Effect of Type 1 Diabetes on Carotid Structure and Function in Adolescents and Young Adults

The SEARCH CVD study

ELAINE M. URBINA, MD, MS[1]
DANA DABELEA, MD, PHD[2]
RALPH B. D'AGOSTINO, JR., PHD[3]
AMY S. SHAH, MD, MS[1]
LAWRENCE M. DOLAN, MD[1]
RICHARD F. HAMMAN, MD, DRPH[2]
STEPHEN R. DANIELS, MD, PHD[4]
SANTICA MARCOVINA, PHD[5]
R. PAUL WADWA, MD[4]

OBJECTIVE—Type 1 diabetes mellitus causes increased carotid intima-media thickness (IMT) in adults. We evaluated IMT in young subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Participants with type 1 diabetes (N = 402) were matched to controls (N = 206) by age, sex, and race or ethnicity. Anthropometric and laboratory values, blood pressure, and IMT were measured. ANCOVA was used to assess differences controlling for demographic risk factors, cardiovascular risk factors, and HbA_{1c}.

RESULTS—Subjects were 18.9 ± 3.3 years old (50% male, 82.7% non-Hispanic white). Youth with type 1 diabetes had thicker bulb IMT, which remained significantly different after adjustment for demographics and cardiovascular risk factors. Age, sex, adiposity, and systolic blood pressure were consistent significant determinants of IMT. Adjustment for HbA_{1c} eliminated the difference, suggesting the difference was attributable to poor glycemic control.

CONCLUSIONS—Carotid IMT may be increased in youth with type 1 diabetes at high risk for cardiovascular disease. Better control of diabetes may be essential in preventing progression of atherosclerosis.

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Type 1 diabetes mellitus leads to increased carotid intima-media thickness (IMT) (1) and higher risk for cardiovascular disease later in life (2). Large studies of carotid ultrasound in youth with type 1 diabetes are lacking. We evaluated adolescents and young adults to determine if increased carotid IMT was present in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

—SEARCH CVD is an ancillary study to SEARCH for Diabetes in Youth (3). Nondiabetic controls (N = 402) were frequency matched to cases with type 1 diabetes (N = 206) by age, sex, and race or ethnicity (mean age, 18.9 ± 3.3 years; 50% male; 82.7% non-Hispanic white). The study received Institutional Review Board approval, and appropriate consent or assent was obtained.

Fasting lipids, glucose, and hemoglobin A_{1c} (HbA_{1c}) measurements were obtained (3). The average of two measures of height and weight was used for calculation of BMI z scores. The average of the second and third resting, seated, and auscultatory (aneroid) systolic blood pressure and diastolic blood pressure was used.

B-mode carotid ultrasounds of the common, bulb, and internal carotid arteries were obtained with a linear array transducer (5–12 MHz) at 90, 120, 150, 210, 240, and 270 degrees. Images were read on Amicas-Vericis (Merge, Chicago, IL). The mean IMT from all angles was used. Coefficients of variability for carotid measures of 800 subjects in our laboratory ranged from 1.8 to 5.5%, within published guidelines for reproducibility.

Statistical analyses with SAS software (version 9.2; SAS Institute, Cary, NC) included case-control comparisons of covariates using χ^2 tests for categorical variables and t tests for continuous variables. ANCOVA was performed to determine if type 1 diabetes was independently associated with carotid measures after controlling for cardiovascular risk factors.

RESULTS

—Youth with type 1 diabetes (Table 1) did not differ from controls regarding age, sex, BMI z score, waist circumference, systolic blood pressure, or diastolic blood pressure. There were more non-Hispanic whites with type 1 diabetes. Cases had higher heart rate, total cholesterol, LDL cholesterol, HDL cholesterol, fasting glucose, and HbA_{1c} and had thicker bulb IMT ($P < 0.03$). These differences persisted after adjustment for demographics and cardiovascular risk factors. Older age, male sex, increased adiposity, and systolic blood pressure z score were the most consistent significant determinants of carotid thickness. LDL cholesterol was a determinant of internal carotid IMT and triglycerides of common and bulb IMT (R^2 for common, 0.12; bulb, 0.15; internal, 0.16; all models $P \leq 0.001$). The addition of HbA_{1c} eliminated the case-control difference for carotid bulb (0.464 in cases compared with 0.447 in controls; P = 0.15), suggesting that glycemic control may be an important factor explaining the difference in carotid thickness.

