Longitudinal Changes in Arterial Stiffness and Heart Rate Variability in Youth-Onset Type 1 Versus Type 2 Diabetes: The SEARCH for Diabetes in Youth Study

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OBJECTIVE

We compared arterial stiffness and heart rate variability (HRV) over time by diabetes type and determined the risk factors associated with worsening arterial stiffness and HRV in young adults with youth-onset diabetes.

RESEARCH DESIGN AND METHODS

Arterial stiffness (pulse wave velocity, augmentation index) and six indices of heart rate variability were measured twice, 4.5 years apart, among participants with either youth-onset type 1 or type 2 diabetes in the SEARCH for Diabetes in Youth study. Multivariable linear regression models were used to assess risk factors associated with arterial stiffness and HRV at follow-up.

RESULTS

Of 1,159 participants studied, 949 had type 1 diabetes (mean age 17.1 ± 4.7 years, 60.3% non-Hispanic White, 55% female) and 210 had type 2 diabetes (mean age 22.1 ± 3.5 years, 23.8% non-Hispanic White, 71% female) at initial assessment when diabetes duration was 7.9 years (both groups). Participants with type 2 versus type 1 diabetes had greater arterial stiffness and more abnormalities in HRV at initial and follow-up assessment and a greater change over time (all $P < 0.05$). Risk factors associated with worse arterial stiffness and HRV at follow-up in both types of diabetes included higher blood pressure, hemoglobin A_{1c}, waist circumference, and triglycerides over time and longer diabetes duration.

CONCLUSIONS

Arterial stiffness and HRV worsened over time with greater changes among participants with type 2 versus type 1 diabetes and among those with features of the metabolic syndrome. The risk factor profile documents potentially modifiable pathways to prevent or limit cardiovascular complications in young adults with youth-onset diabetes.

Risk factors for cardiovascular disease, including hypertension, dyslipidemia, and microalbuminuria, are observed in patients with childhood-onset type 1 and type 2

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diabetes. Data show a higher prevalence in the number and severity of cardiovascular risk factors in youth with type 2 versus type 1 diabetes (1). Higher arterial stiffness and lower heart rate variability (HRV) have also been documented in young adults with type 2 versus type 1 diabetes (1–5).

In adults, arterial stiffness is an early marker of cardiovascular disease and predicts greater cardiovascular morbidity and mortality (6,7). Abnormalities in HRV represent cardiac autonomic dysfunction and are associated with myocardial infarction and sudden death (8–12). Furthermore, alterations in HRV have been associated with increased arterial stiffness in individuals with diabetes (13,14).

Despite the wealth of cross-sectional reports documenting cardiovascular risk factors and arterial stiffness and HRV data in individuals with youth-onset type 1 and type 2 diabetes reported by us and others (15–20), limited data on changes in arterial stiffness and HRV over time exist. Additionally, no previous studies have compared participants with type 1 and type 2 diabetes at follow-up and whether the change in arterial stiffness and HRV over time differs by diabetes type.

We examined changes in arterial stiffness and HRV in participants with youth-onset type 1 and type 2 diabetes enrolled in the observational SEARCH for Diabetes in Youth (SEARCH) study. The objectives of the study were to *1*) compare arterial stiffness and HRV at initial and follow-up assessment by diabetes type, *2*) compare the change over time by diabetes type, and *3*) determine the relationship between burden of risk factors associated with worse arterial stiffness and HRV at follow-up assessment.

RESEARCH DESIGN AND METHODS

Description of the Study Participants

SEARCH is a longitudinal study of individuals with youth-onset (diagnosed at <20 years of age) type 1 or type 2 diabetes. Participants in the SEARCH cohort study were recruited from the population-based SEARCH registry study of individuals with youth-onset type 1 and type 2 diabetes from Colorado, including southwestern American Indian reservations; Ohio; Washington; South Carolina; and California continuously since 2002. Individuals in the current analysis were part of the SEARCH cohort study and diagnosed with type 1 or type 2 diabetes in 2002–2006 or 2008 and participated in a baseline visit shortly after diabetes diagnosis. Arterial stiffness and HRV were measured once initially between 2011 and 2015 and then repeated in 2015–2019. These data focus on the initial and follow-up arterial stiffness (n = 1,159 total, n = 949 with type 1 diabetes, and n = 210 with type 2 diabetes) and HRV (n = 1,056 total, n = 864 with type 1 diabetes, and n = 192 with type 2 diabetes) measurements.

