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Assessment of Subclinical Cardiovascular Abnormalities in Type 1 Diabetic Children with Normal LDL Levels

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ABSTRACT

Background: *Children with type 1 diabetes mellitus (T1DM) are at risk for accelerated atherosclerotic changes and cardiac abnormalities rather than non-diabetics. However, little is known about cardiovascular changes for diabetic children with normal low-density lipoprotein. Here, we assessed atherosclerotic changes and cardiac function by sonography for patients with normal low-density lipoprotein.* ***Methods:*** *A prospective case control study included 38 type 1 Diabetes Mellitus children (aged 8 to 14 years) was performed with same number of matched children as controls. Blood pressure, body mass indices (BMI), glycosylated haemoglobin (HbA1c), complete lipid profile, intimal medial wall thickness measurements for carotid arteries (cIMT) and abdominal aorta (aIMT) with data of left ventricular function by echocardiography were determined for both groups.* ***Results:*** *We found aIMT (mean of 1.2 ± 0.4) and cIMT (mean of 0.52 ± 0.12) were significantly higher in the patient group (P<0.001). Although, aIMT was positively correlated to HbA1c (7.48 ± 0.76%, P<0.001) and negatively correlated to high density lipoprotein, no significant difference between aIMT or cIMT and age, duration of disease, BMI, and blood pressure. Moreover, no significant difference in LV systolic or diastolic function among the studied groups, however the Z score of end systolic dimensions and end diastolic dimensions were significantly changed for patient group ((P=0.012 and P=0.008 respectively).* ***Conclusion:*** *Subclinical atherosclerosis was detected among T1DM children with normal LDL and it was positively correlated to prolonged hyperglycemia and low level of HDL. However, subclinical cardiac function changes were minimal.*

Keywords: Accelerating atherosclerosis, Intimal media walls thickness, Dyslipidaemia, Glycosylated haemoglobin

Abbreviations: cIMT: Carotid Intimal-Medial Thickness; T1DM: Type 1 Diabetes Mellitus; HbA1c: Glycated Haemoglobin; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; LV: Left Ventricle; BMI: Body Mass Index

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a major cardiovascular risk. Diabetic patients have two-fold risk of death from cardio-vascular diseases (CVDs) as compared to non- diabetics [1]. Currently in Egypt, it is thought that T1DM incidence and prevalence showed an increase over the past 20 years [2]. The incidence of T1DM among children below 14 years is reported to be 8 per 100,000 populations per year [3]. Cardiovascular changes may present few years after the onset of the disease during childhood. Complex metabolic disturbances (chiefly hyperglycaemia and dyslipidaemia) in cardiomyocytes may lead to morphological and functional abnormalities of the myocardium [4]. Diabetic cardiomyopathy (DC) represents the adverse effects of the disease on the heart including heart failure. However, silent vascular changes of atherosclerosis were also reported by many studies over diabetic children through a sensitive non-invasive technique which was measurement of carotid artery intimal-medial thickness (cIMT) [5]. Childhood and adolescence are periods during which intensive education and treatment may delay the onset and progression of complications. Therefore, we were motivated to carry out this study over an T1DM children with controlled levels of low density lipoprotein (at least six months) in order to detect presence or absence of subclinical

atherosclerosis and myocardial function changes specially after some recent studies that supported idea of risk factors of CVDs were independently associated together in diabetic youth [6].

MATERIAL AND METHODS

The current study was case control study. The protocol was reviewed and approved by an institutional review board and the ethical approval for the study was obtained from the Ethical Review Committee of Alexandria Faculty of Medicine. On January 4, 2012 with No: 0101896, informed consents were obtained from all patient caregivers and the study was performed at Alexandria Main Children University hospital at Alexandria, Egypt from 2012 till 2013.

