Carotid Intima-Media Thickness in Pediatric Type 1 Diabetic Patients

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OBJECTIVE — To compare the carotid artery intima-media thickness in Hispanic pediatric type 1 diabetic patients against that in healthy control subjects matched for age, sex, height, and BMI.

RESEARCH DESIGN AND METHODS — The evaluation consisted of anthropometric measurements, biochemical parameters, and a carotid Doppler and real-time ultrasound, in which carotid artery intima-media thickness (cIMT), peak systolic velocity, and end diastolic velocity were measured using standardized procedures.

RESULTS — A total of 52 diabetic patients and 47 control subjects were included. No significant differences existed in the characteristics between case and control subjects (mean age 11.8 ± 3.1 vs. 11.8 ± 2.8 years, weight 42.2 ± 15.3 vs. 44.2 ± 14.4 kg, height 1.45 ± 0.15 vs. 1.47 ± 0.15 m, BMI 19.3 ± 3.2 vs. 19.9 ± 4.4 kg/m^2, systolic blood pressure 99.1 ± 9.9 vs. 99.6 ± 9 mmHg, and diastolic blood pressure 63 ± 6.4 vs. 62.0 ± 5.7 mmHg, respectively). The mean duration of diabetes was 4.8 ± 3.2 years (range 6–144 months), and the mean A1C was 8.6 ± 1.6%. A significantly higher cIMT was found in the patients with type 1 diabetes (0.463 ± 0.04 vs. 0.441 ± 0.04 mm; $P = 0.001$). In contrast, both peak systolic velocity (107.1 ± 22.8 vs. 119.3 ± 19.2, $P < 0.005$) and end diastolic velocity (28.4 ± 6.0 vs. 33.0 ± 7.0, $P < 0.001$) were higher in the control subjects.

CONCLUSIONS — Type 1 diabetes is associated with higher cIMT and decreased flow velocities in a Hispanic pediatric population.

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Atherosclerosis is a long-term process that begins early in life. During childhood, potentially reversible lesions have been shown in autopsy studies and in animal models; lesions progress during the first decade of life and become symptomatic usually after the fourth decade of life (1). Long-term follow-up studies have proven the importance of several cardiovascular risk factors during childhood. Their presence increased the likelihood for having cardiovascular complications in adult life (2). The association between type 1 diabetes and coronary heart disease (CHD) has become undisputed during recent years (3,4). It has been demonstrated that there is a dramatic increase in the morbidity and mortality risk caused by atherosclerotic cardiovascular disease in young adults with type 1 diabetes compared with the nondiabetic population (5,6). Carotid artery intima-media thickness (cIMT) is a prognostic factor for having cardiovascular disease in adults with type 1 diabetes.

Recommendations for primary CHD prevention applicable to patients with type 1 and 2 diabetes were published recently (7). There is a growing interest to prevent the cardiovascular disease risk factors early in the course of the disease, even at pediatric stages (8). It is necessary to identify children with type 1 diabetes with the highest risk for CHD using objective and noninvasive studies; if clinically useful information is obtained from its use, it may help to establish additional measures for prevention.

Advances in imaging techniques identify early vascular changes through noninvasive ultrasound; these findings include impaired vasodilation and thickening of the artery wall (9). Intima-media thickness is a well-known marker for atherosclerosis in adults and is an independent predictor of multi-level atherosclerosis (10,11). 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 (12).

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 CHD in pediatric patients has been fairly explored (13,14). Data in pediatric populations are scant, and no publications currently exist in Hispanic patients.

The purpose of this study is to compare cIMT and flow velocities in pediatric patients with type 1 diabetes against those in an age-, sex-, height-, and BMI-matched control group. We find significant differences in the cIMT and the velocity flows between type 1 diabetic pediatric patients and control subjects.

RESEARCH DESIGN AND METHODS

— Pediatric patients with type 1 diabetes (age range 6–17 years old and disease duration ≥6 months) were invited to participate. A control group composed of healthy children matched for age, sex, weight, height, and BMI was selected. The study design was approved

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Abbreviations: CHD, coronary heart disease, cIMT, carotid artery intima-media thickness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

by the Ethics and Investigation Review Board of the Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social. Children and their parents or guardians signed an informed consent form.

