ORIGINAL RESEARCH

Burden of Cardiovascular Risk Factors Over Time and Arterial Stiffness in Youth With Type 1 Diabetes Mellitus: The SEARCH for Diabetes in Youth Study

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Background—The incidence of type 1 diabetes mellitus (T1DM) in children is increasing, resulting in higher burden of cardiovascular diseases due to diabetes mellitus–related vascular dysfunction.

Methods and Results—We examined cardiovascular risk factors (CVRFs) and arterial parameters in 1809 youth with T1DM. Demographics, anthropometrics, blood pressure, and laboratory data were collected at T1DM onset and 5 years later. Pulse wave velocity and augmentation index were collected with tonometry. ANOVA or chi-square tests were used to test for differences in measures of arterial parameters by CVRF. Area under the curve of CVRFs was entered in general linear models to explore determinants of accelerate vascular aging. Participants at the time of arterial measurement were 17.6±4.5 years old, 50% female, 76% non-Hispanic white, and duration of T1DM was 7.8±1.9 years. Glycemic control was poor (glycated hemoglobin, 9.1±1.8%). All arterial parameters were higher in participants with glycated hemoglobin ≥9% and pulse wave velocity was higher with lower insulin sensitivity or longer duration of diabetes mellitus. Differences in arterial parameters were found by sex, age, and presence of obesity, hypertension, or dyslipidemia. In multivariable models, higher glycated hemoglobin, lower insulin sensitivity, body mass index, blood pressure, and lipid areas under the curve were associated with accelerated vascular aging.

Conclusions—In young people with T1DM, persistent poor glycemic control and higher levels of traditional CVRFs are independently associated with arterial aging. Improving glycemic control and interventions to lower CVRFs may prevent future cardiovascular events in young individuals with T1DM. **(*J Am Heart Assoc*. 2019;8:e010150. DOI: 10.1161/JAHA.118.010150.)**

Key Words: arterial compliance • diabetes mellitus • pediatric • risk factor

Diabetes mellitus is one of the most common chronic diseases in children,[1,2] affecting nearly 1 of every 433 youth in the United States,[3]and the majority of diabetes mellitus cases in childhood are due to type 1 diabetes mellitus (T1DM).[4] As the rate of T1DM continues to climb,[3,5,6] this may eventually result in higher cardiovascular diseases (CVD) incidence, and CVD is one of the major causes of death in adults with diabetes mellitus.[7] One mechanism for the increase in CVD may be diabetes mellitus–related abnormalities in vascular structure and function that have been found

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Accompanying Appendix S1, Tables S1 through S4 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010150

*A complete list of the SEARCH for Diabetes in Youth Study Group members can be found in Appendix S1.

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Clinical Perspective

What Is New?

- The relationship between longitudinal burden of cardiovascular risk factors and objective measures of vascular health in youth with type 1 diabetes mellitus (T1DM) has not been previously explored.
- Poor glycemic control over time is a major determinant of accelerated vascular aging in adolescents with T1DM.
- Traditional cardiovascular risk factors including obesity, hypertension, and dyslipidemia also contribute to vascular aging in youth with T1DM.

What Are the Clinical Implications?

- Tighter glycemic control needs to be achieved to reduce the burden of micro- and macrovascular disease in young people with T1DM.
- Individuals with T1DM should strive to increase the number of ideal cardiovascular health metrics they are achieving as adverse levels of traditional cardiovascular risk factors also contribute to vascular aging in youth with T1DM.

in adolescents with diabetes mellitus.[8–10] However, the true prevalence of these abnormalities in youth with T1DM is not known. It is also necessary to elucidate the correlates of vascular dysfunction in young patients with T1DM, which may guide future diabetes mellitus management recommendations. The presence of cardiac autonomic neuropathy (CAN) has also been associated with higher arterial stiffness in both adults and youth with diabetes mellitus, and it could be a potential contributor to vascular aging. Furthermore, analyses have examined the relationship between cardiovascular risk factors (CVRFs) measured at one point in time and arterial health in youth,[11] but CVRF levels vary over time, and few studies have examined the long-term burden of CVRFs on the vasculature in youth with T1DM. Therefore, our aim was to demonstrate that higher burden (area under the curve over time) of CVRFs was associated with measures of arterial stiffness and wave reflections in a cohort of individuals with onset of T1DM before 20 years of age. We also sought to determine if CAN was an independent predictor of arterial parameters.

Methods

In accordance with the Transparency and Openness Promotion Guidelines, the data that support the findings of this study are available from the statistical coordinating center (Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; sisom@wakehealth.edu; rdagosti@wakehealth.edu) upon reasonable request.

Description of the Study Population

Participants who were diagnosed with T1DM prior to 20 years of age who participated in a population-based diabetes mellitus registry at 5 US sites by the SEARCH for Diabetes in Youth Study were eligible.[2] Specifically, we recruited youth with newly diagnosed T1DM in 2002 through 2006 or 2008, who completed a SEARCH baseline examination for CVRFs ≈9 months after diagnosis and were reexamined at a follow up visit at least 5 years after the baseline examination. The average time from diagnosis to collection of arterial stiffness measures was 7.9±1.9 years. Nearly 60% of participants had one or more additional CVRF assessments between the baseline and follow-up where vascular measures were obtained. Diabetes mellitus type was defined at the baseline visit using a classification developed by SEARCH[12,13] on the basis of ≥1 positive diabetes mellitus autoantibodies (see below) and estimated insulin sensitivity score (IS, validated equation including waist circumference, glycated hemoglobin [HbA_{1c}] and triglyceride levels).[12] T1DM was defined as the presence of at least 1 positive antibody, regardless of insulin sensitivity, or no positive antibodies and insulin sensitivity (score ≥8.15). This study included participants with T1DM, as defined above, with at least 1 measure of arterial stiffness, and C-reactive protein levels ≤10 mg/Dl, as acute infection may transiently affect arterial stiffness. The final analytic sample consisted of 1809 participants. Institutional review board approval was obtained at each site, and all participants or their guardians gave informed consent.

CVRF Collection

All testing was performed under standardized conditions by trained personnel. At baseline and at the follow-up visit, participants were examined after an 8-hour overnight fast while refraining from strenuous exercise, smoking, or any caffeinated drinks. Short-acting insulin and oral medications were withheld the morning of the visit until after the blood draw and vascular studies were complete. Race/ethnicity was self-reported using a 2000 US Census–based questionnaire and was classified as non-Hispanic white, non-Hispanic black, Hispanic, and Other. Height was measured in centimeters using a stadiometer and weight in kilograms using a standardized scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and age and sex-specific BMI *z* scores were derived on the basis of the 2000 Centers for Disease Control and Prevention national standards.[14] Waist circumference was measured using the National Health and Nutrition Examination Survey protocol and divided by height in centimeters to calculate waist-to-height ratio.[3] Resting systolic blood pressure (SBP) and diastolic blood pressure were measured 3 times, using an aneroid sphygmomanometer and an

appropriate-sized cuff, after the participants were seated for at least 5 minutes according to published guidelines.[15] The average of multiple measures of anthropometric and blood pressure (BP) variables were used at each visit. Plasma samples were analyzed for HbA_{1c}, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels at the study central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington) as previously described.[16] The study central laboratory measured the diabetes mellitus autoantibodies glutamic acid decarboxylase and insuloma-associated-2 antibody,[17] while zinc-T8 autoantibody was analyzed at the Eisenbarth Laboratory (University of Colorado, Aurora, CO).[18]