Diabetes type was defined based on measures at the baseline visit, termed etiologic diabetes type (21). Individuals with clinically diagnosed diabetes who were insulin sensitive (22) or antibody positive were characterized as having type 1 diabetes (n = 812), and those who were insulin resistant (22) and islet cell antibody negative were characterized as having type 2 diabetes (n = 187). In 197 participants, either islet cell antibodies or insulin sensitivity measures were unavailable; for these participants, diabetes type was based on their provider diagnosis (162 with type 1, 35 with type 2 diabetes). Previous work in SEARCH has shown good agreement between etiologic diabetes type and provider-diagnosed diabetes type (23), and here, we found no differences in age, race, sex, or hemoglobin A_{1c} (HbA_{1c}) by the two methods of determination. All participants or parent/guardians provided written informed consent and assent, as appropriate for age. Institutional review board approval was obtained at each site.

Data Collection

The same methods were used to measure anthropometric, demographic, and metabolic variables at both visits. Sex, race and ethnicity, medical and social history, and current medications were self-reported. Height and weight were measured and BMI calculated as kilograms per meters squared. Waist circumference was measured twice in centimeters using the natural waist defined as midway between the lowest rib margin and the right iliac crest at the midaxillary line. A third measurement was made if the second measure differed from the first by >1.0 cm. Blood was collected after a minimum 8-h fast, and all samples were analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratories at the University of Washington (17). Resting systolic blood pressure (BP) and diastolic BP were measured three times, using an aneroid sphygmomanometer and an appropriate-sized cuff, after the participants were seated for at least 5 min, according to published guidelines (25). Mean arterial pressure (MAP) was calculated as [(2 * diastolic BP) + systolic BP]/3.

Arterial stiffness and HRV were measured using the SphygmoCor Vx device (ATCOR, Sydney, Australia) following the same protocol used at the initial (2011–2015) and follow-up (2015–2019) assessments (1). All measurements occurred in the morning in a room with a stable temperature and the participant lying in the resting supine position for 10 min. Arterial stiffness outcomes included *1*) carotid-femoral pulse wave velocity (PWV) (primary outcome), *2*) carotid-radial PWV, *3*) femoral-foot PWV, and *4*) augmentation index (AIx). PWV is the speed of pressure waves generated by cardiac ejection to reach the periphery. A pressure waveform obtained from the proximal site (carotid artery) is recorded followed by a second arterial waveform recorded from the distal site (femoral, foot, or radial artery) using a tonometer. Waveforms are also recorded on a simultaneous electrocardiogram. PWV is the difference between the two sites, measured to the nearest 0.1 cm, divided by the time delay measured between the feet of the two waveforms, and reported in meters per second. The average of >10 beats was used in the analysis to cover a complete respiratory cycle. Three PWV recordings were obtained per participant at each site and averaged. Repeat measures show a coefficient of variation of <7% (26).

AIx is a measure of wave reflections and systemic arterial stiffness (27). The SphygmoCor tonometer was placed over the right radial artery, and pressure waves were recorded. The device analyzes pulse waves using a generalized transfer function validated in the catheterization laboratory to calculate a central aortic pressure wave (28). The AIx is derived from the central pressure waveform by calculating the difference between the main outgoing wave and the reflected wave and expressed as a percentage of the central pulse pressure. The magnitude of reflected wave represents the increased