The evaluation consisted of a medical history, A1C, and a Doppler and real-time carotid ultrasound performed at the imaging department of the Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social. Doppler and real-time ultrasound studies were performed by a single experienced vascular radiologist who was blinded to the study group. All studies were performed with a high-resolution ultrasound equipment scanner (Philips HDI 5000) with imaging on B mode (real-time), Doppler color, and Doppler duplex spectral equipped with a 7- to 12-MHz linear array transducer. The Doppler and real-time ultrasound studies were performed after an overnight fast and before the administration of a morning insulin dose. Patients were placed in the supine position with the neck in hyperextension. The place of measurement was standardized in every study at the common carotid artery at 1 cm from the carotid bulb. For cIMT measurement, a lateral image of ≥10 mm from the carotid artery far wall was taken. The cIMT was defined as the distance from the leading edge of the first echogenic line to the second hypoechoic line from the upper layer of the tunic adventitia. The measurement was done during diastole (15).

All scans were digitally photographed and stored on the ultrasound hard disk and via Ethernet. The images were subsequently analyzed by the same radiologist with QLAB 4.2.1 Advanced Ultrasound Quantification software from Philips, developed for the automatic analysis of ultrasound images, with the computerized standardized intima-media measurement. Both flow velocities (peak systolic velocity and end diastolic velocity) were also measured. The mean values of both cIMT and flow velocities for the right and left carotid arteries were calculated.

Statistical analysis

Data are expressed as means ± SD. ANOVA was used to compare children with and without type 1 diabetes. Linear regression analysis was done to identify the variables associated with cIMT, end diastolic velocity, and peak systolic velocity. A P value <0.05 was considered statistically significant. The analysis was done using the SPSS program, version 12 for Windows (SPSS, Chicago, IL).

Table 1—*Characteristics of the participants*

	Type 1 diabetic patients	Control subjects	*P*
n (F/M)	52 (26/26)	47 (24/23)	—
Age (years)	11.8 ± 3.1	11.8 ± 2.8	0.9
Weight (kg)	42.1 ± 15.2	44.2 ± 14.3	0.9
BMI (kg/m^2)	19.3 ± 3.2	19.9 ± 4.3	0.4
Systolic blood pressure (mmHg)	99.1 ± 9.9	99.6 ± 8.9	0.7
Diastolic blood pressure (mmHg)	62.9 ± 6.4	62.0 ± 5.7	0.4
cIMT (mm)	0.463 ± 0.04	0.441 ± 0.04	<0.001
Peak systolic velocity (cm/s)	107.1 ± 22.8	119.3 ± 9.2	<0.005
End diastolic velocity (cm/s)	28.4 ± 6.0	33.0 ± 7.0	<0.001

Data are means ± SD.

RESULTS — A total of 52 diabetic patients (26 males and 26 females) and 47 control subjects (24 males and 23 females) participated in the study. The characteristics of the study subjects are shown in Table 1. Case and control subjects were successfully matched.

The duration of type 1 diabetes was 4.8 ± 3.2 years (6 months to 12 years), the daily insulin dose was 0.91 ± 0.32 units · kg^{-1} · day^{-1}, and the average A1C was 8.6 ± 1.6%. Other cardiovascular risk factors were not common and included microalbuminuria (n = 1, 1.9%), arterial hypertension (n = 2, 3.8%), and family history of CHD (n = 9, 17%).

The mean ± SD values of cIMT and flow velocities of both carotid arteries are shown in Table 2. A significantly higher cIMT was found in the patients with type 1 diabetes (0.463 ± 0.04 vs. 0.441 ± 0.04 mm; P = 0.001). In contrast, both peak systolic velocity (107.1 ± 22.8 vs. 119.3 ± 19.2, P < 0.005) and end diastolic velocity (28.4 ± 6.0 vs. 33.0 ± 7.0, P < 0.001) were lower in the diabetic group.

The percentile distribution of the cIMT and the flow velocities found in case and control subjects are shown in Table 2. The percentile distribution of the control subjects may be useful for comparison against future studies. In addition, this is the first report of cIMT in a healthy Mexican pediatric population. Case subject results are shifted to higher values. There was no difference in mean cIMT between sexes in either of the groups.

Several variables were significantly associated with cIMT and flow velocities (Table 3). Only systolic blood pressure (β 1.134 × 10^{-3}) and LDL cholesterol (β 2.757 × 10^{-4}) remained independently associated with cIMT in the multivariate analysis (r^2 = 0.111, P = 0.004). The flow velocities were associated with a different set of variables. A1C was the only variable associated with peak systolic velocity (β −1.39 ± 0.452, P = 0.003); in contrast, the total number of insulin units/day used at the evaluation (β −8.82 ± 1.84, P < 0.001), the BMI (β −0.418 ± 0.165, P = 0.013), and the time since diabetes was diagnosed (β 0.73 ± 0.28, P = 0.01) were associated with the end diastolic velocity (r^2 = 0.235, P < 0.001).

