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Investigating Carotid Intima Media Thickness in Children with Type 1 Diabetes and Its Relationship with HbA1c, Cholesterol, Duration of Disease and BMI: A Cross-Sectional Study

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Abstract

Background: internal carotid intima thickness has been identified as a predictor of atherosclerosis. Patients with type 1 diabetes are at risk for macrovascular complications. Atherosclerosis is 2 to 4 times more common in patients with diabetes, which exposes them to mortality and morbidity. The aim of this study was to determine the thickness of internal carotid intima thickness in children and adolescents with type 1 diabetes and its relationship with cardiovascular risk factors in Iranian children and adolescents with type 1 diabetes.

Method: The present study is a cross-sectional study that was performed in Mofid and Imam Hossein hospitals in Tehran from 2020 to 2021. A total of 91 patients with type 1 diabetes in the age range of 6-18 years, who have been diagnosed with diabetes for at least three years, were included in the study as a diabetic group.

Result: In total, 91 children and adolescents with type 1 diabetes were included in this study, of which 44 (48.4%) were boys and 47 (51.6%) were girls. The mean age of patients was 12.24 ± 3.17 and ranged from 6 to 18 years. The mean age of the patients at the time of diagnosis was 5.86 ± 2.98. In this study, blood pressure of 6 patients (6.6%) was abnormal and the rest had normal blood pressure. In addition, the mean duration of disease in this study was 6.3 ± 2.57 years. The insulin of most patients (93.2%) was Analogue and only 8.8% of patients used Neutral Protamine Hagedorn (NPH) and Regular. The thickness of the intima of the right internal carotid artery is 0.54 ± 0.05 and the thickness of the intima of the left internal carotid artery is 0.48 ± 0.07.

Conclusion: According to the results of this study, none of the factors of disease duration, age of onset, blood pressure, cholesterol, triglycerides, LDL (Low-Density Lipoprotein), HDL (High-Density Lipoprotein), HbA1C (Hemoglobin A1c), history of CHD (Coronary Heart Disease) and hyperlipidemia were significantly associated with the thickness of the intima of internal carotid artery. However, body mass index showed a significant relationship with the thickness of the left internal carotid intima.

Key Words: Blood Pressure, BMI, Carotid Intima Media Thickness, Cholesterol, coronary heart disease, HbA1c, Type 1 Diabetes, Pediatrics.

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1- INTRODUCTION

Diabetes is associated with an increased risk of cardiovascular problems. Measurement of internal carotid intima thickness is a non-invasive factor for the evaluation of subclinical atherosclerosis and is significantly increased in type 1 diabetes [1]. Increased thickness of the internal carotid intima is associated with cardiovascular events [2]. Studies have shown that the atherosclerotic process in the vascular endothelium of diabetic patients begins in childhood [3], so early detection of these changes and associated risk factors can lead to appropriate interventions to prevent disease progression at the beginning of the atherosclerosis process. Studies have shown that modulating cardiovascular risk factors such as overweight, hypercholesterolemia and hyperglycemia leads to preventing the progression, and even reducing the thickness of the internal carotid intima [4]. In a study to investigate the relationship between glycemic control and the progression of atherosclerosis in diabetic patients, it was found that the mean hemoglobin A1c (HbA1c) was associated with an increase in the thickness of the internal carotid intima [5]. On the other hand, in another study, HbA1c and the thickness was not found to be significantly correlated with the amount of the internal carotid intima [6]. In a study in Brazil, a positive relationship was found between the duration of the disease and the thickness of the internal carotid intima [6]. It is useful to identify diabetic children at risk for coronary heart disease (CHD) using non-invasive methods, to control risk factors. On the other hand, this study provides the basis for longitudinal and follow-up studies of risk factors in the future. Few studies have evaluated risk factors in children with type 1 diabetes. The present study aimed to investigate carotid intima-media thickness in Iranian children and adolescents with type 1 diabetes and its relationship with HbA1c, cholesterol, disease duration, and BMI (Body Mass Index).

2- MATERIALS ANDMETHODS

2-1. Design and sampling

The present study is a cross-sectional study that was performed in Mofid and Imam Hossein hospitals in Tehran from 2020 to 2021. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. Through convenient sampling, a total of 91 patients with type 1 diabetes in the age range of 6-18 years, who have been diagnosed with type 1 diabetes for at least three years, were included in the study as the diabetic group.

