Measures of Arterial Stiffness in Youth With Type 1 and Type 2 Diabetes

The SEARCH for Diabetes in Youth study

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OBJECTIVE — Arterial stiffness occurs early in the atherosclerotic process; however, few data are available concerning risk factors for arterial stiffness in youth with diabetes. We identified factors associated with arterial stiffness in youth with diabetes and assessed the effects of these factors on the relationship between arterial stiffness and diabetes type (type 1 vs. type 2).

RESEARCH DESIGN AND METHODS — A subset of patients from the SEARCH for Diabetes in Youth study with type 1 (n = 533) and type 2 diabetes (n = 60), aged 10–23 years (52% male; 82% non-Hispanic white; diabetes duration 65 ± 49 months) had arterial stiffness, anthropometry, fasting lipids, and A1C measured. Arterial stiffness was measured by brachial distensibility (brachD), pulse wave velocity (PWV), and augmentation index adjusted to heart rate of 75 beats/min (AI75).

RESULTS — Youth with type 2 diabetes had worse brachD (5.2 ± 0.9 vs. 6.1 ± 1.2%/mmHg), PWV (6.4 ± 1.3 vs. 5.3 ± 0.8 m/s), and AI75 (6.4 ± 9.9 vs. 2.2 ± 10.2%) than those with type 1 diabetes (P < 0.01 for each). These differences were largely mediated through increased central adiposity and higher blood pressure in youth with type 2 diabetes. We also found a pattern of association of arterial stiffness measures with waist circumference and blood pressure, independent of diabetes type.

CONCLUSIONS — Youth with type 2 diabetes have worse arterial stiffness than similar youth with type 1 diabetes. Increased central adiposity and blood pressure are associated with measures of arterial stiffness, independent of diabetes type. Whether these findings indicate that youth with type 2 diabetes will be at higher risk for future complications requires longitudinal studies.

Vascular dysfunction occurs early in the atherosclerotic process and is associated with obesity and insulin resistance (4). Multiple methods have been developed to evaluate vascular function noninvasively, including several measures of arterial stiffness, such as brachial distensibility, pulse wave velocity (PWV), and augmentation index (5). Because atherosclerosis develops in a nonuniform fashion (6), multiple measures are needed in any noninvasive study of early CVD in youth.

The aim of this report was to identify factors associated with measures of arterial stiffness in youth with diabetes participating in the SEARCH for Diabetes in Youth (SEARCH) study and to assess the effect of these factors on the relationship between arterial stiffness and diabetes type (type 1 vs. type 2).

RESEARCH DESIGN AND METHODS — SEARCH is a multi-center study that began conducting population-based ascertainment of cases of diabetes in youth <20 years of age in 2001 and continues through the present. A detailed description of SEARCH study methods has been published (7). The case ascertainment approach involves networks of pediatric and adult endocrinologists, existing pediatric diabetes databases, hospitals, health plan databases, and other health care organizations. From two of the six SEARCH study sites (Colorado and Ohio), 602 SEARCH participants were recruited between September 2004 and October 2005 to participate in a substudy to examine determinants of arterial stiffness. Eligibility criteria included age at study visit >10 years; diabetes duration >9 months; and participation in an in-person SEARCH research visit.

The study was reviewed and approved by local institutional review boards. Informed consent and assent, where applicable, were obtained from all subjects and parents/guardians of subjects aged <18 years before enrollment.
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Data collection
Youth with diabetes or their parent/guardians completed an initial survey on demographic and diabetes-related factors. Diabetes type was reported by health care professionals or abstracted from medical records. For this report, we have restricted analyses to youth with type 1 and type 2 diabetes. Provider-based definitions of type 1 and type 2 diabetes were consistent with clinical and biochemical characteristics of diabetes type, including the presence of diabetes autoantibodies and residual insulin secretion. Youth with maturity-onset diabetes of the young, hybrid, other, or missing type were excluded (n = 7).

Blood was drawn after an overnight fast, under conditions of metabolic stability, to measure A1C, fasting glucose, and lipids (total, HDL, and LDL cholesterol and triglycerides). Specific methods for these tests have been described previously (7,8). A brief physical examination included height, weight, waist circumference, and systolic (SBP) and diastolic blood pressure (DBP). Weight and height were compared with 2000 Centers for Disease Control and Prevention standards for the U.S. to calculate normalized BMI Z scores.

