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

The SEARCH CVD study

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 HbA1c.

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 HbA1c 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.

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 Adolescents and Young Adults.

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 HbA1c 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 (R² for common, 0.12; bulb, 0.15; internal, 0.16; all models P ≤ 0.001). The addition of HbA1c eliminated the case-control difference for carotid bulb (0.464 in cases compared with 0.15), suggesting that glycemic control may be an important factor explaining the difference in carotid thickness.

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.
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 0.016 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 differing thicker carotid bulb 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 HbA1c) (8), or had a control group with a more favorable cardiovascular risk 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 subclinical atherosclerosis in youth.

The DCCT/EDIC study demonstrated that the intensive treatment group had a slower progression of IMT (5) and that mean HbA1c 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 HbA1c (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.

Acknowledgments—The SEARCH CVD study was funded by R01DK078542 (to D.D.). No potential conflicts of interest relevant to this article were reported.

The SEARCH CVD study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible. The authors also thank all of the study participants and their families for their cooperation and support.

The SEARCH CVD study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible. The authors also thank all of...
the SEARCH for Diabetes in Youth investigators and study staff, whose help was essential in moving this project forward.

References
1. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O’Leary DH, Haffner SM. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. Arterioscler Thromb Vasc Biol 2003;23:1035–1041
2. Krolewski AS, Kosinski EJ, Warram JH, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 1987;59:750–755
3. Dabelea D, Pihoker C, Talton JW, et al.; SEARCH for Diabetes in Youth Study. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 2011;34:1628–1633
4. Stein JH, Douglas PS, Srinivasan SR, et al. Distribution and cross-sectional age-related increases of carotid artery intima-media thickness in young adults: the Bogalusa Heart Study. Stroke 2004;35:2782–2787
5. Nathan DM, Lachin J, Cleary P, et al.; Diabetes Control and Complications Trial; Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294–2303
6. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS; Bogalusa Heart Study. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). Am J Cardiol 2002;90:953–958
7. Margeirsdottr HD, Stensaeth KH, Larsen JR, Bruunborg C, Dahl-Jørgensen K. Early signs of atherosclerosis in diabetic children on intensive insulin treatment: a population-based study. Diabetes Care 2010;33:2043–2048
8. Stakos DA, Schuster DP, Sparks EA, Wooley CF, Osei K, Boudouhas H. Cardiovascular effects of type 1 diabetes mellitus in children. Angiology 2005;56:311–317
9. Schwab KO, Doerfer J, Krebs A, et al. Early atherosclerosis in childhood type 1 diabetes: role of raised systolic blood pressure in the absence of dyslipidaemia. Eur J Pediatr 2007;166:541–548
10. Gunczler P, Lanes R, Lopez E, Esaa S, Villarroel O, Revel-Chion R. Cardiac mass and function, carotid artery intima-media thickness and lipoprotein (a) levels in children and adolescents with type 1 diabetes mellitus of short duration. J Pediatr Endocrinol Metab 2002;15:181–186
11. Parikh A, Sochett EB, McCrindle BW, Dipchand A, Daneman A, Daneman D. Carotid artery distensibility and cardiac function in adolescents with type 1 diabetes. J Pediatr 2000;137:465–469
12. Polak JF, Backlund JY, Cleary PA, et al.; DCCT/EDIC Research Group. Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes 2011;60:607–613
13. Dalla Pozza R, Netz H, Schwarz H-P, Bechtold S. Subclinical atherosclerosis in diabetic children: results of a longitudinal study. Pediatr Diabetes 2010;11:129–133
14. Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. Circulation 2009;119:2913–2919
15. Heilman K, Zilmer M, Zilmer K, et al. Arterial stiffness, carotid artery intima-media thickness and plasma myeloperoxidase level in children with type 1 diabetes. Diabetes Res Clin Pract 2009;84:168–173
16. Atabek ME, Kurtoglu S, Pirgon O, Baykara M. Arterial wall thickening and stiffening in children and adolescents with type 1 diabetes. Diabetes Res Clin Pract 2006;74:33–40