Carotid artery intima-media thickness in pediatric type 1 diabetic patients

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ABSTRACT

Objective: To compare the carotid artery intima-media thickness in pediatric type 1 diabetic patients with that in healthy control subjects matched for age, sex, height, weight, body mass index (BMI) and waist circumference.

Methods: Fifty diabetic patients and forty-five control subjects were enrolled into this observational, cross-sectional, controlled study. Carotid artery intima-media thickness (cIMT), flow-mediated dilation (FMD) and carotid stiffness index were measured by using a carotid Doppler and real-time ultrasound. Student's t, chi-square and Kolmogorov-Smirnov tests and Pearson's correlation coefficient were used for the statistical analysis.

Results: There were no significant differences in the groups for age, sex, height, weight, BMI and waist circumference (mean age 12.10±2.02 vs. 11.49±1.90 years, weight 41.14±11.28 vs. 40.88±11.68 kg, height 149.78±20.3 vs. 145.62±20.14 cm, BMI 18.49±2.64 vs. 18.26±2.59 kg/m^2, waist circumference 69.72±8.6 vs. 66.05±7.47 cm, respectively). A significantly higher cIMT was found in the patients with type 1 diabetes (0.49±0.05 vs. 0.44±0.03 mm; p<0.001). A higher carotid stiffness index was found in the diabetic group when compared with control group (3.11±0.46 vs. 2.6±0.29 mm; p<0.001). Carotid IMT was not affected by mean HbA1c level and median HbA1c level (r=0.112, p=0.437 and r=0.249, p=0.082).

Conclusion: Type 1 diabetes is associated with higher cIMT and carotid stiffness index in a pediatric population.

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Key words: carotid artery intima-media thickness, flow-mediated dilation, type 1 diabetes, carotid stiffness index

Introduction

Type 1 diabetes is an important risk factor for cardiovascular events. Individuals with diabetes have 2-fold to 4-fold increased risk of developing atherosclerotic diseases, which is inadequately explained by differences in the levels of traditional vascular risk factors (1). Observations from postmortem studies have indicated that atherosclerosis in young adults is associated with the prediabetic state (2). Therefore, subjects who are affected by type 1 diabetes in childhood may be at especially high risk of developing subsequent cardiovascular disease. Thus, there is considerable interest in defining factors responsible for the accelerated development of atherosclerosis in individuals with diabetes.

Advances in imaging techniques identify early vascular changes through noninvasive ultrasound; these findings include impaired vasodilation and thickening of the artery wall (3). Intima-media thickness (IMT) is a well-known marker for atherosclerosis in adults and is an independent predictor of multi-level atherosclerosis (4, 5). On the other hand, flow velocity in the carotid artery is strongly related to distentibility and vessel diameter. Its measurement constitutes a homodynamic parameter of vessel function (6).

A noninvasive ultrasound measure of carotid wall intima-media thickness (IMT) is a marker of generalized atherosclerosis that in adults correlates with the extent of coronary artery disease (7, 8) and predicts future cardiovascular events (9). Previous observations suggest that thickening of arterial IMT occurs in children with familial hypercholesterolemia (10, 11).

Therefore, carotid IMT may provide an index of atherosclerotic vascular process that can be used to study subclinical atherosclerosis in vivo in children.

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In children with type 1 diabetes, the measurement of the cIMT as a marker of incipient atherosclerosis may be clinically relevant. However, its ability to predict atherosclerosis in pediatric patients has been fairly investigated (1). Rare publications currently exist in Turkish patients. The present study was undertaken to evaluate carotid intima-media thickness in young children with type 1 diabetes. We measured arterial wall IMT in the common carotid arteries in young children with type 1 diabetes and in healthy control subjects matched for age, sex, and body size and assessed the effects of vascular risk factors.

Methods

Study design

Fifty diabetic patients and forty-five control subjects were enrolled into this observational, cross-sectional, controlled study. The groups were matched in terms of age, gender, and body size. The children with diabetes were recruited consecutively from the outpatient clinic of the Department of Pediatric Endocrinology, Dr. Behçet Uz Children Disease and Surgery Training and Research Hospital. The inclusion criteria for diabetic children were age 7 to 15 years, diabetes duration >12 months, normotensive, body mass index less than the age- and sex-specific <95th percentile and no chronic diseases other than type 1 diabetes. The mean duration of diabetes was 44.7±22.8 months. None of the diabetic children were taking regular medications other than daily insulin. The mean daily insulin dose was 1.12±0.34 IU/kg (range 0.74 to 1.63 IU/kg). None of the diabetic patients had evidence of microvascular complications, such as diabetic retinopathy, neuropathy, or microalbuminuria. In the diabetic group, the mean glycosylated hemoglobin (HbA1c) level was 9.17±2.48% (range 8.1% to 14.2%; reference range 4.7% to 5.7%), and urinary albumin to urinary creatinine ratio was 0.70±0.44 mg/mmol. Participants did not differ in any clinical characteristics from the entire eligible diabetic clinic population of the same age. The control group was recruited from age and sex matched healthy individuals (n=45).