Arterial stiffness measures
Three arterial stiffness measures were performed after 5 min of rest: 1) brachial artery distensibility (brachD); 2) PWV in the carotid to femoral segment; and 3) augmentation index adjusted to heart rate of 75 beats/min (AI75).

Vascular function testing was performed using a DynaPulse Pathway instrument (Pulse Metric, San Diego, CA), which derives brachD using pulse dynamic analysis of arterial pressure signals obtained from a standard cuff sphygmomanometer (9). The pressure waveform was calibrated and incorporated into a physical model of the cardiovascular system, assuming a straight tube brachial artery and T-tube aortic system. BrachD was calculated using an empirical model to estimate baseline brachial artery diameter from sex, height, weight, and mean arterial pressure (MAP). Lower brachD indicates increased arterial stiffness. A blood pressure cuff appropriate for the subject’s arm size was applied. Three automatic blood pressure recordings of SBP, DBP, MAP, and heart rate were obtained. Offline analyses of brachial artery pressure curve data were then performed by Pulse Metric, using an automated system to derive parameters from the pulse curves to calculate brachD (5).

PWV calculates the speed for the pressure wave generated by cardiac ejection to reach the periphery. Higher PWV indicates increased arterial stiffness. PWV was measured with a SphygmoCor Vx System (AtCor Medical, Sydney, Australia). Three electrocardiogram leads were applied to the torso, and the average of three distances from the lowest portion of the sternal notch to the carotid and femoral arterial sites was obtained (10). A pressure waveform was obtained for the proximal site (carotid) and a second was recorded from the femoral artery. Waveforms were gated by the R wave on the simultaneously recorded electrocardiogram. PWV is the difference in the carotid-to-femoral path length divided by the difference in R wave–to–waveform foot times, using an average of at least 10 beats to cover a complete respiratory cycle. The average of three recordings of PWV was used in the analyses.

The augmentation index (AIx) provides a measure of systemic arterial stiffness (11). A higher AIx indicates increased arterial stiffness. The SphygmoCor tonometer was placed over the right radial artery, and data were collected as described previously (12). The pressure waves were calibrated using MAP and DBP obtained in the same arm. The device then analyzed the pulse wave using a validated generalized transfer function. Wave forms collected over a 10-s period were averaged to produce peripheral and corresponding central (ascending aortic) pressure waveforms. Ascending aortic pressure and AIx were derived from the central pressure waveform. The AIx was calculated as the difference between the main outgoing wave and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure. Because AIx is affected by heart rate, values were adjusted to a standard heart rate of 75 beats/min (AI75). An average of three measures was used in the analyses.

Statistical analyses
Statistical analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC). Comparisons of demographic and clinical characteristics according to diabetes type were examined using χ² tests for categorical variables, t tests for normally distributed continuous variables, and Kruskal-Wallis tests for continuous variables with skewed distributions (Table 1). Sequential multiple linear regressions were performed to examine the association of diabetes type (type 2 vs. type 1) with each arterial stiffness measure and the effect of adjustment for covariates on this relationship. Demographic and metabolic variables associated with at least one measure of arterial stiffness at P < 0.05 were considered for inclusion in the multivariate models. Variables examined but not included in the models include BMI Z score, total cholesterol, triglycerides, and albuminuria. Covariates entered into sequential models are shown in Table 2. In these models we examined whether the hypothesized association between diabetes type (type 2 vs. type 1) and measures of arterial stiffness was explained by the addition of a particular (set of) risk factors (Table 3). In addition, in model 7 we examined which of the above variables were independently associated with measures of arterial stiffness (Table 4).

RESULTS — Clinical characteristics of study participants are given in Table 1, according to diabetes type. Of 595 subjects, 90% had type 1 diabetes and 10% had type 2 diabetes. The cohort included 52% male participants and 82% non-Hispanic whites and had a mean ± SD duration of diabetes of 65 ± 49 months and age of 14.9 ± 3.4 years. Subjects with type 2 diabetes were slightly older, were more ethnically diverse, had higher BMI and BMI Z scores, and had lower A1C than subjects with type 1 diabetes. Table 1 also shows that youth with type 2 diabetes had worse measures of arterial stiffness (lower brachD and higher AI75 and PWV) (P < 0.01 for all).