Patients

Total 38 children with type 1 DM, were following up at endocrinology clinic of Alexandria University Children Hospital enrolled in the study. Another 38 healthy children matching in age and sex were included as controls. The diagnosis of type 1 DM was based on the current criteria of the American Diabetes Association [7]. The inclusion criteria of study group included T1DM children below age of 15 years, minimally diagnosed for three years and with normal LDL levels at least for 6 months. While the study excluded all patients who had evidence or history of a clinically relevant systemic disease (e.g. systemic lupus erythematosus, growth hormone deficiency, etc

Methods

All participants were examined for determining the blood pressure (BP) and body mass indices (BMI). The biochemical profile has been performed for all for glycosylated haemoglobin (HbA1c) (7.5% target levels [8]), total cholesterol, triglycerides, and high-density lipoprotein concentrations (HDL-c). Meanwhile, low density lipoprotein (LDL) was estimated by using Friedewald equation:

LDL-c = Total cholesterol – (HDL-c + Triglyceride/5)

Cases and controls were subjected to transthoracic echocardiography though M-mode, 2-Dimensional and Doppler studies using a 5 MHz transducer of Madison 990 echocardiography by single person for estimation of systolic and diastolic left ventricular function; ejection fraction (EF), fraction shortening (FS), end-systolic, diastolic dimensions (EDD-ESD), early peak flow velocity (E) and atrial filling velocity (A) and interventricular septum thickness (IVS). Also, intimal medial wall thickness (IMT) measurements were obtained for the study and control groups though using a Toshiba Nemio Ultrasonic scanner with a 7.5 MHz transducer. Both carotid arteries were scanned 10 mm from the bifurcation of the common carotids. The value of the IMT was defined as the mean value of measurements between the right and left carotid arteries calculated from three consecutive measurements of the maximum far wall thickness on each side. Meanwhile, abdominal aorta was assessed anterior and posterior walls and followed distally until the aortic bifurcation. the image was focused on dorsal arterial wall of the most distal 15 mm of the abdominal aorta using a 13 MHz transducer as post mortem series have shown it is the most lesion-prone site (8 mm was the cut off level of normal) [9]. All data were fed to the computer and analysed using IBM SPSS software package version 20.0. Data are expressed as means, standard deviations and percentages. Comparisons between groups or within the same group were made using the Pearson coefficient and ANOVA test and others. $P<0.05$ was considered statistically significant.

RESULTS

Thirty-eight children with type 1DM were enrolled (16 males and 22 females) with mean of age 10.56 ± 3.2 year (ranged 7-14 years) and mean of disease duration 5.56 ± 2.4 years. Table 1. Another group of healthy children were matched as controls. Sixty-five percent of diabetic group were between age of 7 and 12 years. The daily dose of insulin ranged between 0.70 to 1.20 unit with mean of 1.02 ± 0.14 U/Kg. There was no significant difference in BMI and/or diastolic blood pressure between studied groups. However, systolic blood pressure was significantly higher in the diabetic group when compared to controls (98.25 ± 6.85 mmHg versus 91.63 ± 6.54 mmHg, $P<0.001$). The difference in HbA1c values was significant among the study group when compared to controls ($P<0.001$) with higher values among cases. The difference in HDL-C values between the studied groups were statistically significant being lower for the diabetic children in comparison to controls (50.72 ± 5.62 versus 59.0 ± 13.13 respectively and $P<0.001$) as shown in Table 1.

Table 1 Demographic, clinical, laboratory and ultrasound data of the studied groups

Data	Study group		Control group		P-value
	Range	Mean	Range	Mean	
Age	7-14 year	10.5 ± 1.7	8.0 - 12.0	9.98 ± 1.44	tp=0.103
Male	16 (60%)	-	15 (57.5%)	-	
Female	22 (40%)	-	23 (42.5%)	-	-
Duration	3.0 - 11.0	5.56 ± 2.40 y	-	-	-
Dose of insulin	0.70 - 1.20	1.02 ± 0.14	-	-	-
BMI	17.30 - 23.2	20.60 ± 1.86	17.40 - 23.20	20.49 ± 2.03	tp=0.797
Systolic BP (mmHg	90.0 - 110.0	98.25 ± 6.85	80.0 - 105.0	91.63 ± 6.54	<0.001*
Diastolic blood pressure (mmHg)	50.0 - 75.0	64.38 ± 5.33	55.0 - 75.0	64.0 ± 5.33	0.754
Total cholesterol level	116.0 - 292.0	172.88 ± 34.61	80.0 - 190.0	-113.18 ± 20.99	MWp <0.001*
LDL	40.0 - 127.0	90.47 ± 28.92	55.0 - 117.0	86.45 ± 19.27	-
HDL	38.0 - 60.0	50.72 ± 5.62	23.0 - 75.0	59.0 ± 13.13	<0.001*
Fasting blood glucose	87.0 - 210.0	139.0 ± 29.40	59.0 - 112.0	76.05 ± 12.31	<0.001*
HbA1c (%)	6.40 - 9.20	7.83 ± 0.76	4.40 - 5.90	4.95 ± 0.31	<0.001*
c IMT (mm)	0.31 - 1.00	0.52 ± 0.12	0.30 - 0.48	0.37 ± 0.05	<0.001*
a IMT (mm)	0.50 - 2.3	1. 2 ± 0.4	0.30 - 0.50	0.41 ± 0.05	<0.001*