2-2. Inclusion and exclusion criteria

The diabetic group included children and adolescents aged 6-18 years with type 1 diabetes under treatment with Neutral Protamine Hagedorn (NPH) and regular insulin or analog insulin; they were diagnosed with type 1 diabetes for at least three years, and had a desire to participate in the study. Exclusion criteria were having other autoimmune diseases, chronic drug use, congenital heart disease, history of kidney disease, and dissatisfaction of individuals or their parents.

2-3. Data collection

At the beginning of the study, patients' information including age, sex, type of insulin used, age of diagnosis of type 1 diabetes, history of hyperlipidemia in parents, history of chronic heart disease (CHD) in first-degree relatives (before the age of 55 in men and 65 in women) were recorded. Height and weight were measured and recorded by a trained person by standard methods in meters (m) and kilograms (kg), respectively. Height in the barefoot position was measured by a standing wall-mounted meter and weight by a Seca scale. Blood pressure was measured twice, 30 minutes apart while

the patient was sitting for 5 minutes, and the average of the two measurements was taken as the mean blood pressure. A sonographer measured carotid intima-media thickness (CIMT) in the supine position in B-mode with a linear probe (frequency more than 7Hz). This measurement was in the wall away from the probe of the proximal part of the common carotid artery and before the bulb in the longitudinal view, which was measured 3 times for each patient, and a numerical average was recorded.

Blood samples were taken from all subjects at 7-8 in the morning in the hospital laboratory (Mofid and Imam Hossein hospitals) and used for laboratory tests. Laboratory assays included triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol, measured with an autoanalyzer. HbA1C was measured in patients by high performance liquid chromatography (HPLC). The laboratory sample was taken while the patient had not had an episode of diabetic ketoacidosis in the past month. Body mass index (BMI) was calculated using the formula weight (kg) / height squared (m).

3- RESULTS

3-1. Demographic characteristics

A total of 91 children and adolescents with type 1 diabetes were included in this study. Among them, 44 (48.4%) were boys and 47 (51.6%) girls. The mean ± standard deviation of the current age of patients was 12.24 ± 3.17 and ranged from 6 to 18 years. The age difference between the two sexes was not significant (P = 0.629). **Table 1** shows the results of the demographic profile.

Table-1: Demographic characteristics of the studied patients

Variable	Mean ± standard deviation	Minimum	Maximum
Age	12.24 ± 3.17	6	18
Weight (kg)	44.93 ± 15.62	13	83
Height (cm)	150.58 ± 17.86	98	187
Sex	N (%)	-	-
Girl	47 (51.6)	-	-
Boy	44 (48.4)	-	-

In addition, **Fig. 1** shows the frequency status of body mass index percentiles. According to this chart, the 50^{th}-to-75^{th} percentile has the highest frequency of body mass index.

3-2. Clinical characteristics of patients

The mean ± standard deviation of the patients' age at the time of diagnosis was 5.86 ± 2.98 and ranged from 1 to 13 years.

In this study, the blood pressure of 6 patients (6.6%) was abnormal for age and the rest had normal blood pressure for age. In addition, the duration of the disease in this study was 6.3 ± 2.57 years and ranged from 3 to 14 years. The underlying diseases of the subjects included anemia, seizures, and asthma, which are shown in **Table 2**. Insulin type in most patients (91.2%) was analog and only 8.8% of patients used NPH and regular insulin. **Table 2** shows the clinical characteristics of the studied patients.