Table 1—Characteristics of participants with arterial stiffness data

Characteristic	All (*N* = 1,159)	Type 1 diabetes (*n* = 949)	Type 2 diabetes (*n* = 210)	*P*
Data at initial assessment				
Age (years)	18.0 (4.9)	17.1 (4.7)	22.1 (3.5)	<0.0001
Duration of diabetes (years)	7.9 (1.9)	7.9 (1.9)	7.9 (2.0)	0.8654
Race				<0.0001
Non-Hispanic White	622 (53.7)	572 (60.3)	50 (23.8)	
Non-Hispanic Black	219 (18.9)	125 (13.2)	94 (44.8)	
Hispanic	224 (19.3)	181 (19.1)	43 (20.5)	
Other race group*	94 (8.1)	71 (7.5)	23 (11.0)	
Sex				<0.0001
Female	667 (57.5)	518 (54.6)	149 (71.0)	
Male	492 (42.5)	431 (45.4)	61 (29.0)	
BMI (kg/m^2)	25.8 (7.7)	23.6 (5.3)	35.9 (8.6)	<0.0001
Waist circumference (cm)	88.3 (19.8)	82.5 (14.8)	114.6 (18.3)	<0.0001
Systolic BP (mmHg)	108.0 (12.5)	105.7 (11.1)	118.6 (13.4)	<0.0001
Diastolic BP (mmHg)	69.8 (9.7)	68.4 (9.0)	76.1 (10.1)	<0.0001
HbA_{1c} (%)	9.2 (2.2)	9.2 (1.9)	9.3 (3.0)	0.5072
LDL-C (mg/dL)	98.1 (30.3)	96.0 (27.4)	107.6 (39.3)	<0.0001
HDL-C (mg/dL)	52.9 (14.6)	55.6 (14.0)	41.4 (11.2)	<0.0001
Triglycerides (mg/dL)	79.0 (56.0; 115.0)	72.0 (53.0; 102.0)	121.0 (85.0; 201.0)	<0.0001
Antihypertension medications				<0.0001
ACE inhibitors or ARBs	80 (6.9)	47 (5.0)	33 (15.8)	
Other hypertension	28 (2.4)	11 (1.2)	17 (8.1)	
Lipid-lowering medications				0.0008
Statins	33 (2.9)	21 (2.2)	12 (5.7)	
Fibrates	2 (0.2)	1 (0.1)	1 (0.5)	
Other	16 (1.4)	9 (0.9)	7 (3.3)	
Data at follow-up assessment				
Age (years)	22.6 (4.9)	21.8 (4.8)	26.5 (3.4)	<0.0001
Duration of diabetes (years)	12.5 (2.2)	12.5 (2.2)	12.3 (2.1)	0.2780
BMI (kg/m^2)	127.6 (7.2)	25.8 (5.2)	35.8 (9.0)	<0.0001
Waist circumference (cm)	94.0 (17.9)	89.3 (14.0)	115.3 (18.3)	<0.0001
Systolic BP (mmHg)	111.9 (13.5)	109.7 (11.4)	122.1 (17.1)	<0.0001
Diastolic BP (mmHg)	72.7 (10.3)	71.1 (9.3)	79.8 (11.4)	<0.0001
HbA_{1c} (%)	9.2 (2.2)	9.1 (2.0)	9.6 (3.0)	0.0021
LDL-C (mg/dL)	104.6 (33.0)	103.1 (30.8)	111.1 (41.0)	0.0012
HDL-C (mg/dL)	52.7 (14.7)	55.0 (14.3)	42.5 (12.0)	<0.0001
Triglycerides (mg/dL)	83.0 (60.0; 123.0)	77.0 (57.0; 107.0)	124.0 (92.0; 204.0)	<0.0001
CRP (mg/dL)	0.2 (0.1; 0.5)	0.1 (0.0; 0.4)	0.5 (0.2; 1.1)	<0.0001
Physically active	430 (38.9)	366 (40.4)	64 (32.2)	0.0318
Antihypertension medications				0.0010
ACE inhibitors or ARBs	98 (9.0)	69 (7.6)	29 (15.9)	
Other hypertension	22 (2.0)	17 (1.9)	5 (2.7)	
Lipid-lowering medications				0.0010
Statins	57 (5.2)	41 (4.5)	16 (8.8)	
Fibrates	2 (0.2)	0 (0.0)	2 (1.1)	
Other	2 (0.2)	2 (0.2)	0 (0.0)	

Data are *n* (%), mean (SD), or median (25th percentile; 75th percentile). ARB, angiotensin receptor blocker; HDL-C, HDL cholesterol. *Other race group included 2.2% American Indian/Alaskan Native, 1.0% Asian, 4.6% multiple races, and 0.4% unknown.

afterload that the left ventricle must cope with. A higher AIx indicates increased vessel stiffness and has been used to predict cardiovascular events in adults (29). Since AIx is affected by heart rate, all values were adjusted to a standard heart rate of 75 beats/min. The average of three AIx measurements was used in the analysis. Reproducibility studies in our laboratory demonstrated intraclass correlation coefficients between 0.7 and 0.9. For both PWV and AIx, a higher value indicates greater stiffness.

