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VALUATION OF SUBCLINICAL CARDIOVASCULAR ANOMALIES IN CHILDREN WITH TYPE 1 DIABETES MELLITUS BY 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.*

Place and Duration: *In the Department of Pediatrics and Radiology of Benazir Bhutto Hospital Rawalpindi for one-year duration from March 2019 to February 2020.*

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 less than 0.001). Although, aIMT was positively correlated to HbA1c (7.48 ± 0.76%, P less than 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: *Acceleration of atherosclerosis, Intimal media walls thickness, dyslipidemia, glucose and hemoglobin.*

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INTRODUCTION:

Type 1 diabetes (T1DM) is an important cardiovascular risk. The risk of dying from cardiovascular disease (CD) in patients with diabetes mellitus is twice as high as in patients without diabetes. The cult and prevalence of T1DM in Egypt is now believed to have increased over the past 20 years[1-2]. Cardiovascular changes can occur several years after the onset of the disease in childhood. Complex metabolic changes in cardiomyocytes (especially hyperglycemia and dyslipidemia) can lead to morphological and functional abnormalities of the heart muscle. Diabetic cardiomyopathy (DC) represents the side effects of heart disease, including heart failure. However, in many studies on children's diabetes, silent vascular atherosclerosis has also been reported with a precise non-invasive technique that measures almost medial carotid artery thickness (cIMT)[3-4]. Childhood and adolescence are periods in which intensive education and treatment can delay the onset and progression of complications[5-6]. Therefore, after several new studies that specifically support the idea of CVD risk factors, we were motivated to do this study on low-density lipoprotein (at least six months) controlled levels to determine the presence or absence of subclinical atherosclerosis and changes in myocardial function[7-8].

MATERIALS AND METHODS:

The current study was a case control study held in the Department of Pediatrics and Radiology of Benazir Bhutto Hospital, Rawalpindi for one-year duration from March 2019 to February 2020 for one-year duration from March 2019 to March 2020. The study was reviewed and approved by the Ethics Review Committee of the Faculty of Medicine.

Patients

A total of 38 children with type 1 DM were observed at the endocrinology department. 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 scanned to determine blood pressure (BP) and body mass index (BMI). The biochemical profile was created for everyone for hemoglobin (HbA1c) (7.5% target level, total cholesterol, triglycerides and high-density lipoprotein (HDL-c) glucose levels. Meanwhile, Low Density Lipoproteins (LDL) were estimated by Friedewald's equation: LDL-c = total cholesterol - (HDL-c + triglyceride / 5). using a Madison 990 5 MHz echocardiography probe by one person to evaluate left ventricular systolic and diastolic function; ejection fraction (EF), fraction shortening (FS), end-systolic, diastolic dimensions (EDD-ESD), early peak flow velocity (E) and atrial filling velocity (A), and ventricular septal thickness (IVS). Medial intimal wall thickness (IMT) measurements were also obtained in the test and control groups 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 carotid arteries. The IMT value was defined as the mean value of the measurements between the right and left carotid arteries, calculated from three consecutive measurements of the maximum thickness of the distal wall on each side. In the meantime, the anterior and posterior abdominal aorta was assessed and followed distally up to aortic bifurcation. the image was focused on the wall of the dorsal artery of the most distal 15 mm of the abdominal aorta using a 13 MHz probe, as the postmortem series showed that this is the most susceptible site to damage (8 mm was the normal cut-off point). All data was transferred to the computer and analyzed using IBM SPSS version 20.0 software package. Data are expressed as means, standard deviations and percentages. Comparisons between groups or within the same group were performed using the Pearson's coefficient and ANOVA and others. A P below 0.05 was considered statistically significant.

RESULTS:

38 children with type 1 diabetes (16 men and 22 women) with mean age 10.56 ± 3.2 years (range 7-14 years) and mean disease duration 5.56 ± 2.4 years were included in the study. Table 1. Another group of healthy children was selected as a control group. Sixty-five percent of people with diabetes were between the ages of 7 and 12. The daily insulin dose ranged from 0.70 to 1.20 units with an average of 1.02 ± 0.14 units / kg. There were no significant differences in BMI and / or diastolic blood pressure between the study groups. However, systolic blood pressure was significantly higher in the diabetic group compared to the control group (98.25 ± 6.85 mmHg versus 91.63 ± 6.54 mmHg, P less than 0.001). The difference in HbA1c values was significant in the study group compared to the control group (P <0.001) with higher values among the cases. The difference in HDL-C values between the study groups was statistically significant and was lower for children with diabetes compared to the control group (50.72 ± 5.62 versus 59.0 ±

13.13, respectively, and P less than 0.001), which 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 ≤ 0.05

The sonographic data of the studied groups are summarized in Table 1. The difference in the mean value of cIMT was statistically significant and was higher in diabetic children compared to the control group (0.52 ± 0.12 vs. 0.37 ± 0.05, P less than 0.001) . In addition, cIMT was positively correlated with age and disease duration (P ≤ 0.05) while it was significantly negatively correlated with 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 ≤ 0.05; p: p-value for Mann Whitney test; HDL: High Density Lipoprotein; HbA1c: Glycosylated Hemoglobin; BMI: Body Mass Index