Arterial Parameters

At the follow-up visit, the average of 3 measurements of each modality was obtained in a room with a stable temperature after the participant rested for >10 minutes using previously published protocols.[10,19] Pulse wave velocity (PWV) was collected using the SphygmoCor CPVH (AtCor Medical, Sydney, Australia) from the carotid to the femoral artery (PWVcf) representing central arterial stiffness in a large elastic artery. Carotid to radial (PWVcr) and femoral to foot (PWVft) were also obtained as measures of peripheral (muscular) artery stiffness. Briefly, ECG-gated pressure wave data were obtained with a tonometer placed on the artery. PWV is the difference in proximal-to-distal artery path length (suprasternal notch to femoral artery measured directly with a caliper minus suprasternal notch to carotid pulse measured with a tape measure) divided by the difference in timing from the peak of the ECG R-wave to foot of the proximal or distal pressure wave. Augmentation index (AIx), a measure of wave reflections influenced by vascular tone, heart rate, and cardiac function, was collected with the same device. For AIx, the pressure waves were calibrated by using mean arterial pressure (MAP) and diastolic BP obtained in the same arm. Using MAP instead of SBP is less prone to errors in calibration attributable to pulse pressure amplification along the brachial artery.[20] A validated generalized transfer function was used to calculate central aortic pressure and AIx (augmentation of central pressure indexed to pulse pressure and adjusted to a heart rate of 75 bpm). These techniques are highly reproducible with coefficients of variability of 7% for PWV and intraclass correlation coefficients of 0.7 to 0.9 for AIx.[10] For both PWV and AIx, a higher value indicates a stiffer vessel. To define increased arterial stiffness, the 90th percentile for all measures in healthy, lean adolescents and young adults of similar age range, obtained via the same technique in our laboratory, was used. The prevalence of increased stiffness (≥90th percentile) was determined.

Assessment of CAN

At follow-up, presence of CAN was assessed by heart rate variability testing using the SphygmoCor device (Atcor Medical Inc, Sydney, Australia) as previously described.[9] A 10-minute continuous ECG recording was obtained in the supine position after a 5-minute rest. ECG tracings were examined to ensure that R-waves were adequately identified from artifacts and ectopic beats. The device analyzed time- and frequency-domain parameters including SD of NN interval, root mean square difference of the successive NN interval, high-frequency power, low-frequency power, and low frequency–to–high frequency ratio. The heart rate variability test was considered abnormal if the values were below the fifth percentile observed in age- and sex-matched healthy controls (age 10–28 years, 54% females) from the SEARCH CVD study.[21] CAN was defined as presence of >3 abnormal heart rate variability indices.

Statistical Analysis

In participants aged ≥18 years, normal or underweight was defined as BMI<25 kg/m^2, overweight as BMI 25 to 29.99 kg/m^2, and obesity as BMI ≥30 kg/m^2. In participants aged <18 years, normal or underweight was defined as age- and sex-specific BMI <85th percentile. Overweight was defined as BMI at the 85th to 94th percentile, and obesity was defined as a BMI ≥95th percentile.[22] Hypertension was defined as being on BP-lowering medication; BP ≥140/90 mm Hg for young adults[23]; or ≥95th percentile for age, sex, and height for adolescents.[15] Dyslipidemia was defined as being on lipid-lowering medication or low-density lipoprotein ≥130 mg/dL, HDL ≤40 mg/dL, triglycerides ≥150 mg/dL, or non-HDL cholesterol ≥145 mg/dL.[24] Smoking status was obtained by self-report and categorized as never, current, or former smoker as previously described.[25] Physical activity status was defined as participating in moderate or vigorous activity for at least 20 minutes at least 3 or more times per week. Sedentary behavior was defined as having >2 hours/day of screen time regardless of physical activity pattern.

The longitudinal cumulative exposure to CVRFs for each participant was calculated as the weighted average of the measures of interest during the participant's time in the study for waist-to-height ratio, SBP, and diastolic BP *z* scores, MAP, and non-HDL cholesterol (potentially collected at baseline and 1-, 2-, and 5-year follow-up visits and weighted for the interval between each measurement, similar to the area under the curve [AUC]).

Statistical analyses were performed using SAS for Windows (version 9.4; SAS Institute, Cary, NC), and $P<0.05$ was considered significant. Mean (SD) or median (minimum, maximum) as appropriate was used for continuous variables

and counts (percentages) for categorical variables were calculated for the entire study population. Participants were categorized by demographics, duration of T1DM, and various CVRFs at follow-up (presence of obesity, hypertension, dyslipidemia, and lifestyle behaviors including smoking, physical activity and sedentary behavior levels). ANOVA or chi-square tests were used to test for differences in measures of arterial stiffness and wave reflections in individuals with or without an adverse CVRF. Bivariate correlations between CVRFs, AUC for CVRFs, and arterial stiffness and wave reflection measures were obtained to guide development of multivariable general linear models (as all variables were continuous) to explore factors associated with increased arterial stiffness and wave reflections in the population. Variables with a skewed distribution were log-transformed. The first models constructed adjusted for age at diabetes mellitus diagnosis, sex, race/ethnicity, clinic site, duration of diabetes mellitus, and 1 CVRF at a time. CVRF interactions with HbA_{1c} AUC were also evaluated in the first series of models. The final models included all covariates, and reduced models retained only significant covariates.

Results

At the follow-up visit, the cohort (Table 1, N=1809) was 17.6±4.5 years old (range, 6–30) and 50% were female, 76% non-Hispanic white, 10% non-Hispanic black, 12% Hispanic, and 2% Other. The mean duration of T1DM was 7.8±1.9 years (range, 5–13). The mean BMI was 23.9±5.2 kg/m^2, although 26% of the participants were overweight and 14% had obesity. Mean BP was 106/68±11/9 mm Hg within the normal range, with 13% classified as having hypertension, including 6% on BP-lowering medication. Mean lipid values were also within the normal range, although 29% were categorized as having dyslipidemia and 3% were on lipid-lowering medication. Glycemic control was poor, with mean HbA_{1c} 9.1±1.8% (range, 4–16). The mean daily dose of insulin was 0.9 (±0.4 units/kg body weight/day). While 68% of participants had never smoked and 58% reported adequate levels of physical activity, 92% reported high levels of sedentary behavior (data not shown).