Heart beats from an electrocardiogram were recorded for 10 min to determine HRV. The SphygmoCor Vx device takes into account the normal heart beats, ignoring ectopic beats, to derive the normal R-R intervals (N-N intervals) of the electrocardiogram and estimates several time-domain HRV indices. Both time- and frequency-domain HRV parameters are derived. Time domains include *1*) the SD of the N-N intervals (SDNN), *2*) the root mean square differences of successive N-N intervals (RMSSD), and *3*) the percentage of adjacent N-N intervals with a difference >50 ms (PNN50). Frequency domains are calculated using fast Fourier analysis, which separates the heart rate spectrum into various components, including *1*) normalized high frequency (HF) power, *2*) normalized low frequency (LF)

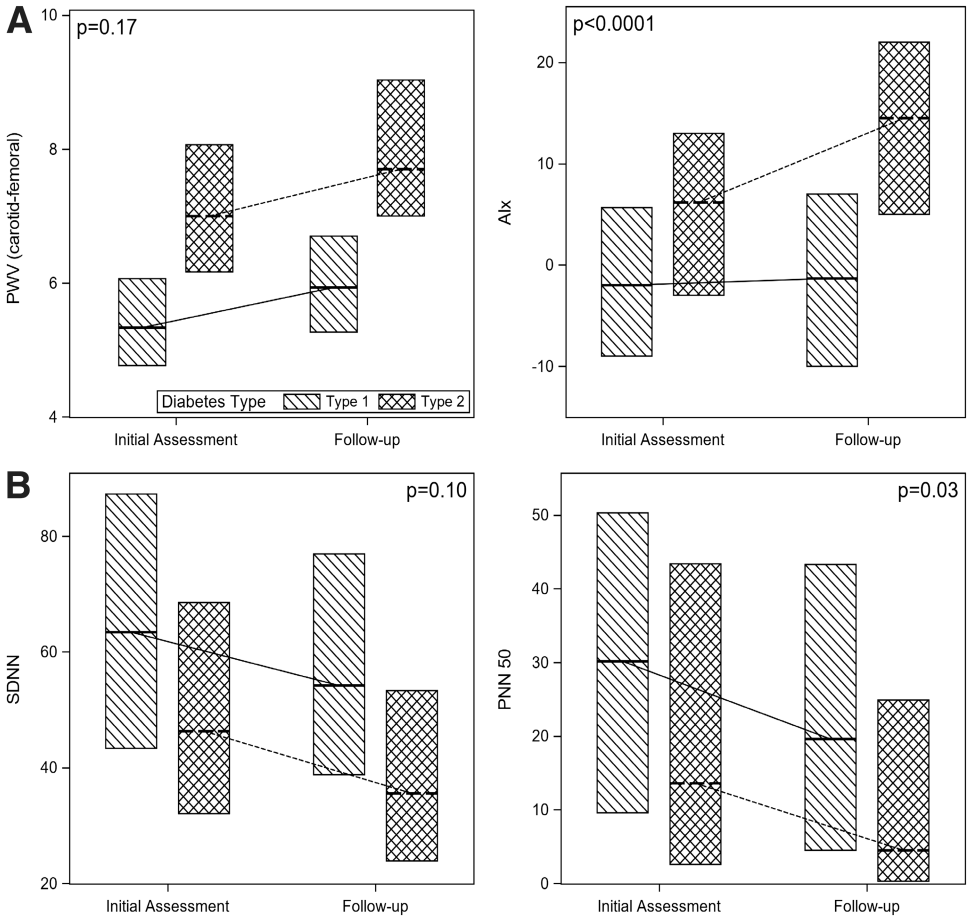

Figure 1—Arterial stiffness (carotid-femoral PWV and AIx) and HRV (SDNN and PNN50) at initial to follow-up assessment by diabetes type. *A*: Arterial stiffness measures. *B*: HRV measures. Data are median and interquartile range. *P* values represent the difference between the two diabetes type groups with regard to change from initial assessment to follow-up.

power, and *3*) their ratio (LF:HF ratio). SDNN is a measure of overall HRV. RMSSD and PNN50 represent the parasympathetic component of the HRV; thus, parasympathetic loss is quantified by the reduction in RMSSD and HF power (30). HF and LF power have traditionally been thought to represent parasympathetic and sympathetic components of HRV, respectively (31). More recent literature has suggested that this view is overly simplistic, as LF and HF may be influenced by respiratory sinus arrhythmia, position, movement, and other vagal components (32). For all HRV measures (except LF:HF ratio), a lower value indicates worse HRV. Arterial stiffness and HRV measurements were attempted in all participants. All data were checked for clinical and statistical outliers. Of the participants studied, 140 had arterial stiffness measurements only, 37 had HRV measurements only, and 1,019 had both arterial stiffness and HRV measurements.