Table 2 shows bivariate associations between risk factors of interest and measures of arterial stiffness (brachD, PWV, and AI75), stratified by diabetes type. Associations were similar for youth with type 1 and type 2 diabetes across several measures of arterial stiffness for waist circumference and blood pressure (especially systolic), whereas A1C and lipids (HDL and LDL cholesterol) tended to be associated with measures of arterial stiffness only in youth with type 1 diabetes.

Table 3 presents the association between each measure of arterial stiffness and diabetes type (type 2 vs. type 1) in sequential multiple linear regressions models. Of note, brachD and PWV measures already take into account the height or length of the vascular segment being studied. Addition of height to any of the
models for brachD and PWV did not significantly alter the relationship between diabetes type and these arterial stiffness measures. Regression models for AI75 included adjustment for subjects’ height. After adjustment for age, sex, race/ethnicity, study site, and diabetes duration, type 2 diabetes status was significantly associated with lower brachD, higher PWV, and AI75 (Table 3, model 1). On additional adjustment for A1C, associations were virtually unchanged (model 2). On additional adjustment for differences in waist circumference (model 3), type 2 diabetes status was no longer significantly associated with brachD and PWV, although AI75 still remained significantly higher in participants with type 2 diabetes. In the following three models, we explored whether adjustment for lipids (HDL cholesterol and LDL cholesterol, model 4), SBP (model 5), and DBP (model 6), in addition to A1C and demographic factors, influenced the associations of interest. Whereas addition of lipid levels had no substantial impact, addition of SBP and, to a lesser extent, addition of DBP removed differences in brachD and AI75, but not differences in PWV between youth with type 2 and type 1 diabetes. Finally, adjustment for all potential risk factors in model 7 virtually removed all differences in measures of arterial stiffness according to diabetes status. Adjustment for pulse pressure instead of SBP and DBP in a model including all other covariates (model 8) had an effect on the relationship between arterial stiffness measures and diabetes type similar to that of blood pressure levels.

Table 2 shows B coefficients and corresponding P values for associations between each measure of arterial stiffness and all covariates included in model 7. In this model, lower brachD was independently associated with higher waist circumference, SBP, and DBP; increased PWV was associated with older age, higher waist circumference, and DBP; and increased AI75 was associated with female sex, minority racial/ethnic background, longer diabetes duration, higher LDL cholesterol, and DBP. No measure of arterial stiffness was associated with A1C in multivariate models.

CONCLUSIONS — Our data indicate that youth with type 2 diabetes have significantly worse arterial stiffness measures than similar youth with type 1 diabetes. These differences are not accounted for by differences in demographic characteristics (age, sex, and race/ethnicity), diabetes duration, and A1C...
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Table 3—Association between diabetes type (type 2 vs. type 1 diabetes) and measures of arterial stiffness in multiple linear regression analysis

| Arterial stiffness measure | BrachD | P | PWV | P | AI75* | P |
|---------------------------|--------|---|-----|---|------|---|
| Model 1: diabetes type, age, race, sex, site, and duration | -0.57 ± 0.20 (0.004) | 0.62 ± 0.12 (<0.0001) | 4.27 ± 1.47 (0.004) |
| Model 2: model 1 + A1C | -0.51 ± 0.20 (0.01) | 0.67 ± 0.13 (<0.0001) | 4.53 ± 1.51 (0.003) |
| Model 3: model 1 + A1C + waist circumference | 0.13 ± 0.21 (0.51) | 0.24 ± 0.13 (0.07) | 3.59 ± 1.69 (0.03) |
| Model 4: model 1 + A1C + LDL cholesterol, HDL cholesterol | -0.45 ± 0.21 (0.04) | 0.57 ± 0.13 (<0.0001) | 3.73 ± 1.58 (0.02) |
| Model 5: model 1 + A1C + SBP | -0.25 ± 0.17 (0.15) | 0.45 ± 0.13 (0.0004) | 2.57 ± 1.61 (0.11) |
| Model 6: model 1 + A1C + DBP | -0.50 ± 0.20 (0.01) | 0.45 ± 0.12 (0.0002) | 2.23 ± 1.57 (0.16) |
| Model 7: model 1 + A1C + waist + LDL cholesterol, HDL cholesterol + SBP and DBP | -0.01 ± 0.16 (0.0) | 0.15 ± 0.13 (0.23) | 1.75 ± 1.74 (0.31) |
| Model 8: model 2 + waist + LDL cholesterol, HDL cholesterol + pulse pressure | -0.01 ± 0.16 (0.93) | 0.14 ± 0.14 (0.32) | 1.74 ± 1.78 (0.33) |