Mean levels of arterial stiffness and wave reflections with participants stratified by a single CVRF at follow-up are displayed in Table 2. The prevalence of increased wave reflections or arterial stiffness (value ≥90th percentile for lean, healthy youth) was 7.0% for AIx, 19.4% for PWVcf, 13.0% for PWVft, and 12.4% for PWVcr. All measures of arterial stiffness and wave reflections were higher in individuals with HbA_{1c} ≥9% compared with those with better glycemic control (P≤0.05, Figure). These remained significant after adjusting for MAP, age, and sex for all measures except PWVcf (Figure S1). All measures of PWV were higher in participants with lower insulin sensitivity or longer duration of diabetes mellitus. PWVcf and PWVft were significantly higher in people classified as having CAN with a nonsignificant trend for PWVcr. In analyses stratified by levels of other CVRFs, differences in arterial parameters were found by sex (higher AIx in females, higher PWVft and PWVcr in males) and race (highest in non-Hispanic blacks for all measures). Higher arterial parameters were also found for older individuals at follow-up for all measures except wave reflections (AIx), which

Table 1. Description of the Study Population at Follow-Up (N=1809)

Parameter	Mean (SD), Median (min, max), or Percent
Age, y	17.6 (4.5)
Sex (% female)	49.5
Race/Ethnicity (%)	
Non-Hispanic white	76.2
Non-Hispanic black	9.7
Hispanic	11.8
Other	2.4
Duration of T1DM, y	7.8 (1.9)
Height, m	1.7 (0.1)
Weight, kg	66.5 (19.6)
Waist-to-height ratio	0.5 (0.1)
Body mass index, kg/m^2	23.9 (5.2)
Body mass index (z score) AUC	0.6 (0.9)
Systolic blood pressure, mm Hg	106.0 (11.0)
Systolic blood pressure (z score) AUC	−0.4 (0.9)
Diastolic blood pressure, mm Hg	68.4 (8.9)
Diastolic blood pressure (z score) AUC	0.0 (1.1)
MAP (z score) AUC	78.3 (7.4)
Heart rate, bpm	69.5 (11.7)
Total cholesterol, mg/dL	169.7 (34.8)
LDL-cholesterol, mg/dL	96.2 (28.1)
Triglycerides, mg/dL	73.0 (17.0, 992.0)
HDL-cholesterol, mg/dL	55.2 (13.6)
HDL-cholesterol (mg/dL) AUC	56.0 (11.7)
Non–HDL-cholesterol, mg/dL	114.4 (34.7)
Non–HDL-cholesterol (mg/dL) AUC	109.4 (26.3)
Fasting glucose, mg/dL	212.8 (92.2)
Insulin dose (units/kg of body weight per day)	0.9 (0.4)
Glycated hemoglobin, %	9.1 (1.8)
Glycated hemoglobin (%) AUC	8.5 (1.3)
C-reactive protein, mg/dL	0.1 (0.0, 7.9)

AUC indicates area under the curve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; T1DM, type 1 diabetes mellitus.

Table 2. Arterial Stiffness Overall and Stratified by Demographic and Clinical Characteristics at Follow-Up, Mean (SE)*

	AIx (%)		PWVcf (m/s)		PWVft (m/s)		PWVcr (m/s)	
Covariate	Mean (SE)	*P* Value	Mean (SE)	*P* Value	Mean (SE)	*P* Value	Mean (SE)	*P* Value
Overall	−2.33 (0.28)		5.44 (0.03)		8.09 (0.03)		7.42 (0.03)	
Age		0.007		<0.0001		<0.0001		<0.0001
Older (≥18)	−3.08 (0.39)		5.87 (0.04)		8.54 (0.05)		7.67 (0.05)	
Younger (<18)	−1.60 (0.39)		5.06 (0.03)		7.69 (0.04)		7.19 (0.04)	
Age at diagnosis		<0.0001		<0.0001		<0.0001		<0.0001
Older (10–19)	−3.49 (0.38)		5.80 (0.04)		8.42 (0.05)		7.57 (0.05)	
Younger (<10)	−1.09 (0.40)		5.08 (0.03)		7.77 (0.05)		7.27 (0.04)	
Sex		<0.0001		NS		<0.0001		0.01
Female	0.47 (0.39)		5.44 (0.04)		7.89 (0.05)		7.34 (0.05)	
Male	−4.99 (0.37)		5.44 (0.04)		8.28 (0.05)		7.50 (0.04)	
Race		<0.0001		<0.0001		0.0003		<0.0001
Non-Hispanic white	−3.01 (0.31)		5.37 (0.03)		8.07 (0.04)		7.33 (0.04)	
Non-Hispanic black	0.97 (1.01)		5.72 (0.09)		8.45 (0.13)		8.12 (0.11)	
Hispanic	−0.33 (0.76)		5.58 (0.08)		7.86 (0.10)		7.36 (0.09)	
Other	−2.73 (1.38)		5.79 (0.23)		8.41 (0.23)		7.57 (0.16)	
Glycated hemoglobin		0.0001		<0.0001		0.005		0.006
<9	−3.35 (0.39)		5.33 (0.04)		8.00 (0.05)		7.33 (0.04)	
≥9	−1.22 (0.39)		5.56 (0.04)		8.19 (0.05)		7.51 (0.05)	
Insulin sensitivity		NS		<0.0001		<0.0001		0.01
<8.15 (insulin resistant)	−2.48 (0.32)		5.63 (0.03)		8.20 (0.04)		7.47 (0.04)	
8.15+ (insulin sensitive)	−2.07 (0.56)		4.96 (0.04)		7.81 (0.06)		7.29 (0.06)	
Duration of diabetes mellitus		NS		<0.0001		<0.0001		0.002
<8 y	−2.63 (0.39)		5.26 (0.03)		7.90 (0.05)		7.33 (0.05)	
≥8 y	−2.02 (0.39)		5.65 (0.04)		8.31 (0.05)		7.53 (0.04)	
Cardiac autonomic neuropathy		NS		0.0002		0.0005		
No	−2.75 (0.30)		5.45 (0.03)		8.08 (0.04)		7.42 (0.04)	0.09
Yes	−2.68 (0.85)		5.76 (0.08)		8.46 (0.11)		7.60 (0.09)	

AIx indicates augmentation index; NS, nonsignificant; PWVcf, pulse wave velocity, carotid-femoral; PWVcr, pulse wave velocity, carotid-radial; PWVft, pulse wave velocity, femoral-foot.

are lower with greater height with age, and in those with obesity (PWVcf), hypertension (all PWV), or dyslipidemia (PWVcf and PWVft); higher C-reactive protein (AIx, PWVcf, and PWVft), reported smoking (PWV); and lower physical activity levels (all measures) with a trend for higher sedentary behavior (P=0.052 for PWVcf). Patterns were similar among all measures of arterial stiffness and wave reflections (see Tables S2 through S5 where differences were seen with 7, 14, 14, and 10 CVRFs for AIx, PWVcf, PWVft, and PWVcr, respectively).

Generalized linear models exploring the association of the burden of CVRFs over time on measures of arterial stiffness and wave reflections are presented in Table 3. For each of the CVRF AUCs, a model was adjusted for demographics, clinic site, and duration of diabetes mellitus. Higher HbA_{1c} AUC was associated with adverse levels of all vascular parameters. A measure of adiposity (either higher BMI and/or waist-to-height ratio) or a measure of BP (higher SBP, diastolic BP, and/or MAP) or lipids (lower HDL and/or higher non-HDL cholesterol) was associated with higher stiffness and wave reflections. Presence of CAN was significant for PWVcf only after adjustments. The models in Table 3 were repeated with the addition of adjustment for HbA_{1c} AUC or log(IS) AUC (data not shown). Adjusting for HbA_{1c} resulted in no changes, except non-HDL cholesterol was no longer statistically significantly associated with PWVcr.