The healthy control children included in the study were friends of the diabetic children studied and children of the outpatient clinic of the Department of Pediatrics. Written informed consent was acquired from the legal guardians of the children. The study was conducted according to the Declaration of Helsinki, and the study protocol had been approved by the local Ethics Committee.

Study protocol

Ultrasound studies

All studies were performed with a GE vivid 3s (Vingmed Ultrasound AS, Horten, Norway) with a 5-10 MHz linear-array transducer by previously described techniques (12). All ultrasound scans were performed by a single experienced vascular sonographer. The studies were performed in the morning between 7 and 9:30 AM in a fasting subject. In the diabetic children, the ultrasound studies and blood sampling were done before administration of morning insulin.

Brachial artery physiology

Brachial artery diameter was measured from B-mode ultrasound images as described previously (12). Briefly, a resting scan was performed, and arterial flow velocity was measured with a Doppler signal. Increased flow was then induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 200 mm Hg for 3 minutes, followed by release. A second scan was taken continuously 40 to 120 seconds after cuff deflation, including a repeat flow-velocity recording for the first 15 seconds after the cuff was released. Vessel diameter was measured at a fixed distance manually by an experienced blinded observer using ultrasonic calipers at end diastole, incident with the R wave on a continuously recorded ECG. Peak flow-mediated dilation (FMD, %) and the total dilation response, defined as the area under the FMD versus time curve during 40 to 120 seconds after hyperemia (AUC, %×s), were assessed (12).

FMD is expressed as follows: FMD (%)=[(hyperaemic diameter-resting diameter)/resting diameter]×100 (13), where resting diameter is the diameter of the brachial artery before any flow stimulus in the artery is created, and hyperaemic diameter is the diameter of the artery observed after release of the inflated cuff.

Measurement of carotid IMT

All studies were done according to a predetermined, standardized scanning protocol for the right and left carotid arteries, as described previously (14). Briefly, the proximal part of the carotid bulb was identified on both sides, and the segments of the common carotid arteries 1 to 2 cm proximal to the bulb and the left bulb region were scanned. The image was focused on the posterior (far) wall, and the resolution box function was used to magnify the arterial far wall. Two angles were used in each case for common carotid IMT on both sides: anterior oblique and lateral. All scans were digitally stored for subsequent offline analysis. One end-diastolic frame (captured adjacent to the R wave on a continuously recorded ECG) for each interrogation angle was selected and analyzed for mean and maximum IMT. The images were analyzed by 2 independent readers who were blinded to the subject's clinical details. Six to eight measurements of far-wall IMT were taken manually, by both observers, for each image using ultrasound calipers, and the average values of these readings were used in the analyses. The mean and maximum IMTs from these 5 arterial wall segments were used in the analyses.

Ultrasound and brachial blood pressure measurements were used to calculate the carotid artery compliance, CAC=[(D_s-D_d)/D_d)]/(P_s-P_d), where D_s is the systolic diameter, D_d, the diastolic diameter, P_s, systolic blood pressure, and P_d, diastolic blood pressure. CAC measures the ability of the arteries to expand as the response to pulse pressure caused by cardiac contraction and relaxation (15). The carotid stiffness index(β) was defined as follows (16):

β=ln (P_s/P_d)/[(D_s-D_d)/D_d]

Blood pressure measurements

Blood pressure (BP) measurement during the regular 3-month follow-up visits was performed in a quiet room. BP was obtained using a conventional oscillatory measurement system positioned at the right-upper arm (DINAMAP; GE Healthcare, Munchen, Germany). The size of the cuff was chosen depending on the patient's arm circumference, with the cuff bladder covering at least 40% and a maximum of 100% of the arm circumference. sd scores were calculated adopting normative values from the literature (17).