Table 2—*Percentile distribution of the cIMT and flow velocities (peak systolic velocity and end diastolic velocity) of type 1 diabetic patients versus healthy control subjects*

	Percentile	Type 1 diabetic group	Control group
cIMT mean (mm)	25	0.4300	0.4200
	50	0.4500	0.4400
	75	0.4975	0.4700
PSV mean (cm/sec)	25	87.63	108.00
	50	104.75	120.50
	75	124.88	133.50
EDV mean (cm/sec)	25	23.625	28.500
	50	26.500	31.500
	75	32.875	37.500

EDV, end diastolic velosity; PSV, peak systolic velosity.

Table 3—*Correlation coefficients between cIMT, peak systolic velocity, and end diastolic velocity and several risk factors*

	cIMT	Peak systolic velocity	End diastolic velocity
Age (years)	0.168	−0.051	−0.175
Systolic blood pressure	0.201*	0.079	−0.145
A1C	0.209*	−0.3*	−0.372*
Time since diagnosis (years)	0.258*	−0.224*	−0.138
Cholesterol	0.235*	−0.29*	−0.328*
Triglycerides	0.232*	−0.3*	−0.381*
LDL cholesterol	0.250*	−0.289*	−0.331*
Insulin dosage (units · kg^{-1} · day^{-1})	0.191	−0.3*	−0.370*
HDL cholesterol	0.154	−0.258*	−0.269*

*$P < 0.01$.

CONCLUSIONS — 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 (7). 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-, 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.

Several groups have demonstrated that patients with type 1 diabetes have higher mean cIMT compared with matched control subjects. The Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that intensive insulin therapy slows the increment of cIMT values compared with conventional insulin therapy (16). However, many questions remain unanswered. For example, the minimal time of exposure required for a clinical event, the type 1 diabetes–specific determinants of the vascular damage, and whether the atherosclerotic process is already active in prepubertal years remain to be determined. Studies in pediatric groups are required to investigate these issues. Regrettably, the majority of the studies done in pediatric patients have had limitations in sample size and design (17); as a result, the extrapolation of the conclusions to other ethnic groups or to the majority of the cases with type 1 diabetes is not feasible. Thus, additional studies are required to be done in non-Caucasian populations and in subsets of case subjects with special characteristics (e.g., subjects with or without microalbuminuria or stratified by design based on the age at which diabetes was diagnosed and/or the time of exposure to the disease).

This study confirms that the atherosclerotic burden (assessed by cIMT) is increased in Hispanic children with type 1 diabetes. Only systolic blood pressure and LDL cholesterol remained significantly associated with cIMT in the multivariate analysis. This observation suggests that LDL cholesterol and systolic blood pressure have the same prominent role in the pathogenesis of atherosclerosis in type 1 diabetes as that found in other clinical conditions.

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 Järvisalo et al. (14,18,19) (mean cIMT 0.44 ± 0.04 vs. 0.42 ± 0.04 mm, respectively). The use of standard automatic procedures for cIMT measurements limits the variability related to human error and allows comparability between studies. In spite of that, the difference found in the mean cIMT between control subjects and diabetic patients in our study was lower than that reported by Järvisalo et al. (0.02 vs. 0.05 mm), despite the similar age and mean diabetes duration of the study samples. Other authors have reported differences in mean cIMT above or below the difference reported here; differences between case and control subjects vary from 0.01 mm (20) to 0.20 mm (13).

In addition, patients with type 1 diabetes had decreased flow velocities (Table 1), suggesting that vascular compliance is abnormal. Regrettably, no data are available in the literature in this field in pediatric patients. The biological consequences of decreased carotid flow velocities cannot be proposed with the current data, but it could be an indirect confirmation of the abnormal vascular response found using other methods (i.e., flow-mediated vasodilation in the brachial artery or pulse-wave velocity) (21,22).

Strengths and limitations should be recognized. This report is the initial description of the quartile distribution of the cIMT in Hispanic children and adolescents (for both control subjects and type 1 diabetic case subjects). The matching process between case and control subjects was highly successful. However, the cross-sectional design and the modest sample size limit our conclusions.

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