Full models including all CVRFs, adjusted for clinic site and race, are presented in Table 4 (models with standardized beta

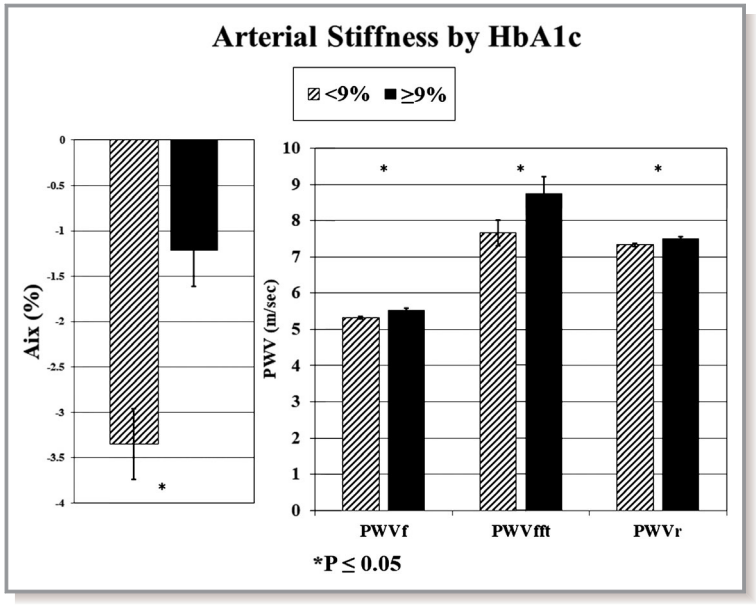

Figure. Arterial stiffness means with standard error bars by glycosylated hemoglobin (HbA_{1c} levels, %) in youth and young adults with type 1 diabetes mellitus. AIx indicates augmentation index; PWVcf, pulse wave velocity, carotid-femoral; PWVcr, pulse wave velocity, carotid-radial; PWVft, pulse wave velocity, femoral-foot.

estimates are found in Table S1). HbA_{1c} AUC was statistically significantly associated with all arterial measures, except there was only a trend for PWVcr. There was a HbA_{1c} AUC by non-HDL interaction term that entered the model for AIx, HbA_{1c} by CAN for AIx and PWVft, and HbA_{1c} by waist-to-height ratio term for PWVcf. Duration of T1DM was positively associated with higher stiffness or wave reflections. A measure of adiposity (for all measures except PWVcr) and MAP entered all the PWV models. Non-HDL cholesterol was significantly associated with AIx and PWVcf. CAN was not significant for any measure. Use of BP or lipid-lowering medication, smoking, and sedentary behavior were not significant, and being physically active was significantly associated with PWVft and PWVcr (in a favorable direction).

Table 3. Association of Arterial Stiffness With AUC of Metabolic and Cardiovascular Risk Factors in Youth and Young Adults with T1DM*

Cardiovascular Risk Factor Included in the Model	AIx		PWVcf		PWVft		PWVcr	
	Beta (SE)	*P* Value	Beta (SE)	*P* Value	Beta (SE)	*P* Value	Beta (SE)	*P* Value
HbA_{1c} (%) AUC	0.97 (0.20)	<0.0001	0.07 (0.02)	0.0002	0.09 (0.03)	0.0002	0.08 (0.02)	0.0005
BMI *z* score AUC	0.05 (0.30)	NS	0.23 (0.02)	<0.0001	−0.10 (0.04)	0.007	−0.09 (0.03)	0.01
WHR AUC	24.95 (4.45)	<0.0001	4.12 (0.39)	<0.0001	−0.38 (0.57)	NS	−0.15 (0.50)	NS
SBP *z* score AUC	1.44 (0.32)	<0.0001	0.13 (0.03)	<0.0001	0.10 (0.04)	0.009	0.07 (0.04)	0.08
DBP *z* score AUC	1.40 (0.26)	<0.0001	0.09 (0.02)	0.0003	0.07 (0.03)	0.02	0.11 (0.03)	0.0005
MAP (mm Hg) AUC	0.05 (0.04)	NS	0.03 (0.00)	<0.0001	0.03 (0.01)	<0.0001	0.02 (0.00)	0.0006
HDL (mg/dL) AUC (10 mg/dL change)	−0.03 (0.24)	NS	−0.05 (0.02)	0.02	−0.01 (0.03)	NS	0.02 (0.03)	NS
Non-HDL AUC (10 mg/dL change)	0.47 (0.11)	<0.0001	0.05 (0.01)	<0.0001	0.01 (0.01)	NS	0.03 (0.01)	0.02
CAN (yes vs no)	1.12 (0.82)	NS	0.13 (0.07)	0.08	0.21 (0.10)	0.050	0.12 (0.10)	NS

AIx indicates augmentation index; AUC, area under the curve; BMI, body mass index; CAN, cardiac autonomic neuropathy; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoblobin; HDL, high-density lipoprotein; MAP, mean arterial pressure; NS, nonsignificant; PWVcf, pulse wave velocity, carotid-femoral; PWVcr, pulse wave velocity, carotid-radial; PWVft, pulse wave velocity, femoral-foot; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; WHR, waist-to-height ratio.
*Generalized linear models for each cardiovascular risk factor AUC adjusted for age at diagnosis, sex, race, clinic site, duration of diabetes mellitus, and 1 cardiovascular risk factor AUC.

Table 4. Multivariable Associations of Metabolic and CVRFs with Arterial Stiffness in Youth and Young Adults With T1DM*

	AIx		PWVcf		PWVft		PWVcr	
Parameter	Beta (SE)	*P* Value	Beta (SE)	*P* Value	Beta (SE)	*P* Value	Beta (SE)	*P* Value
HbA_{1c} (%) AUC	4.08 (1.04)	0.0004	−0.32 (0.15)	0.03	−0.01 (0.07)	0.94	0.05 (0.03)	0.08
Duration of T1DM, y	0.62 (0.16)	<0.0001	0.10 (0.01)	<0.0001	0.11 (0.02)	<0.0001	0.06 (0.02)	0.003
Waist circumference AUC*	0.06 (0.03)	0.03						
Waist-to-height ratio AUC					−1.58 (0.66)	0.02		
MAP (mm Hg) AUC			0.02 (0.00)	<0.0001	0.03 (0.01)	<0.0001	0.02 (0.01)	0.0002
Non-HDL AUC (10 mg/dL increase)	1.87 (0.67)	0.01	0.02 (0.01)	0.05	0.01 (0.01)	NS	0.02 (0.01)	0.07
CAN: N (Y is ref)	13.36 (5.28)	0.01	−0.13 (0.08)	0.09	−1.13 (0.70)	0.11	−0.08 (0.10)	NS
Physically active: N (Y is ref)	0.48 (0.55)	NS	0.05 (0.05)	NS	0.15 (0.07)	0.04	0.15 (0.07)	0.03
HbA_{1c} (%) AUC×Non-HDL AUC (10 mg/dL increase)	−0.19 (0.08)	0.01						
HbA_{1c} (%) AUC×CAN: N (Y is ref)	−1.64 (0.60)	0.006			0.11 (0.08)	0.15		
HbA_{1c} (%) AUC×waist-to-height ratio AUC			0.75 (0.30)	0.01				
Model R^2	0.23		0.30		0.18		0.14	
Reduced model R^2	0.22		0.29		0.18		0.14	