Laboratory methods

Blood samples were taken during the patients' follow-up visit. Fasting HbA1c, triglycerides, total cholesterol, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured by standard laboratory methods. Each sample was processed immediately after the patient's visit with a maximum delay of 1 hour. Median HbA1c value was described as the numerical value separating the higher half of HbA1c levels of type 1 diabetic children. Mean HbA1c value was equal to the sum of HbA1c levels divided by the number of type 1 diabetic children.

Study variables

The characteristics of the study groups are shown in Table 1. There were no significant differences in the groups for age, sex, height, weight, body mass index and waist circumference. The diabetic group had higher serum total cholesterol and very low density cholestorel (VLDL) cholesterol concentration compared with control subjects (165.9±38.8 vs. 130.4±25 mg/dL total cholesterol; p<0.001 and 13,32±8.48 vs. 10.22±2.76 mg/dL; p=0.018 VLDL cholesterol). There were no differences in serum triglycerides, LDL and HDL cholesterol between the study groups. While there was no difference in systolic blood pressure between the study groups, the diabetic group had lower diastolic blood pressure than control group (60.2±7.69 vs. 65.33±8.06 mm Hg; p=0.02) (Table 1).

Table 1. Characteristics of study groups

	Diabetic children	Control children	*P*
No. of subjects, boys	50 (27)	45 (24)	0.126
Age, year	12.10±2.02	11.49±1.9	0.324
Height, cm	149.78±20.03	145.62±20.14	0.378
Weight, kg	41.14±11.28	40.88±11.68	0.470
Body mass index, kg/m^2	18.49±2.64	18.26±2.59	0.520
Waist circumference, cm	69.72±8.6	66.05±7.47	0.325
Total cholesterol, mg/dL	165.9±38.8	130.4±25	<0.001*
LDL cholesterol, mg/dL	93.42±34.5	79.38±27.4	0.032*
VLDL cholesterol, mg/dL	13.32±8.48	10.22±2.76	0.018*
HDL cholesterol, mg/dL	51.68±9.74	37.8±9.7	<0.001*
Triglycerides, mg/dL	84.4±64	75.09±28.5	0.353
Systolic blood pressure, mm Hg	103.8±9.2	102.44±9.3	0.480
Diastolic blood pressure, mm Hg	60.2±7.69	65.33±8.06	0.020*

*P<0.05
HDL - high density lipoprotein; LDL - low density lipoprotein; VLDL - very low density cholestorel

Statistical analyses

Calculations were performed using the statistical package SPSS for Windows (version 16; SPSS, Inc., Chicago, IL). Cumulative distributions of two groups was compared with Kolmogorov-Smirnov test. Differences within the patient group, and between the patient and control groups were tested using t tests. Correlations were analyzed using Pearson's correlation coefficient. All significance testing was fixed at p<0.05 (two-sided). The chi-square test was used to compare proportions in the 2 groups.

Results

Results of ultrasound studies in study groups are shown in Table 2. The children with type 1 diabetes mellitus had a significantly greater carotid IMT than control subjects (0.49±0.05 mm vs. 0.44±0.03 mm; p<0.001) (Fig. 1). While there were no difference in the carotid artery systolic and diastolic diameters between the study groups, the diabetic group had significantly lower carotid artery compliance than control group (2.16±0.98 vs. 3.38±0.16 mm; p<0.001) (Fig. 2). A higher carotid stiffness index was found in the diabetic group when compared with control group (3.11±0.46 vs. 2.6±0.29 mm; p<0.001). There was no difference in the FMD between the study groups (9.7±3.4 vs. 11.5±6.13 mm; p=0.073) (Fig. 3).

The correlations between risk factors and carotid IMT are shown in Table 3, separately for children with diabetes and control subjects. Although there was a correlation between carotid IMT and weight in children with diabetes, carotid IMT was not affected by age, body mass index, waist circumference, lipids levels, systolic blood pressure, diastolic blood pressure, HbA1c levels, median HbA1c level, type 1 diabetes mellitus duration. The carotid artery compliance negatively correlated with weight, body mass index, waist circumference, systolic blood pressure, HbA1c levels in children with diabetes, type 1 diabetes mellitus duration. Furthermore, low-mediated dilation negatively correlated with weight, systolic blood pressure and median HbA1c level.

When carotid IMT, carotid artery compliance and flow-mediated dilation, indicators of endothelial structure and function, in the children with type 1 diabetes mellitus were analyzed with each others, flow-mediated dilation negatively correlated with carotid IMT and carotid artery compliance (p<0.05) (Table 4). There was no patient with plaque in the carotid artery in our study.