cIMT: carotid intimal wall thickness, aIMT aortic intimal wall thickness, LDL: low density lipoprotein, HDL: high density lipoprotein, HbA1c: glycosylated hemoglobin, BMI: body mass index. *Statistically significant at $p \leq 0.05$

The sonographic data of the studied groups were summarized in Table 1. The difference in mean value of cIMT was a statistically significant being higher for diabetic children when compared to controls (0.52 ± 0.12 versus 0.37 ± 0.05, P<0.001). Moreover, cIMT was positively correlated to age and to the duration of the disease ($P \leq 0.05$) while it was significantly negative correlated to HDL-c (P=0.024) as shown in Table 2.

Table 2 Correlation between aIMT and cIMT with different risk factors of atherosclerosis in type 1 diabetic children

Variables	Statistics	cIMT	aIMT
BMI	r	-0.037	-0.23
	p	0.821	0.153
Duration	r	0.514*	0.527*
	p	0.001	<0.001
Age	r	0.456*	0.489*
	p	0.003	0.001
Systolic BP	r	0.021	0.289
	p	0.898	0.07
Hb A1c	r	0.196	0.903*
	p	0.765	<0.001
HDL-c	r	-0.356*	-0.728*
	p	0.024	<0.001
Triglycerides	r	0.007	0.019
	p	0.964	0.907

r: Pearson coefficient; * Statistically significant at $p \leq 0.05$; p: p-value for Mann Whitney test; HDL: High Density Lipoprotein; HbA1c: Glycosylated Hemoglobin; BMI: Body Mass Index

Additionally, aIMT for the study group (ranged 0.5 to 2.3 mm) was statistically significant higher when compared to controls (1.2 ± 0.4 versus 0.41 ± 0.05, P<0.001). Positive correlations were detected between aIMT and age, duration of the disease ($P \leq 0.05$) and with HbA1c (P<0.001) as shown in Table 2. A significant regression model (P<0.05) displayed the latter correlation in Figure 1.

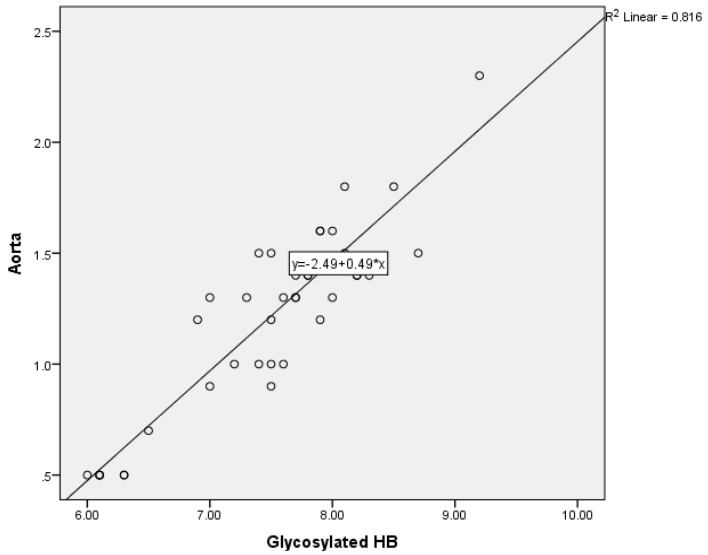

Figure 1 Positive correlation between glycosylated haemoglobin and aortic intimal medial wall thickness (aIMT)

Also, aIMT showed significant negative correlation to HDL-c (P<0.001) as shown in Table 2 and displayed in Figure 2.