This reduced model excludes the variables that were not significant. AIx indicates augmentation index; AUC, area under the curve; CAN, cardiac autonomic neuropathy; HbA_{1c}, glycated hemoblobin; HDL, high-density lipoprotein; MAP, mean arterial pressure; PWVcf, pulse wave velocity, carotid-femoral; PWVcr, pulse wave velocity, carotid-radial; PWVft, pulse wave velocity, femoral-foot; T1DM, type 1 diabetes mellitus.

*In generalized linear models, all variables listed, age, sex, race, use of blood pressure or lipid medication, smoking, sedentary behavior, and clinic site were included simultaneously. For AIx, model was adjusted for height at the time of the measure and waist AUC, other outcomes use the National Health and Nutrition Examination Survey waist-to-height ratio AUC.

Removal from the model of variables that did not demonstrate a statistically significant association did not change the R^2 substantially but did result in a significant association of HbA_{1c} and non-HDL with PWVcr (data not shown).

Discussion

Our data demonstrate that in adolescents and young adults, the duration of T1DM and glycemic control over time (HbA_{1c} AUC) are consistent determinants of association with arterial stiffness and wave reflections regardless of sex and race and after adjustment for other known CVRFs. However, increased adiposity, higher BP, and adverse lipid levels were also important correlates, suggesting that T1DM does affect the vasculature but traditional CVRFs are also important. In our previous work in a substudy of SEARCH (N=298), we also found that CVRFs were important in predicting change in PWVcf.[11] These new data extend the observations to a larger cohort with more racial and ethnic diversity that includes additional arterial stiffness and wave reflection parameters and examines the burden of risk factors over time (AUC).

Studies in adults have examined the relationship between presence and control of T1DM and arterial stiffness and wave reflections. One study of 89 adults (mean age, 34 years) found that diabetes mellitus was an important determinant of Aix, but the relationship was stronger in men and an interaction with age suggested that duration of disease also had an influence.[26] In a smaller case-control study, AIx was significantly higher in participants with T1DM as compared with controls (7.1±1.6% versus 0.4±−2.0%; *P*=0.01).[27] They also estimated PWV by calculating the time from the foot of the aortic pressure wave to the inflection point and found this higher in adults with diabetes mellitus.[27] However, when PWV was directly measured in another study, no significant difference in PWV was seen between T1DM cases and controls, although this study suffered from a small sample size (N=17 with T1DM).[28] Other investigators have found higher PWV in participants with T1DM,[29,30] consistent with our previous work in the SEARCH study where we demonstrated higher AIx and PWV in adolescents and young adults (mean age, 17.8 years) with T1DM as compared with controls,[10] and presence of diabetes mellitus remained a significant correlate even after adjusting for other CVRFs.[31] In the SEARCH CVD substudy, higher HbA_{1c} was significantly associated with change in only carotid-femoral PWV over time.[11] Our current study is able to demonstrate the effect of burden of glycemic dyscontrol over time on a variety of vascular parameters.

The relationship between duration of diabetes mellitus and arterial stiffness and wave reflections has also been examined. Adults with T1DM for >10 years had higher PWV than

those with shorter exposure to disease, with duration and SBP remaining important determinants in multivariable analyses.[32] In a small study of 30 children with T1DM, PWV correlated with duration of diabetes mellitus, but AIx did not.[33] Our previous study (N=535) found a relationship between duration and both AIx and PWV.[34]

The effect of metabolic control and arterial stiffness and wave reflections is complex. Although induction of acute hyperglycemia was found to increase both PWV and AIx in adults with T1DM,[35] no relationship was found between chronic glycemic control (HbA_{1c}) and AIx in a study that included only adult women.[36] When we looked at glycemic control in younger adolescents (mean age, 14.6 years) of both sexes with T1DM, we also found that although HbA_{1c} correlates with arterial stiffness and wave reflections, it was not a significant determinant of AIx or PWV once adjusted for BP and lipids.[34] Similarly, in children with T1DM, no relationship was seen between HbA_{1c} and ultrasound-based abdominal aortic distensibility, a measure that correlates with PWV.[37] However, in a study using magnetic resonance imaging, perhaps a more precise measure than ultrasound, an inverse relationship was found between HbA_{1c} and aortic distensibility in adolescents with T1DM.[38] Furthermore in a previous smaller substudy of the SEARCH study, we examined 298 adolescents with T1DM from 2 of the SEARCH sites who had CVRFs and PWV at baseline (mean age, 14.5 years) and after 5 years of follow up. A lower insulin sensitivity score, which contains HbA_{1c} in the calculation, was associated with a greater rate of change in PWV over 5 years.[11] These observations along with our current work suggest that there is a relationship between glycemic control and arterial stiffness, but the effect is modest, requiring a larger sample size or longer duration of follow-up to detect.

In adults, adiposity and BP have been found to be important predictors of arterial parameters.[31,39] Pediatric studies also show a direct relationship between greater AIx and higher BMI,[40] and higher PWV and higher lipid and BP levels.[41] Previous SEARCH analyses confirm these relationships, demonstrating that adiposity, BP, and lipids are determinants of higher arterial stiffness in cross-sectional analyses[31,42] and contribute to increasing arterial stiffness over time.[11] Our current work extends these observations by demonstrating the effect of burden of risk factors over time (using AUC) on arterial stiffness in young adults with T1DM.

There are numerous mechanisms by which poor metabolic control may affect vascular parameters. Animal models have shown that in the setting of insulin resistance, there is reduced activation of the nitric oxide signaling pathway (vasodilating) and enhanced activation of the endothelin pathway (vasoconstricting), resulting in increased vascular tone.[43] Because nitric oxide attenuates production of proinflammatory cytokines, insulin resistance also leads to an inflammatory milieu and increased reactive oxygen species, which also contribute to vascular dysfunction.[44] Hyperglycemia also leads to formation of advanced glycation end products, which may result in abnormal cross-linking of collagen and elastin fibers.[45] These advanced glycation end products were independently associated with PWV in adults with T1DM.[46] Diabetes mellitus is also associated with development of CAN[47] with concomitant sympathetic predominance, resulting in increased arterial stiffness in adults with T1DM.[48–50] SEARCH investigators have demonstrated a similar relationship in youth with T1DM between reduced heart rate variability, reflecting CAN, and increased arterial stiffness.[9] Our data suggest that the burden of CAN over time has only a modest effect on arterial stiffness when other CVRFs are taken into account.

