suspected left ventricular dysfunction (Senni *et al*., 1999).

In the current study, there was no statistically significant difference between diabetic patients suffering from left ventricular hypertrophy with diastolic dysfunction and those not having such changes regarding left ventricular systolic function, serum lipids profile, duration of illness (since the discovery of diabetes mellitus), albuminuria, body dimensions and blood pressure. This was comparable to results in the study conducted by Suys *et al*. (2004) regarding LV wall thickness involving adolescents with type I DM compared with the control. Left ventricular hypertrophy has been demonstrated to predict cardiovascular related mortality in adults with diabetes mellitus (Okin *et al*., 2004). However, Adel *et al*. (2006) stated that abnormal Left ventricular diastolic function abnormalities in patients with mean DM1 duration of 8.2 years were associated with glycemic control, free and total carnitine and LDL- and HDL-cholesterol levels and this could not be elicited in patients with mean DM1 duration 3.5 years. It worth mentioning that mean DM I duration in our study group is 4.55±56 years. In this study group patients' though there was a trend for patients with LVH to have the level of HbA1c to be higher than those without LVH, but this trend was not significant statistically. Other authors also reported that there is no correlation between HbA1c with the development of cardiovascular changes in children and adolescents with type I diabetes mellitus, which is similar to results of the current study (Lo *et al*., 1995; Giunti *et al*., 2003). In the same previous study, Giunti *et al*. (2003) reported that the left ventricualr systolic function was comparable in both diabetics and controls which was the same result obtained in our study. Similarly also, Giunti *et al*. (2003) concluded that diastolic abnormalities are common in patients with type I diabetes mellitus and are not related to the duration of the disease. Regarding BMI, present results paralleled results of Krishnan *et al*. (2004), who found no correlation between BMI and LV wall thickness. However, others stated that body mass index, surface area and blood pressure influence left ventricular mass and geometry (Fox *et al*., 2004). Some authors stated that decreased myocardial performance was associated with albuminuria in diabetic patients (Orem *et al*., 2004). In the current study, by investigating the association of left ventricular wall hypertrophy and diastolic dysfunction with urinary albumin excretion in diabetic patients, we found no statistically significant correlation between them. Similarly, Sato *et al*. (1999) failed to show a significant correlation between albumenuria and diastolic dysfunction in patients with type I DM, also Galicka-Latala *et al*. (2005) showed that diabetic nephropathy was not correlated with left ventricular

diastolic dysfunction in echocardiographic study. Annone *et al.* (2001) and Braga *et al.* (2005) showed same results in type II diabetic patients.

After a follow-up period of about two years, 46.5% of the LVH +ve group achieved improvement in their glycemic control. By comparing echocardiographic parameters of those patients who achieved improvement in their glycemic control to their baseline results mean value of LV wall thickness dimensions (IVSd and PWd) decreased significantly however diastolic dysfunction represented by IVRT and E/A did not show a statistically significant change. Aepfelbacher *et al.* (2004) showed similar results and concluded that improved glycemic control in patients with type 1 diabetes mellitus is associated with regression of septal thickness and left ventricular mass without significant effect on systolic or diastolic function. Also Weinrauch *et al.* (2006) 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.

Similarly, Shapiro *et al.* (1981) showed that Isovolumetric relaxation time was prolonged in diabetics and it was not affected by hypoglycemic therapy. Regan *et al.* (1981) in animal study demonstrated there is myocardial stiffness causing diastolic dysfunction in diabetic dogs, these changes could not be reversed with correction of hyperglycemia or prevented by insulin. Other studies have shown a lack of correlation between impaired diastolic function and improvement of HbA1c levels. All were performed in type 1 diabetics (Ruddy *et al.*, 1988; Lo *et al.*, 1995; Holzman *et al.*, 2002).

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 (Pitale *et al.*, 2000) that is similar to our results that showed no improvement of diastolic dysfunction. However, Fiorina *et al.* (2000) 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 (Poirier *et al.*, 2000). And Grandi *et al.* (2006) 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.* (2004) 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 present study, patients with baseline LVH and diastolic dysfunction who did not achieve improvement in glycemic control: IVS wall thickness and diastolic dysfunction changes deteriorated in these patients after 2 years follow-up, whereas PWd did not. Similarly Chlumsky (1994) 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 occur early. Shivalkar *et al.* (2006) 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.* (2006) in a Gated Single Positron emission tomography study in asymptomatic DM1 patients showed that four years after the basal study there is an increase of left ventricular dimensions and volumes. Suys *et al.* (2004) found that young adult diabetic patients already have significant changes in left ventricular dimensions and myocardial relaxation. Also, Mizushige *et al.* (2000) 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. Also, Dent *et al.* (2001) 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.

CONCLUSIONS

Good glycemic control in diabetic patients could improve some structural parameters of the heart while failure to achieve glycemic control leads to deterioration in functional and structural parameters of the heart.

Follow up and early detection of myocardial structural and functional changes 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.

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