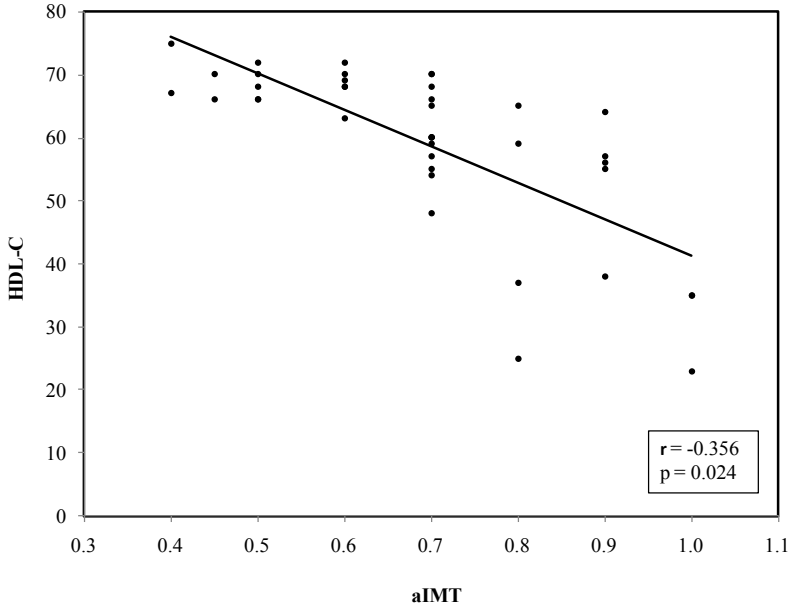

Figure 2 Negative correlation between HDL-C and aIMT

However, our results stated no significant correlation between cIMT or aIMT and body mass indices or blood pressure measurements. The abnormal measurements of a IMT (normal <0.8 mm) were superior to cIMT (normal <0.5 mm) in detecting subclinical atherosclerotic changes among patients group (86.25% cases in contrast to 56.5% cases).

Table 3 Echocardiographic data of studied groups

2D standard parameters	Diabetes children (n=38)	Control (n=38)	P-value
LV-EDD (mm)	41.8 ± 5.3	42.4 ± 4.1	0.6
Z-score LV-EDD	-0.29 (-0.89; 0.15)	0.17 (-0.63; 0.8)	0.008*
LV-ESD (mm)	26.3 ± 3.8	29.5 ± 3.4	0.16
Z-score LV-ESD	-0.15 ± 0.89	0.49 ± 0.86	0.012*
IVS-EDD (mm)	7.5 (6; 8.3)	6 (5.8; 7)	0.002*
Z-score IVS-EDD	0.36 (-0.01; 0.84)	-0.06 (-0.83; 0.5)	0.002*

PW-EDD (mm)	7 (6; 8)	7 (6; 7)	0.24
Z-score PW-EDD	0.53 (-0.3; 1)	0.38 (-0.16; 0.91)	0.94
LVM (g)	91 (70; 129.8)	82 (60.8; 129)	0.005*
LVEF (%)	64 (57.8; 68.3)	62 (59; 67.3)	0.97
E (cm/s)	96.8 ± 13.5	105.9 ± 20.6	0.053
A (cm/s)	53.5 (45.5; 61.3)	62 (47.8; 70.5)	0.1
E/A	1.9 (1.5; 2.1)	1.8 (1.6; 2.1)	0.9
EDD: End Diastolic Dimensions; ESD: End-Systolic Dimensions; IVS: Interventricular Septum Thickness; LVM: Left Ventricle Mass; LVEF: Ejection Fraction; E: Early Peak Flow Velocity; A: Atrial Filling Velocity; * Statistically significant			

Table 3 summarized echocardiographic data of patients and controls which revealed normal systolic function of the left ventricle for all. However, diastolic function of the heart as E, A and E/A ratio were abnormal in the diabetic group but with no statically significant difference to controls. Meanwhile, the Z score of end systolic dimension, end diastolic dimension and interventricular thickness were significantly changed for diabetic group when compared to controls (P=0.012, P=0.008 and P=0.002, respectively).