Discussion

The present study revealed a significantly increased IMT in a group of children and adolescents with diabetes mellitus type

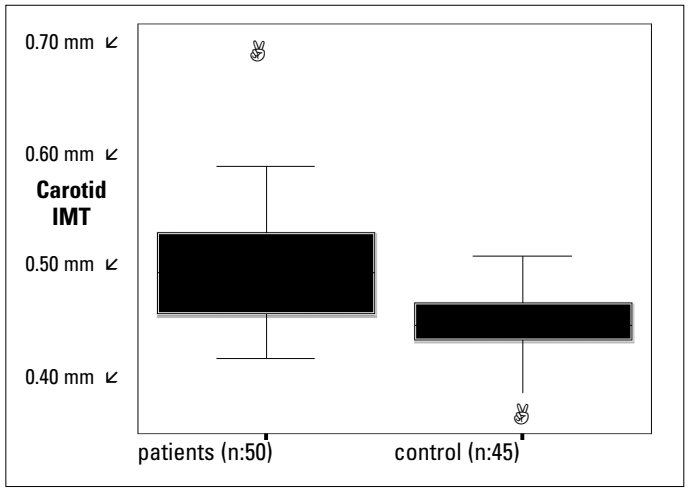

Figure 1. Dispersion of carotid IMT in groups

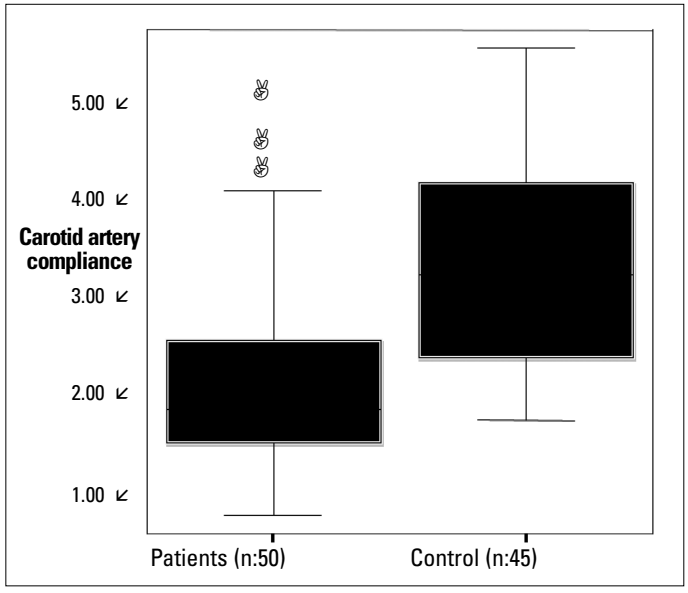

Figure 2. Dispersion of carotid artery compliance in groups

1. The atherogenicity of type 1 diabetes has been increasingly recognized. However, controversy still exists about the moment at which interventions with proven efficacy to reduce cardiovascular event rates (i.e., lipid-lowering therapy, antiplatelet agents) should be started (18). This is especially true for pediatric populations. Data reported here show that atherosclerotic burden (assessed by cIMT) is already increased in children and adolescents with type 1 diabetes compared with an age-, sex-,weight-, height-, and BMI-matched control group. In addition, flow velocities were significantly lower in case subjects with diabetes, suggesting that vascular function is abnormal. These data demonstrate that the atherosclerosis process has already started in our pediatric type 1 diabetic patients-cIMT is increased and vessel compliance is decreased. Our cIMT data for the control group are remarkably similar to those reported in the literature. The mean cIMT value and the percentile distribution are almost identical to those reported by Jarvisalo et al. (14, 19, 20) (mean cIMT 0.44±0.04 vs. 0.44±0.03 mm, respectively). The use of

Table 2. Results of ultrasound studies in study groups

	Diabetic children	Control children	*P*
Mean carotid IMT, mm	0.494±0.051	0.442±0.032	<0.001*
Carotid diastolic diameter, mm	6.21±0.36	6.26±0.46	0.568
Carotid systolic diameter, mm	5.69±0.32	5.59±0.41	0.210
Carotid artery compliance, %	2.16±0.98	3.38±0.16	<0.001*
Brachial artery baseline diameter, mm	3.054±0.249	2.773±0.315	<0.001*
Brachial artery hyperaemic diameter, mm	3.350±0.257	3.089±0351	<0.001*
FMD, %	9.707±3.401	11.530±6.135	0.073
Carotid stiffness index, mm	3.11±0.46	2.6±0.29	<0.001*