Limitations

Our study examines the effect of CVRF burden on arterial parameters in young individuals with T1DM. Therefore, our findings may not be generalizable to healthy youth or those with other high-risk conditions such as uncomplicated obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, or chronic kidney disease. We were also unable to compare the effect of CVRFs on arterial parameters in people without diabetes mellitus because of constraints of the overall design of the parent SEARCH study, but case-control comparisons were thoroughly explored in our ancillary SEARCH CVD study.[31] Although we have CVRF data over time, we collected only arterial parameters measures at follow-up, so we can only demonstrate association and cannot conclude that the risk factors caused any vascular dysfunction.

There are many controversies in the measurement of arterial parameters. The usefulness of AIx, a measure of wave reflection, to evaluate arterial health has been challenged[51] because it may be affected by factors such as anatomy or peripheral vascular resistance, not directly related to arterial stiffness. Furthermore, the contribution of the forward and backward waves may be different,[52] and we were not able to assess these features in the current study. However, a large meta-analysis in adults demonstrated that higher AIx was associated with greater incidence of cardiovascular events[53]; therefore, we believe our examination of AIx in a young diabetic population adds to the literature. The relevance of the peripheral stiffness measures is not entirely clear, as no studies have evaluated the relationship between PWVcr or PWVft and cardiovascular events. These measures may be more sensitive to vascular tone. However, we include these measures because few studies have evaluated the relationship between arterial stiffness and peripheral artery disease,[54] but limited studies in adults with diabetes mellitus suggest a relationship between PWV in the leg and presence

of peripheral artery disease,[55] and one group has found higher PWVcr in women with insulin resistance[56] and offspring of adults with diabetes mellitus,[57] so there may be utility in measuring PWV in the arm in diabetes mellitus. We also used the "subtraction" rather than "80% direct" method to measure arterial path length purported to be more accurate compared with magnetic resonance imaging.[58] However, another larger study suggested the subtraction method is more accurate compared with magnetic resonance imaging.[59]

Conclusion

The major factors associated with wave reflections (AIx) and arterial stiffness (PWV) in young people with T1DM are duration of diabetes mellitus, glycemic control over time, and traditional CVRFs including obesity, BP, and lipids. Because presence of greater numbers of ideal cardiovascular health metrics in youth with T1DM is associated with lower arterial stiffness,[42] efforts to improve glycemic control combined with interventions to lower CVRFs may prevent future cardiovascular events in young individuals with T1DM.

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Disclosures

This study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of this study or its conclusions. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases.

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SUPPLEMENTAL MATERIAL

Appendix

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Table S1. Multivariable Associations of Metabolic and CVRFs with Arterial Stiffness in Youth and Young Adults with T1D (standardized beta estimates).*

Parameter†	AIx		PWVcf		PWVft		PWVcr	
Intercept	56.00 (5.95)	<.0001	5.76 (0.18)	<.0001	8.22 (0.25)	<.0001	7.69 (0.24)	<.0001
HbA1c (%) AUC	0.81 (0.30)	0.0072	0.06 (0.03)	0.0188	0.12 (0.04)	0.0017	0.11 (0.05)	0.0159
Duration of T1D (yrs)	1.19 (0.30)	<.0001	0.20 (0.03)	<.0001	0.21 (0.04)	<.0001	0.07 (0.04)	0.0756
Age at diagnosis (yrs)	0.45 (0.42)	0.2861	0.31 (0.03)	<.0001	0.27 (0.05)	<.0001	0.11 (0.04)	0.0031
Female	0.52 (0.33)	0.1135	-0.02 (0.03)	0.3539	-0.14 (0.04)	0.0003	-0.09 (0.04)	0.0150
Height (m)	-40.28 (3.48)	<.0001						
Waist circumference AUC	0.06 (0.03)	0.0304						
Waist to Height ratio AUC			0.21 (0.03)	<.0001	-0.10 (0.04)	0.0173	-0.05 (0.04)	0.1765
MAP (mmHg) AUC	0.37 (0.36)	0.2952	0.16 (0.03)	<.0001	0.24 (0.05)	<.0001	0.16 (0.04)	0.0002
On BP med	0.22 (0.27)	0.4227	0.01 (0.03)	0.7820	0.02 (0.04)	0.5303	-0.02 (0.03)	0.5458
Non-HDL AUC (10 mg/dl increase)	0.77 (0.30)	0.0114	0.05 (0.03)	0.0469	0.02 (0.04)	0.5896	0.06 (0.04)	0.0744
CAN	0.20 (0.28)	0.4599	0.04 (0.03)	0.0930	0.06 (0.04)	0.1201	0.03 (0.03)	0.4541
On Lipid med	-0.14 (0.25)	0.5781	-0.01 (0.02)	0.6038	-0.04 (0.03)	0.3063	-0.02 (0.03)	0.5781
Smoking (Never is ref)								
Current	0.12 (0.30)	0.6742	-0.01 (0.03)	0.7362	0.03 (0.04)	0.4639	0.01 (0.04)	0.7639
Former	-0.30 (0.29)	0.3125	-0.00 (0.03)	0.9972	0.03 (0.04)	0.4641	-0.01 (0.04)	0.7823
Physically Active	-0.24 (0.27)	0.3878	-0.02 (0.03)	0.3475	-0.07 (0.04)	0.0449	-0.07 (0.03)	0.0328
Sedentary	-0.05 (0.28)	0.8682	0.02 (0.03)	0.3296	-0.03 (0.04)	0.4903	-0.03 (0.03)	0.3446
HbA1c (%) AUC ^{x} Non-HDL AUC (10 mg/dl increase)	-0.66 (0.27)	0.0140						
HbA1c (%) AUC ^{x} CAN: N(Y is ref)	0.72 (0.26)	0.0061						
HbA1c (%) AUC ^{x} Waist to Height ratio AUC			0.06 (0.02)	0.0110	-0.05 (0.03)	0.1536		
Model R^2	0.23		0.30		0.18		0.14	
Reduced model R^2	0.22		0.29		0.18		0.14	

*In generalized linear models, all variables listed, race and clinic site were included simultaneously. For AIx, model was adjusted for height at the time of the measure and waist AUC, other outcomes use NHANES waist to height ratio area under the curve (AUC). AIx = augmentation index; PWVcf = pulse wave velocity, carotid-femoral; PWVft = pulse wave velocity, femoral-foot, PWVcr = pulse wave velocity, carotid-radial. Reduced model excludes the variables that in the tables have a p-value labeled as NS. †HbA1c = glycated hemoblobin, T1D = type 1 diabetes, MAP = mean arterial pressure, BP med = blood pressure lowering medication, CAN = cardiac autonomic neuropathy, lipid med = lipid lowering medication.