DISCUSSION

Diabetes mellitus has become a rapidly growing epidemic in recent decades with cardiovascular complication being the leading cause of death among adults. Atherosclerotic lesions develop slowly but continuously since childhood and it is believed to be accelerated if inflicted with type 1 diabetes as described by many studies over children [5,7]. Diabetic cardiomyopathy may result in heart failure with preserved ejection fraction [4,10]. The current study identified subclinical atherosclerosis changes among T1DM children although they had normal LDL levels. That was evidenced by significant higher values of cIMT and aIMT when compared to healthy controls. This matched a study done by Bayır who did not find a direct correlation of the LDL and peripheral vascular structural changes. The same was stated by Sukardi, et al. and other studies [11-13]. Although the vascular changes were positive for both carotid and abdominal aorta arteries, abdominal aorta changes were predominating among 83% of children in comparison to 56% for carotid artery. The atherosclerotic changes of aorta to carotid represented a ratio of 1.4 to 1 near to ratio found by Jarvisalo study who concluded that in children, abdominal aorta is early site for silent atherosclerosis similar to the reports by Harrington, et al. [14,15].

Our study highlighted the influence of risk factors on accelerating atherosclerosis for diabetic children. It showed a potent significant effect for prolonged hyperglycaemia on vascular changes through positive correlation between aIMT and HbA1C which matched Abdelghaffar, et al. [16], Özlem Bayır, et al. [11] and Sukardi, et al. [12]. As prolonged hyperglycaemia may facilitate the accumulation of glycated end products and increases the oxidative stress which stress, subsequently may lead to cell damage as explained by Singha, et al. specially with normal LDL values which clarify the main role of hyperglycemia on vascular changes. [17]. Moreover, most of study group (65%) were between 7-12 years old children with mean HbA1C of 7.47 (ranged 6.5-9.6), and showed subclinical atherosclerotic changes which emphasizes the recent updated recommendation of American Diabetic Association and ISPAD to keep diabetic children between 6 years and 18 years with HbA1C below 7.5% [6,18].

In agreement with Hanna Dis Margeirsdottir, et al. which concluded that diabetic children under euglycemic state after intensive insulin control showed subclinical vascular changes higher rather than healthy people and that because of other risk factors rather than prolonged hyperglycaemia [19]. Our results revealed that low levels of HDL-C were contributing in high values of aIMT and cIMT. Similarly, to results found by Abdelghaffar, et al. [16] and Faienza, et al. [20]. They explained the protective effect of HDL-c against atherosclerosis. Additionally, our study found that vascular changes are directly related to older age patients with prolonged duration of disease matched to Pozza, et al. [21], Harrington, et al. [15] and Gupta, et al. [22]. However, our study showed no significant effect of blood pressure which was contradictory to Järvisalo, et al. [23] but it matched Margeirsdottir study [19]. This difference may be due to the variations in measurement techniques or due to confounders like race, genetics, and environmental factors and or the effect of LDL.

The echocardiographic results in the current study, revealed normal LV systolic function for the cases which was in consistent with previous similar studies [24,25]. However, our results revealed no significant difference of LV diastolic function parameters between cases and controls which was contradictory to these studies but, it matched results of

Korean study [26]. The current study did not report any case with diabetic cardiomyopathy. This may be explained by lacking the effect of high LDL which may aggravate the functional changes of the heart. On the other side, there were significant increase in thickness of the inter ventricular septum and reduction in both left ventricular end systolic and end diastolic dimensions of patients rather than controls which was consistent with Hodzik, et al. It explained LV structural changes by the effect of metabolic derangement on cardiac remodelling [27]. This recommends further research to investigate cardiac changes for those patients specially after longer disease duration.

CONCLUSION

Type 1 diabetic children are at risk for accelerated subclinical atherosclerosis and myocardial structural or functional changes even with normal LDL levels under the effect of prolonged hyperglycaemia and low levels of HDL-c. Diabetic children deserve to be periodically screened for early cardiovascular changes by echocardiography and ultrasonography of abdominal aorta.

DECLARATIONS

Acknowledgment

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Conflict of Interest

The authors have no relevant conflict of interest to disclose.

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