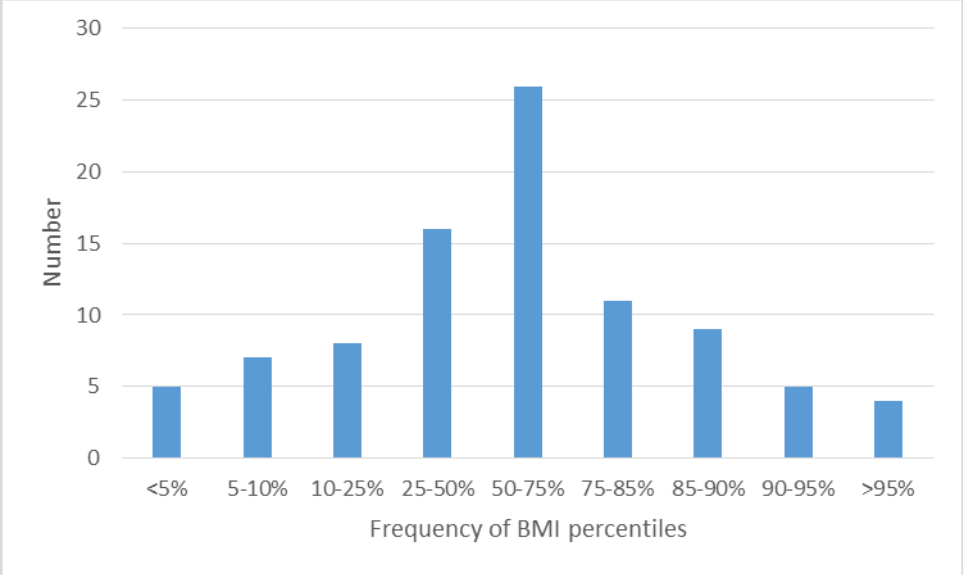

Fig. 1: Frequency status of BMI percentiles

Table-2: Clinical characteristics of the studied patients

Variable	Mean ± standard deviation	Minimum	Maximum
Age of diagnosis	5.86 ± 2.98	1	13
Duration of the disease	6.3 ± 2.57	3	14
HbA1C	9.24 ± 1.82	5.75	14.8
Cholesterol	165.03 ± 30.51	105	275
Triglyceride	106.17 ± 48.55	30	309
LDL	92.27 ± 26.31	35	180
HDL	52.16 ± 12.32	32	99
Variable		N (%)	
Blood pressure	Normal for age	85 (93.4)	
	Abnormal for age	6 (6.6)	
CHD history in the family	Yes	25 (27.5)	
	No	66 (72.5)	
History of hyperlipidemia in the family	Yes	42 (46.2)	
	No	49 (53.8)	
Insulin type	NPH, Regular	8 (8.8)	
	Analog	83 (91.2)	

3-3. Analytical results

The thickness of the right and left internal carotid intima was measured. The thickness of the right carotid intima was 0.54 ± 0.05 and the left was 0.48 ± 0.07.

The relationship between the left and right internal carotid intima thickness was evaluated with different factors. Results indicate that none of the factors of disease duration, age of onset, blood pressure, cholesterol, triglyceride, LDL, HDL, HbA1C, history of CHD, and hyperlipidemia in the family has no significant relationship with the thickness of the intima of the right and left internal carotid arteries (**Table 3**).

Table-3: Relationship between disease factors and internal carotid intima thickness

Carotid intima thickness	Predictor	B	Std.Error	Beta	t	P-value
Right	Duration of the disease	0.000	0.019	0.001	0.007	0.995
	Age of onset of the disease	0.007	0.016	0.048	0.447	0.656
	Systolic blood pressure	0.004	0.005	0.09	0.842	0.402
	Diastolic blood pressure	0.005	0.005	0.097	0.909	0.366
	Cholesterol	- 0.002	0.002	- 0.113	- 1.071	0.287
	Triglyceride	0.000	0.001	- 0.047	- 0.443	0.659
	LDL	- 0.001	0.002	- 0.058	- 0.535	0.594
	HDL	- 0.004	0.004	- 0.115	- 1.079	0.284
	HbA1C	0.002	0.027	0.007	0.063	0.95
	CHD in family	- 0.044	0.108	- 0.043	- 0.408	0.684
	Hyperlipidemia in family	0.141	0.096	0.153	1.464	0.147
	BMI	0.024	0.025	0.102	0.965	0.337
Left	Duration of the disease	- 0.001	0.003	- 0.024	- 0.224	0.823
	Age of onset of the disease	0.001	0.003	0.059	0.555	0.580
	Systolic blood pressure	0.000	0.001	- 0.033	- 0.309	0.758
	Diastolic blood pressure	0.001	0.001	0.102	0.957	0.341
	Cholesterol	2.06	0.000	0.008	0.079	0.938
	Triglyceride	0.000	0.000	0.083	0.784	0.435
	LDL	0.000	0.000	- 0.045	- 0.411	0.682
	HDL	0.000	0.001	0.031	0.289	0.774
	HbA1C	0.003	0.004	0.078	0.736	0.464
	CHD in family	- 0.006	0.018	- 0.038	0.359	0.720
	Hyperlipidemia in family	0.022	0.016	0.143	1.365	0.176
	BMI	0.011	0.004	0.290	2.854	0.005

However, body mass index showed a significant relationship with the thickness of the left internal carotid intima (P = 0.005). However, this relationship between BMI and the thickness of the intima of the right internal carotid was not significant (P = 0.337).