Data are β coefficients ± SEM. β coefficients represent the differences in BrachD, PWV, and AI75 in subjects with type 2 diabetes compared with those with type 1 diabetes when adjusting for the variables included in the regression model. *Regression models for AI75 include an adjustment for height.

but are largely mediated through increased central adiposity and increased blood pressure levels in youth with type 2 diabetes. We also found a pattern of association of arterial stiffness measures with central adiposity (waist circumference) and blood pressure, independent of diabetes type. Thus, worse patterns of arterial stiffness seen in youth with type 2 diabetes are probably due to the higher prevalence of CVD risk factors seen in such subjects. The presence of CVD risk factors including hypertension, obesity, and subclinical hyperglycemia may contribute to vascular change before diagnosis of diabetes for patients with both type 1 and type 2 diabetes, although given the relatively acute onset of type 1 diabetes, this is more likely to occur in patients with type 2 diabetes.

These results suggest that increased adiposity may contribute to increased arterial stiffness in youth with diabetes, regardless of diabetes type. Other studies have also found a relationship between body size and vascular function in adults (13,14) and youth with type 2 diabetes (15), but data in youth with type 1 diabetes are limited (16). Prevention and control of obesity with both diabetes types may therefore play a significant role in reducing the risk of early vascular changes.

Blood pressure was also a significant independent correlate in our analyses, which is consistent with previous studies of arterial stiffness in adults. Evidence from such studies suggests that subclinical changes in blood pressure may have an impact on arterial stiffness before hypertension is clinically evident (5,17).

We did not observe a cross-sectional association between glycemic control (A1C) and arterial stiffness in this study. Our data are similar to previous publications regarding the relationship between A1C and AIx in younger type 1 diabetic patients (18). There are several possible explanations for this finding. First, our data only explore cross-sectional associations between a single A1C measure and

Table 4—Determinants of arterial stiffness measures in multiple linear regression analysis

| Arterial stiffness measure | BrachD | PWV | AI75* |
|---------------------------|--------|-----|------|
| Diabetes type (type 2 vs. type 1) | -0.01 ± 0.16 (0.9) | 0.15 ± 0.13 (0.2) | 1.75 ± 1.74 (0.3) |
| Age at visit | -0.03 ± 0.07 (0.6) | 0.29 ± 0.06 (<0.0001) | -0.66 ± 0.88 (0.4) |
| Sex (female vs. male) | -0.14 ± 0.07 (0.05) | -0.05 ± 0.06 (0.3) | 1.93 ± 0.85 (0.02) |
| Race (other vs. non-Hispanic white) | -0.15 ± 0.10 (0.1) | 0.01 ± 0.08 (0.9) | 2.94 ± 1.12 (0.01) |
| Duration of diabetes | -0.07 ± 0.05 (0.1) | 0.07 ± 0.04 (0.09) | 1.24 ± 0.55 (0.02) |
| A1C | 0.0004 ± 0.02 (0.9) | 0.01 ± 0.02 (0.5) | -0.06 ± 0.24 (0.8) |
| Waist circumference | -0.08 ± 0.02 (<0.0001) | 0.07 ± 0.01 (<0.0001) | -0.0003 ± 0.20 (0.9) |
| LDL cholesterol | -0.002 ± 0.01 (0.7) | 0.005 ± 0.01 (0.3) | 0.17 ± 0.08 (0.03) |
| HDL cholesterol | -0.005 ± 0.02 (0.7) | -0.01 ± 0.01 (0.3) | -0.04 ± 0.17 (0.8) |
| SBP | -0.32 ± 0.03 (<0.0001) | 0.02 ± 0.02 (0.4) | -0.48 ± 0.28 (0.09) |
| DBP | 0.51 ± 0.03 (<0.0001) | 0.20 ± 0.03 (<0.0001) | 1.94 ± 0.39 (<0.0001) |
| R² | 0.5675 | 0.5263 | 0.3118 |