Additionally, the aIMT value for the study group (in the range from 0.5 to 2.3 mm) was statistically significantly higher than in the control group (1.2 ± 0.4 versus 0.41 ± 0.05, P less than 0.001). Positive correlations were detected between aIMT and age, disease duration (P ≤ 0.05) and HbA1c (P less than 0.001) as shown in Table 2. However, our results showed no significant correlation between cIMT or aIMT and body mass indexes or blood pressure measurements. Abnormal IMT measurements (normal below 0.5 mm) in detecting subclinical atherosclerotic lesions in a group of patients (86.25% of cases versus 56.5% of 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 summarizes the echocardiographic data of patients and controls which revealed normal left ventricular systolic function in all of them. However, diastolic cardiac function as a ratio of E, A, and E / A was abnormal in the diabetic group, but no statistically significant difference compared to the control group. In the meantime, the Z-score of end-systolic dimension, end-diastolic dimension, and ventricular thickness in diabetic patients changed significantly compared to the control group (p = 0.012, p = 0.008 and p = 0.002, respectively).

DISCUSSION:

Diabetes has become a rapidly growing epidemic in recent years, becoming the leading cause of death among adults with cardiovascular complications. Atherosclerotic injuries develop slowly but continuously from childhood and are believed to accelerate if you believe type 1 diabetes, as explained in many studies on children. Diabetic cardiomyopathy can cause heart failure with a preserved ejection fraction. In the current study, changes in subclinical atherosclerosis were detected in children with T1DM, but LDL levels are normal[9-10]. This was seen in higher important CIMT and AIMT values than in healthy controls. This coincided with a study conducted by Bayer, which did not directly correce ldl and peripheral structural changes in the vessels. The same sukardi, and is determined by the ark. and other studies. Although vascular changes in the carotid arteries and abdominal aorthian were positive, changes in the abdomen were dominated by 56% of children in the carotid artery. Atherosclerotic lesions, from aortic to cervical, accounted for a ratio of 1.4 to 1 in the Jarvisalo study, which found that abdominal aorta is the first region of quiet atherosclerosis similar to Harrington[11]. Our study highlighted the impact of risk factors on accelerating atherosclerosis in children with diabetes. Abdelghaffar, et al. Azlem Bayer et al. positive correlation between aIMT and HBA1C and a strong significant effect on long-term hyperglycemia in vascular lesions. and Sukardi, et al. Long-term hyperglycemia can facilitate the accumulation of glycemia and cause cell damage, as explained in Singha, et al, as stress increases more oxidative stress. with normal LDL values, which clearly explain the role of hyperglycemia in vascular lesions. In addition, the majority of the working group (65%) between the ages of 7 and 12 years, and the average HBA1C was 7.47 (oscillating 6.5-9.6), and the American Diabetes Association and ISPAD showed subclinical atherosclerotic changes that highlighted hba1c's updated recommendation to keep children with diabetes aged 6 to 18 years[12]. After intensive insulin control, children with diabetes with euglycemic disease showed higher subkalic vascular changes than healthy individuals and

occurred due to other risk factors instead of long-term hyperglycemia. Our results showed that low HDL-C levels contribute to high aIMT and cIMT values. Similarly, abdelghaffar, et al. and Faienza, et al. Explained the protective effect of hdl-c against atherosclerosis[13]. In addition, our study showed that vascular changes are directly related to long-term elderly patients in combination with pose and others. and Gupta, et al. However, our research showed that J-rvisalo was contradictory and the arc had a significant effect on blood pressure. But it coincided with Margeirsdottir's work. This difference may be due to differences between measurement techniques or founders, such as race, genetic and environmental factors, and the effects of LDL. In the current study, echocardiography revealed normal systolic function vi in cases consistent with previous similar studies[14]. However, our results did not show a significant difference between facts and controls that contradict these studies, but corresponded to the results of the Korean study. Cases of diabetic cardiomyopathy have not been reported in the current study. This can be explained by the lack of a high LDL effect, which can exacerbate functional changes in the heart. On the other hand, instead of a significant increase in the thickness of the interventricular septum and hodzic-compliant controls, both the systolic dimensions of the left end of patients and the last diastolic patients decreased. Vi explained the structural changes with the effect of metabolic disorders on the reconstruction of the heart[15]. It specifically recommends more research to examine changes in the heart for these patients after a longer period of illness.

CONCLUSION:

Children with type 1 diabetes are at risk of accelerated subclinical atherosclerosis and structural or functional changes in the heart muscle despite normal LDL levels under the influence of prolonged hyperglycemia and low LEVELS of HDL-c. Children with diabetes deserve periodic examination of early changes in the cardiovascular system with echocardiography and ultrasound of the abdominal aorta.

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