*P<0.05, FMD - flow-mediated dilation; IMT - intima media thickness

Table 3. Correlation coefficients between carotid IMT, carotid artery compliance, and FMD and several risk factor

	Carotid IMT		Carotid artery compliance		FMD	
	r	*P*	r	*P*	r	*P*
Age	0.293	0.039*	-0.348	0.013*	-0.294	0.038*
Weight	0.272	0.056	-0.345	0.014*	-0.240	0.093
Body mass index	0.246	0.085	-0.315	0.026*	-0.225	0.116
Waist circumference	0.124	0.281	-0.046	0.691	-0.217	0,058
Total cholesterol	0.228	0.111	-0.404	0.004*	-0.296	0.037*
LDL cholesterol	0.361	0.132	-0.012	0.936	-0.233	0.103
VLDL cholesterol	-0.012	0.933	-0.211	0.142	-0.188	0.191
Triglycerides	0.063	0.664	-0.205	0.152	-0.191	0.184
Systolic blood pressure	0.047	0.746	0.074	0.610	0.034	0.812
Diastolic blood pressure	0.057	0.692	0.176	0.222	0.186	0.196
Mean HbA1c	0.112	0.437	-0.275	0.053	-0.279	0.049
Median HbA1c	0.249	0.082	-0.314	0.026*	-0.412	0.003*
Duration of diabetes	0.022	0.881	-0.285	0.045*	-0.198	0.168

*P<0.05, FMD - flow-mediated dilation; IMT - intima media thickness

standard automatic procedures for cIMT measurements limits the variability related to human error and allows comparability between studies. Our cIMT data for the control group are higher than those reported in Pirgon et al. (21) (mean cIMT 0.44±0.03 vs. 0.37±0.13 mm, respectively).

A significant increase of the IMT in our patient group compared with controls and normative values gives evidence for subclinical atherosclerosis. Our patients had higher total and VLDL cholesterol levels. Surprisingly, a direct correlation of the LDL cholesterol to vascular structural changes could not be detected in the present study. In pediatric patients with familial hypercholesterolemia, increased IMT values depend on total and LDL cholesterol levels (22). We suspect that in our patients, the range of the LDL-cholesterol levels was too narrow to account for a direct, single effect on the vascular structure as in

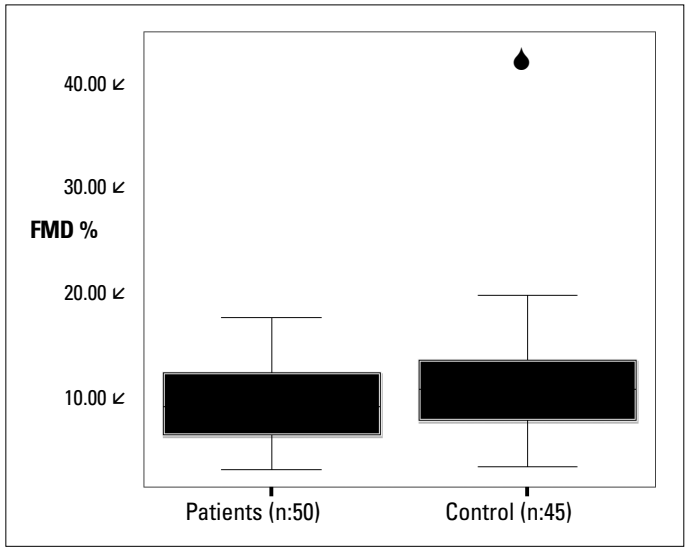

Figure 3. Dispersion of FMD in groups
FMD - flow-mediated dilation

familial hypercholesterolemia. Diabetes mellitus itself has impaired endothelial function by reducing the amount of nitric oxide produced by endothelial cells (23). Endothelial dysfunction has proved to be correlated to the HbA1c level in diabetic children (24). Consistent with previous studies, we were not able to establish a direct correlation between the HbA1c and values of IMT.