Data are β coefficients ± SEM (P values). A1C is per 1 unit change; all other continuous measures are per 5 units change. Significant associations are in bold. *Model for AI75 includes adjustment for height (β = -0.28 ± 0.04, P < 0.0001).
arterial stiffness. Longitudinal studies of vascular changes in diabetic youth may provide further insight into how long-term glycemic control may affect arterial stiffness, even before clinical onset of chronic vascular complications. Second, the effects of hyperglycemia on the vascular lature may not be seen with measures of arterial stiffness. However, studies of carotid intima-media thickness (cIMT) in youth with type 1 diabetes also did not show an association with A1C (19). Hyperglycemia might not affect vascular structure and function measurably in persons with a relatively short duration of diabetes. In our cohort, the median (interquartile range) duration of diabetes was 4.75 (2.42–8.00) and 3.13 (2.08–4.54) years for patients with type 1 and type 2 diabetes, respectively. Parikh et al. (20) noted an association between carotid distensibility and A1C in a cohort of adolescents with type 1 diabetes (aged 15.8 years) with longer diabetes duration (9.3 years). Worse glycemic control during the Diabetes Control and Complications Trial (DCCT) was associated with increased progression of cIMT (21) and a higher incidence of CVD events in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (22). However, the DCCT findings were observed in older subjects (mean age 35 years) with longer diabetes duration (mean duration 13.8 years).

To our knowledge, this is the first study to compare measurements of arterial stiffness in youth with type 1 and type 2 diabetes. The cohort of 595 subjects is relatively large. Other studies of arterial stiffness (18,20) and cIMT (19) have been conducted in smaller cohorts of youth with type 1 diabetes. Moreover, our study included multiple methods to evaluate arterial stiffness (brachD, PWV, and AI75) and showed consistent results across all of these measures. Of the methods used in this study, PWV appeared to be the most robust. PWV was significantly higher in youth with type 2 diabetes even after adjustment for SBP and DBP, whereas differences in brachD and AI75 by diabetes type seemed to be more sensitive to adjustments for blood pressure.

Our study has limitations. A nondiabetic control group was not included, thus limiting our ability to compare these diabetic patients with the general population of healthy youth. Of note, data are sparse among nondiabetic youth of similar age (11,18,23). Data were collected in only 60 subjects with type 2 diabetes. However, this relatively small sample is representative of youth with type 2 diabetes participating in the larger SEARCH study (24), and only Urbina et al. (25) have reported on arterial stiffness in a larger cohort of youth with type 2 diabetes; however, PWV and AI75 were not included in that study.

A potential methodological limitation for PWV is the distance measured externally on the body from the suprasternal notch to the femoral pulse. If the distance is longer for subjects with larger waist circumference, calculated PWV may be higher. We measured the distance from the suprasternal notch to the femoral pulse with a tape measure laid on the body to use the most reproducible technique. Alternatives include a measure over the body or intra-arterial measurement of the artery using imaging techniques. Measuring over the body was not done to avoid potential reproducibility issues. Imaging of the vascular segment to obtain a measurement was not feasible. Although other measurement techniques may have altered the findings for PWV, it is important to note that brachD and AI75, techniques not requiring such a measurement, showed a similar pattern of reduced difference in arterial stiffness by diabetes type after adjustment for waist circumference.

The cross-sectional design of this study also limits our ability to conclude which factors cause the development of altered arterial stiffness in diabetic patients. Longitudinal studies of vascular changes in diabetic patients are needed to further understand the role of glycemic control, blood pressure, and adiposity on arterial stiffness over time.

In summary, youth with type 2 diabetes have significantly worse arterial stiffness measures than youth with type 1 diabetes, probably because of their patterns of elevated blood pressure and central adiposity. Increased central adiposity and blood pressure levels are associated with measures of arterial stiffness, independent of diabetes type. Longitudinal studies are needed to determine whether increased arterial stiffness is an early sign of future progression to CVD in youth with diabetes. Further studies could potentially delineate key modifiable CVD risk factors and the utility of preventive interventions to decrease the rates of CVD in patients with youth-onset type 1 and type 2 diabetes.
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