4- DISCUSSION

The aim of this study was to determine the thickness of internal carotid intima in children and adolescents with type 1 diabetes and its relationship with cardiovascular risk factors in Iranian children and adolescents with type 1 diabetes.

According to the results of this study, the mean thickness of the right carotid intima was 0.54 ± 0.45 and, on the left, it was 0.48 ± 0.07. The relationship between carotid intima thickness and various factors was evaluated and the results indicate that none of the factors of disease duration, age of onset, blood pressure, cholesterol, triglyceride, LDL, HDL, HbA1C, history of CHD and hyperlipidemia in the family, have any significant relationship with the thickness of the right and left carotid intima. However, body mass index showed a significant relationship with the thickness of the left internal carotid intima (P = 0.005), while the relationship between BMI and the thickness of the intima of the right internal carotid was not significant (P = 0.337).

These results were similar to those of the study by Samahy et al., in which no

significant relationship was found between carotid intima thickness and TG, Cholesterol, and HbA1C [7]. In the study of Park et al., Similar to the results of the present study, a positive relationship was reported between the thickness of the internal carotid intima and obesity [8]. Also, in the studies of Gul et al. [9] and Pozza et al. [10], no significant relationship was found between the mean thickness of the internal carotid intima and HbA1c. Another study indicated that unlike endothelial dysfunction, structural changes were not associated with a single parameter such as HbA1c at a young age [10]. In a study by Friedemann et al., similar to the present study, having a body mass index outside the normal range was found to significantly increase the thickness of the internal carotid intima and the risk parameters of cardiovascular disease in school children [11]. In the study by Bohm et al., A positive relationship was found between the increase in internal carotid intima thickness and BMI only in girls. However, in boys, the correlation between the increase in internal carotid intima thickness and BMI could not be confirmed [12]. In the study by Jordan et al., The results of a univariate analysis of potential factors affecting the thickness of the internal carotid intima were examined. In this study, as in the present study, apart from a slight increase in chronological age and body height, the thickness of the internal carotid intima and the thickness of the femoral intima were positively correlated with BMI [13]. In the study by Mittleman et al., the thickness of the internal carotid intima in men and in African-Americans was significantly more than that in women and other ethnic groups, respectively. In this study, as in the present study, there was no association between age, diastolic blood pressure, or fasting levels of triglycerides, total cholesterol, or low-density lipoprotein levels and thickness of the internal carotid intima, regardless of gender or ethnic background [14]. The results of this study were inconsistent with those of Fusaro et al. [6] and Rodriguez et al. [15], both of whom reported that carotid intima thickness was significantly higher in diabetic patients; and it was associated with cardiovascular disease risk factors. One hypothesis for the cause of this discrepancy could be that the mean age of the subjects in the study of Fusaro et al. was higher than that of the subjects in the present study and also the mean duration of disease was 3 years longer than the mean of this variable in our study.

4-1. Limitations of the study

One of the limitations of our study is the measurement of mean HbA1c over three months to a maximum of one year, and daily changes in blood glucose as well as long-term blood sugar levels were not evaluated. Studies have shown that the atherosclerotic process in the vascular endothelium of diabetic patients begins in childhood [3], so early detection of these changes and associated risk factors can lead to appropriate interventions to prevent disease progression at the beginning of the atherosclerosis process. Although cardiovascular risk factors have been identified in diabetic patients, the importance of each of them separately needs to be further evaluated in prospective studies.

5- CONCLUSION

According to the results of this study, none of the factors of disease duration, age of onset, blood pressure, cholesterol, triglyceride, LDL, HDL, HbA1C, history of CHD and hyperlipidemia in the family have a significant relationship with the thickness of the internal carotid intima. However, body mass index showed a significant relationship with the thickness of the left internal carotid intima. The relationship between body mass index and internal carotid intima thickness indicates

that this variable is more predictive than other variables such as cholesterol, disease duration, HbA1c and LDL, HDL, and triglyceride levels. The Systematic Review by Lamotte et al., on studies from 1986 to 2010, which examined the parameters of obesity, insulin-dependent diabetes, dyslipidemia, hypertension, and chronic renal failure in relation to internal carotid intima thickness, showed that Despite the different methods of measuring the thickness of the internal carotid intima, carotid intima-media thickness (CIMT) increased significantly in 55 of 67 studies and confirms that premature vascular injury in the pediatric population will increase the risk of future vascular disease [16]. Due to the differences between this study and other studies, as well as the limitations in measuring blood sugar and the extent of its changes, it can be suggested that prospective and longitudinal studies be performed to further investigate these factors.

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