From the [1]Cincinnati Children's Hospital and University of Cincinnati, Department of Pediatrics, Cincinnati, Ohio; the [2]Department of Epidemiology, Colorado School of Public Health, University of Colorado, Denver, Aurora, Colorado; the [3]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [4]Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado; and the [5]Northwest Lipid Research Laboratories, University of Washington, Seattle, Washington.
Corresponding author: Elaine M. Urbina, elaine.urbina@cchmc.org.
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Table 1—*Case-control contrasts*

	Type 1 diabetes (*N* = 402)		Controls (*N* = 206)		
Variable	Mean	SD	Mean	SD	*P**
Site, % Colorado	52.5		51.0		0.72
Age, years	18.8	3.3	19.2	3.3	0.11
Sex, % female	47.5		54.4		0.11
Race, %					0.006
Non-Hispanic white	86.6		75.2		
African American	5.5		8.7		
Hispanic	7.0		13.6		
Other	1		2.4		
Diabetes duration, years	9.8	3.8	NA		NA
Height, m	1.7	0.1	1.7	0.1	0.38
Weight, kg	71.3	16.4	74.2	21.8	0.10
BMI, kg/m^2	24.5	4.7	25.2	6.5	0.17
Systolic blood pressure, mmHg	110.9	9.8	110.4	10.7	0.59
Diastolic blood pressure, mmHg	70.3	8.9	68.8	8.6	0.04
HR, bpm	68.2	11.8	62.6	9.5	<0.0001
Total cholesterol, mg/dL	170.5	34.3	162.9	30.6	0.008
LDL cholesterol, mg/dL	98.0	28.6	92.8	25.8	0.03
HDL cholesterol, mg/dL	53.4	13.5	49.6	13.6	0.001
Triglycerides, mg/dL	95.0	58.1	102.0	58.1	0.16
Fasting glucose, mg/dL	201.0	99.5	89.0	7.4	<0.0001
HbA_{1c}, %	8.9	1.8	5.0	0.3	<0.0001
Common IMT, mm	0.449	0.073	0.450	0.067	0.82
Bulb IMT, mm	0.461	0.073	0.445	0.069	0.01
Internal IMT, mm	0.399	0.078	0.396	0.073	0.68

NA, not available. *The *t* test was used for continuous variables, and χ^2 analyses were used for categorical variables.

CONCLUSIONS—We present the largest comparison of carotid IMT in adolescents and young adults with type 1 diabetes and healthy controls, demonstrating thicker carotid bulb IMT in cases after adjustment for cardiovascular risk factors. Because the rate of progression of IMT in healthy subjects (mean age, 40 years) in the Bogalusa Heart study was 0.017–0.020 mm/year (4), our difference of 0.016 mm suggests that our type 1 diabetic subjects had a vascular age 1 year advanced from their chronological age. We found that IMT was related to type 1 diabetes, age, sex, adiposity, and systolic blood pressure, with triglycerides playing a role in common and bulb IMT, and LDL played a role in internal carotid IMT. Further adjustment for HbA_{1c} ablated the case-control difference in IMT, suggesting that the thicker carotid IMT in the subjects with diabetes could be attributed to diabetes-related hyperglycemia.

In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, progression of IMT over the course of 6 years was faster in subjects with type 1 diabetes, yielding a thicker final IMT in cases (5). There was no difference in IMT at baseline. However, DCCT/EDIC did not image the bulb, which is likely the earliest site of thickening according to the Bogalusa Heart Study, which found the carotid bulb to be significantly thicker than the other two segments (6).

Previous studies of youth reported case-control differences in the common carotid IMT, which is in contrast to our finding of no difference. However, they were conducted in a different country with a different ethnicity (7), enrolled patients with poorer glycemic control (higher HbA_{1c}) (8), or had a control group with a more favorable cardiovascular risk factor profile than our controls (9). Other studies that found no case-control difference in IMT in youth either examined a much smaller number of younger subjects (10) or failed to image the carotid bulb (11). Our analyses reinforce the importance of imaging the carotid bulb, often the site of earliest detectible subclinical atherosclerosis in youth.

The DCCT/EDIC study demonstrated that the intensive treatment group had a slower progression of IMT (5) and that mean HbA_{1c} levels explained most of the differences in IMT progression between treatment groups (12). One longitudinal study of youth found children with type 1 diabetes who had progression of IMT over the course of 2 years had higher HbA_{1c} (13). Our data emphasize the role of diabetes-related hyperglycemia in increasing IMT in youth with type 1 diabetes.

As seen in other studies of IMT in youth with diabetes (14), very little of the variance in IMT is explained by our models. Another limitation is our cross-sectional design, which precludes us from determining the causative factors for increased IMT. Our use of a slightly more overweight control group, although representative of our clinic population, may have obscured some case-control difference. However, we were adequately powered to see a difference with our sample size and variability such that we were powered to detect a mean difference of 0.017 compared with published studies of youth with type 1 diabetes that showed a difference of 0.034 mm (15) to 0.15 mm (16).

In summary, our study provides novel evidence that carotid thickness is increased in youth with type 1 diabetes compared with healthy controls and that this difference is not accounted for by traditional cardiovascular risk factors. Better control of diabetes-related hyperglycemia may be needed to reduce future cardiovascular disease.

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E.M.U., D.D., R.B.D., L.M.D., R.F.H., S.R.D., S.M., and R.P.W. were involved in the design and collection of the data. E.M.U., D.D., R.B.D., A.S.S., L.M.D., R.F.H., S.R.D., S.M., and R.P.W. were involved in data analyses and manuscript preparation and contributed to editing. E.M.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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