Epidemiologic and clinical evidence has emphasized the role of hyperglycemia in explaining the increased cardiovascular morbidity and mortality in diabetes. Chronic state of hyperglycemia may induce atherogenesis by increasing oxidative stress (25), leading to increased LDL oxidation (26, 27) and decreased nitric oxide bioavailability, including endothelial dysfunction (28, 29). In the present study, the HbA1c levels in the children with diabetes were comparable to those reported previously in a population-based sample of children and adolescents (30). We were unable to show a relationship between HbA1c and carotid IMT in children with diabetes. The present study demonstrates that impaired brachial artery FMD response is a common vascular manifestation in young children with type 1 diabetes that may predispose to the development of increased carotid artery IMT. This result is consistent with the hypothesis that endothelial dysfunction is a risk factor for the development of atherosclerosis and important in the pathogenesis of premature macrovascular disease in individuals with diabetes. Alternatively, hyperglycemia may exert its deleterious effects by leading to glycosylation of LDL, which may increase its atherogenicity (31, 32).

Flow-mediated dilation (FMD) of the brachial artery is a marker of endothelial function that can be assessed by measuring arterial diameter responses to increased flow (33). Wiltshire et al. (34) studied flow-mediated dilation in 36 diabetic children with a mean age of 14 years and a mean duration of diabetes of under 6 years and in 20 healthy controls. These diabetic children without diabetic complications had attenuated endothelial function compared with controls. Previously, Donaghue et al. (35) demonstrated in a study of 20 diabetic adolescents that young diabetics with

Table 4. Correlation coefficients of carotid IMT, carotid artery compliance, and FMD with each others

	Carotid IMT		Carotid artery compliance		FMD	
	r	*P*	r	*P*	r	*P*
Carotid IMT	-	-	-0.342	0.015*	-0.442	0.001*
Carotid artery compliance	-0.342	0.015*	-	-	0.528	0.000*
FMD	-0.442	0.001*	0.528	0.000*	-	-

*$P<0.05$, FMD - flow-mediated dilation; IMT - intima - media thickness

clinical complications had decreased endothelial and smooth muscle function compared with healthy controls. Hurks et al. (36) demonsrated that although carotid IMT was not significantly different in diabetics with moderate metabolic control compared with controls, FMD was significantly impaired in type 1 diabetics. Babar et al. (37) showed that children with type 1 diabetes had lower FMD% than control children, whereas carotid IMT did not differ between groups. There was no statistical difference in the FMD between the study groups in the present study. The lack of a statistically significant difference in FMD between the groups might be explained by inadequate sample size. The study included a relatively small number of participants, especially regarding subjects with data on flow-mediated dilation.

From a clinical point of view, the measurement of the IMT may give additional information about the structural status of the vascular system in diabetic children, even in the absence of clinically apparent macrovascular complications. As mentioned previously, atherosclerosis is a progressive change, with its roots in childhood. The assessment of the IMT is a noninvasive method and easy to perform, and may provide complimentary information, especially in a patient group at increased risk for cardiovascular complications. In adult diabetic patients, the IMT has responded to optimized metabolic control of the disease, resulting in slower IMT progression over the years (38). In children, a case report about the regression of a formerly increased IMT in a boy receiving intensified insulin therapy may be indicative for similar effects (39). So, longitudinal IMT measurements may offer a reliable tool for the calculation of the cardiovascular risk status of the patients and may be used for the monitoring of therapeutic effects. However, it has to be mentioned that the method is limited by the need for high-end technical equipment and appropriately trained personnel to obtain reliable data. Our study has several limitations. First, we did not evaluate the susceptibility of LDL to oxidation on arterial IMT, because we did not study oxidized LDL and glycated LDL. In addition, we did not administer nitroglycerin to our preadolescents for assessment of smooth-muscle reactivity. Despite these limitations, we report our novel findings of adverse vascular effects of type 1 diabetes in preadolescents.

Conclusion

Our data suggest that carotid IMT and stiffness are increased in type 1 diabetic children. As diabetes is a chronic disease and

cardiovascular morbidity is very high among individuals with diabetes, noninvasive methods for monitoring vascular changes might be useful in clinical practice. Studies in children with type 1 diabetes would therefore be needed to reduce developing atherosclerotic vascular complications.

Conflict of interest: None declared.

Peer-review: Partially external peer-reviewed.

Authorship contributions: Concept - C.D.; Design - Ö.B.; Supervision - T.M.; Resource - C.D.; Materials - Ö.B.; Data collection&/or Processing - Ö.B.; Analysis &/or interpretation - H.A.K.; Literature search - H.A.K.; Writing - H.A.K.; Critical review - V.T.

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