Table S2. Generalized Linear Multivariable Models of Associations of Metabolic and CVRFs with Augmentation Index in Youth and Young Adults with T1D.*

Parameter†	Min. Adjusted		*Full Model		**Reduced Model	
	beta (se)	p-value	beta (se)	p-value	beta (se)	p-value
HbA1c (%) AUC	0.97 (0.20)	<.0001	4.08 (1.04)	<.0001	3.97 (1.02)	0.0001
Waist circumference AUC	0.01 (0.03)	0.72	0.06 (0.03)	0.03	0.11 (0.02)	<.0001
BMI z-score AUC	0.05 (0.30)	0.88				
Non-HDL AUC (10 mg/dl increase)	0.47 (0.11)	<.0001	1.87 (0.67)	0.005	1.86 (0.66)	0.005
HDL AUC (10 mg/dl increase)	-0.03 (0.24)	0.90				
SBP z-score AUC	1.44 (0.32)	<.0001				
DBP z-score AUC	1.40 (0.26)	<.0001				
MAP AUC	0.05 (0.04)	0.29	0.05 (0.05)	0.30		
CAN: No (Yes is ref)	-1.12 (0.82)	0.17	13.36 (5.28)	0.01	11.98 (5.17)	0.02
Physically Active: No (Yes is ref)	1.26 (0.54)	0.02	0.48 (0.55)	0.39		
HbA1c (%) AUC x Non-HDL AUC (10 mg/dl increase)	-0.17 (0.08)	0.02	-0.19 (0.08)	0.01	-0.18 (0.07)	0.01
HbA1c (%) AUC x CAN	-1.57 (0.57)	0.006	-1.64 (0.60)	0.006	-1.50 (0.59)	0.01
Model R^2			**0.23**		**0.22**	

Variables included in the minimally adjusted models are the variable of interest, age at diagnosis, duration of diabetes, sex, race, and clinical site. When testing interactions, the main effects were also included in the model (not presented).
*The full model includes variables with results, age at diagnosis, duration of diabetes, sex, race, use of BP or lipid medication, smoking, sedentary behavior, height, and clinic site.
**This reduced model includes variables used in the full model that were significant and main effects of interactions. Variables included in the model that are not in the table include duration of diabetes, race, height, and clinic site.
†HbA1c = glycated hemoglobin, MAP = mean arterial pressure, BP med = blood pressure lowering medication, CAN = cardiac autonomic neuropathy, lipid med = lipid lowering medication.

Interaction interpretation for Aix: When both HbA1c & non-HDL AUC, there is lower effect on AIx.

	HbA1c AUC level			
	5	7	9	11
Change in Aix when non-HDL AUC is increased by 10 mg/dl	0.96	0.60	0.24	-0.12

When both HbA1c increases and CAN is present there is greater increase in AIx

		Non-HDL AUC level			
	CAN status	60	90	120	150
Change in Aix when HbA1c AUC increases by one unit	No	1.35	0.80	0.25	-0.30
	Yes	2.85	2.30	1.75	1.20

Table S3. Generalized Linear Multivariable Models of Associations of Metabolic and CVRFs with Carotid-Femoral Pulse Wave Velocity in Youth and Young Adults with T1D.*

Parameter†	Min. Adjusted		*Full Model		**Reduced Model	
	beta (se)	p-value	beta (se)	p-value	beta (se)	p-value
HbA1c (%) AUC	0.07 (0.02)	0.0001	-0.32 (0.15)	0.03	-0.30 (0.14)	0.04
Waist to Height ratio AUC (0.1 increase)	0.41 (0.04)	<.0001	-0.30 (0.25)	0.23	-0.27 (0.25)	0.28
BMI z-score AUC	0.23 (0.03)	<.0001				
Non-HDL AUC (10 mg/dl increase)	0.05 (0.01)	<.0001	0.02 (0.01)	0.05	0.02 (0.01)	0.04
HDL AUC (10 mg/dl increase)	-0.05 (0.02)	0.02				
SBP z-score AUC	0.13 (0.03)	<.0001				
DBP z-score AUC	0.09 (0.02)	0.0003				
MAP AUC	0.03 (0.00)	<.0001	0.02 (0.00)	<.0001	0.02 (0.00)	<.0001
CAN: No (Yes is ref)	-0.13 (0.07)	0.08	-0.13 (0.08)	0.09	-0.14 (0.08)	0.07
Physically Active: No (Yes is ref)	0.07 (0.05)	0.14	0.05 (0.05)	0.35		
HbA1c (%) AUC x Waist to Height ratio AUC	0.50 (0.25)	0.05	0.75 (0.30)	0.01	0.07 (0.03)	0.02
Model R^2			**0.30**		**0.29**	

Variables included in the minimally adjusted models are the variable of interest, age at diagnosis, duration of diabetes, sex, race, and clinical site. When testing interactions, the main effects were also included in the model (not presented).
*The full model includes variables with results, age at diagnosis, duration of diabetes, sex, race, use of BP or lipid medication, smoking, sedentary behavior, and clinic site.
**This reduced model includes variables used in the full model that were significant and main effects of interactions. Variables included in the model that are not in the table include age at diagnosis, duration of diabetes, race, and clinic site
†HbA1c = glycated hemoglobin, MAP = mean arterial pressure, BP med = blood pressure lowering medication, CAN = cardiac autonomic neuropathy, lipid med = lipid lowering medication.

Interaction interpretation:
As HbA1c AUC and waist to height ratio AUC increase the effect they have on PWVcf increases.

	HbA1c AUC level			
	5	7	9	11
Change in PWVcf when increasing waist to height ratio AUC by 0.1	0.08	0.22	0.36	0.50

This table shows the effect on PWVcf by a one unit change in HbA1c AUC when waist to height ratio AUC is held constant at the different values.

	Waist to Height ratio AUC level			
	0.4	0.5	0.6	0.7
Change in PWVcf when increasing HbA1c AUC by one	-0.02	0.05	0.13	0.20

Table S4. Generalized Linear Multivariable Models of Associations of Metabolic and CVRFs with Femoral-Foot Pulse Wave Velocity in Youth and Young Adults with T1D.*

Parameter†	Min. Adjusted		*Full Model		**Reduced Model	
	beta (se)	p-value	beta (se)	p-value	beta (se)	p-value
HbA1c (%) AUC	0.09 (0.03)	0.0002	-0.01 (0.07)	0.94	0.09 (0.03)	0.0003
Waist to Height ratio AUC (0.1 increase)	-0.04 (0.06)	0.51	-0.16 (0.07)	0.02	-0.15 (0.06)	0.0140
BMI z-score AUC	-0.10 (0.04)	0.007				
Non-HDL AUC (10 mg/dl increase)	0.01 (0.01)	0.37	0.01 (0.01)	0.59		
HDL AUC (10 mg/dl increase)	-0.01 (0.03)	0.69				
SBP z-score AUC	0.10 (0.04)	0.009				
DBP z-score AUC	0.07 (0.03)	0.02				
MAP AUC	0.03 (0.01)	<.0001	0.03 (0.01)	<.0001	0.03 (0.01)	<.0001
CAN: No (Yes is ref)	-0.21 (0.10)	0.05	-1.13 (0.70)	0.11	-0.14 (0.11)	0.1861
Physically Active: No (Yes is ref)	0.17 (0.07)	0.01	0.15 (0.07)	0.04	0.17 (0.07)	0.0119
HbA1c (%) AUC ^{x} CAN	0.16 (0.07)	0.03	0.11 (0.08)	0.15		
Model R^2			**0.18**		**0.18**	

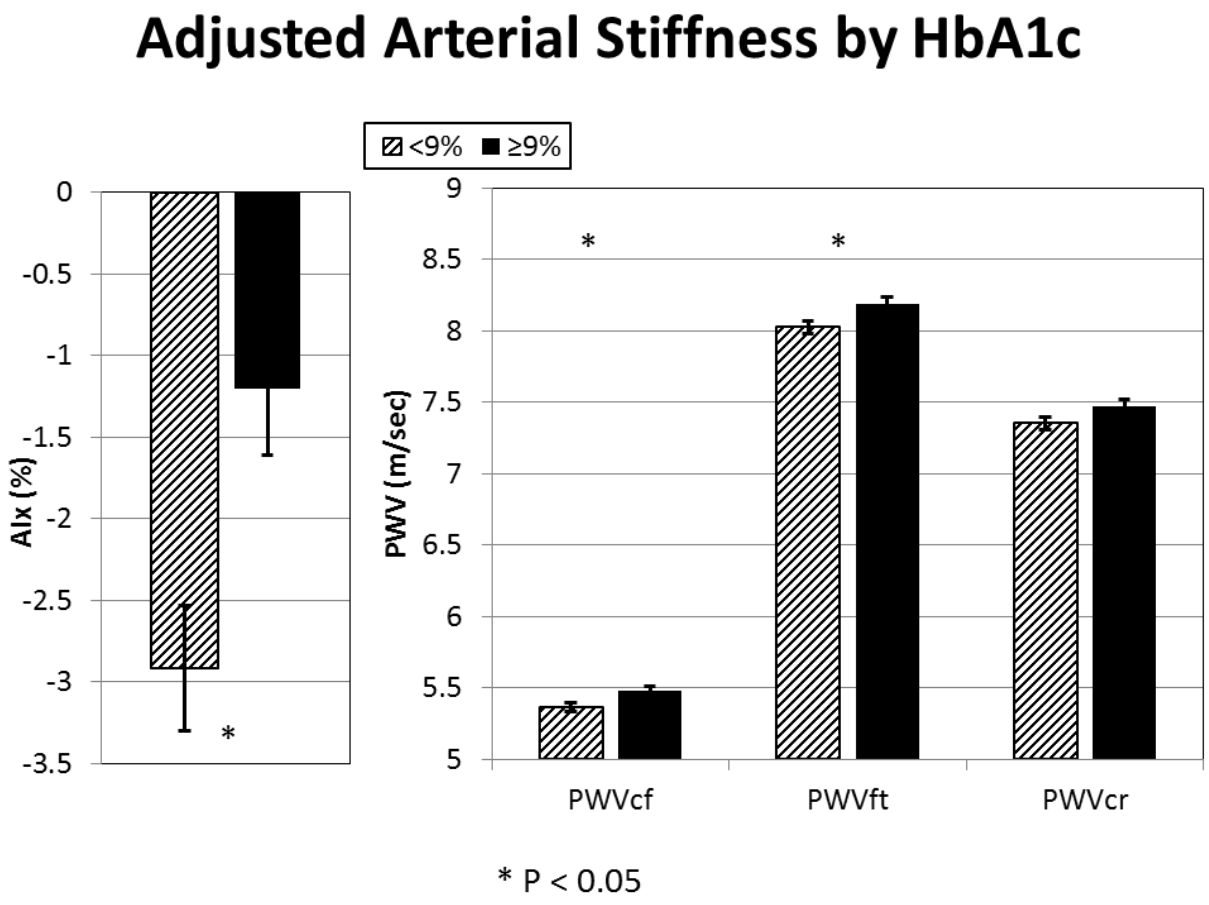
Variables included in the minimally adjusted models are the variable of interest, age at diagnosis, duration of diabetes, sex, race, and clinical site. When testing interactions, the main effects were also included in the model (not presented).
*The full model includes variables with results, age at diagnosis, duration of diabetes, sex, race, use of BP or lipid medication, smoking, sedentary behavior, and clinic site.
**This reduced model includes variables used in the full model that were significant and main effects of interactions. Variables included in the model that are not in the table include age at diagnosis, duration of diabetes, sex, race, and clinic site.
†HbA1c = glycated hemoglobin, MAP = mean arterial pressure, BP med = blood pressure lowering medication, CAN = cardiac autonomic neuropathy, lipid med = lipid lowering medication.

Table S5. Generalized Linear Multivariable Models of Associations of Metabolic and CVRFs with Carotid-Radial Pulse Wave Velocity in Youth and Young Adults with T1D.*

Parameter†	Min. Adjusted		*Full Model		**Reduced Model	
	beta (se)	p-value	beta (se)	p-value	beta (se)	p-value
HbA1c (%) AUC	0.08 (0.02)	0.0005	0.05 (0.03)	0.08	0.06 (0.03)	0.03
Waist to Height ratio AUC (0.1 increase)	-0.02 (0.05)	0.76	-0.08 (0.06)	0.18		
BMI z-score AUC	-0.09 (0.03)	0.01				
Non-HDL AUC (10 mg/dl increase)	0.03 (0.01)	0.02	0.02 (0.01)	0.07	0.02 (0.01)	0.22
HDL AUC (10 mg/dl increase)	0.02 (0.03)	0.48				
SBP z-score AUC	0.07 (0.04)	0.08				
DBP z-score AUC	0.11 (0.03)	0.0005				
MAP AUC	0.02 (0.00)	0.0006	0.02 (0.01)	0.0002	0.01 (0.01)	0.007
CAN: No (Yes is ref)	-0.12 (0.10)	0.24	-0.08 (0.10)	0.45		
Physically Active: No (Yes is ref)	0.15 (0.06)	0.02	0.15 (0.07)	0.03	0.14 (0.07)	0.04
Model R^2			**0.14**		**0.13**	

Variables included in the minimally adjusted models are the variable of interest, age at diagnosis, duration of diabetes, sex, race, and clinical site. When testing interactions, the main effects were also included in the model (not presented).
*The full model includes variables with results, age at diagnosis, duration of diabetes, sex, race, use of BP or lipid medication, smoking, sedentary behavior, and clinic site.
**This reduced model includes variables used in the full model that were significant and main effects of interactions. Variables included in the model that are not in the table include age at diagnosis, duration of diabetes, sex, race, and clinic site.
†HbA1c = glycated hemoglobin, MAP = mean arterial pressure, BP med = blood pressure lowering medication, CAN = cardiac autonomic neuropathy, lipid med = lipid lowering medication.

Figure S1. Arterial Stiffness means with standard error bars by glycosylated hemoglobin (HbA1c levels, %) in Youth and Young Adults with Type 1 Diabetes adjusted (for mean arterial pressure, age, and sex).



AIx = augmentation index; PWVcf = pulse wave velocity, carotid-femoral; PWVft = pulse wave velocity, femoral-foot, PWVcr = pulse wave velocity, carotid-radial.