Statistics

Summary statistics were calculated using means and SDs, median and interquartile ranges, or counts and percentages. Comparisons of diabetes types (type 1 vs. type 2) were done using *t* tests, Kruskal-Wallis tests, or χ^2 tests, depending on the distribution, with $P < 0.05$ indicating a significant difference between groups.

Multivariable linear regression models were used to determine whether diabetes type was associated with the arterial stiffness or HRV at follow-up assessment. Clinical considerations were used to identify the candidate variables, and then, through backward selection, variables that did not have an association with the outcome were removed. Diabetes type and study site were forced into the model since diabetes type was the comparison of interest and study site can account for variability in many unmeasurable attributes. Models included diabetes type, age, race and ethnicity, sex, and arterial stiffness or HRV value from the first assessment; physical activity (no: at least 10 min of exercise 0–2 days/week, yes: 3–7 days/week), healthy eating index, smoking status, use of hypertension medications, use of lipid medications, and diabetes duration at the follow-up assessment, study site; and time-weighted values for MAP, LDL cholesterol (LDL-C), HbA_{1c}, log triglycerides, and waist circumference. Time-weighted values for BP (MAP), LDL-C, HbA_{1c}, log triglycerides, and waist circumference were created using all available data from participants, including data that may have preceded the initial arterial stiffness and HRV measurements, to assess burden of the risk factors. C-reactive protein (CRP) from the follow-up visit was also included in all models, as CRP was not available at the initial assessment. Height was added in the model for AIx, and heart rate was added in the models for all stiffness measures.

Data and Resource Availability

All data and materials are available upon request.

Table 2—Arterial stiffness and HRV measurements at initial and follow-up assessment in youth with diabetes

	All	Type 1	Type 2	*P*
Arterial stiffness at initial assessment				
PWV (m/s)				
Carotid-femoral	5.5 (4.9; 6.4)	5.3 (4.8; 6.1)	7.0 (6.2; 8.1)	<0.0001
Femoral-foot	8.1 (7.1; 9.1)	8.0 (7.0; 8.9)	8.9 (7.8; 9.8)	<0.0001
Carotid-radial	7.4 (6.7; 8.2)	7.3 (6.6; 8.0)	8.0 (7.3; 9.3)	<0.0001
AIx (%)	−0.7 (−8.0; 7.3)	−2.0 (−9.0; 5.7)	6.2 (−3.0; 13.0)	<0.0001
Arterial stiffness at follow-up assessment				
PWV (m/s)				
Carotid-femoral	6.2 (5.4; 7.2)	5.9 (5.3; 6.7)	7.7 (7.0; 9.0)	<0.0001
Femoral-foot	8.8 (7.9; 10.0)	8.7 (7.8; 9.8)	9.9 (8.6; 10.9)	<0.0001
Carotid-radial	7.9 (7.0; 9.2)	7.7 (6.8; 8.7)	9.2 (8.0; 10.8)	<0.0001
AIx (%)	1.0 (−8.7; 11.0)	−1.3 (−10.0; 7.0)	14.5 (5.0; 22.0)	<0.0001
Change in arterial stiffness over time				
PWV				
Carotid-femoral change (m/s)	0.7 (1.2)	0.7 (1.1)	0.8 (1.7)	0.1686
Femoral-foot change (mm)	0.8 (1.6)	0.8 (1.6)	0.9 (1.7)	0.4161
Carotid-radial change (mm)	0.6 (1.7)	0.5 (1.6)	1.2 (2.0)	<0.0001
AIx change (%)	1.8 (11.6)	0.7 (11.6)	6.5 (10.5)	<0.0001
HRV at initial assessment				
SDNN (ms)	60.1 (41.2; 85.0)	63.4 (43.4; 87.3)	46.3 (32.1; 68.6)	<0.0001
PNN50 (%)	28.7 (7.3; 48.9)	30.2 (9.6; 50.3)	13.6 (2.6; 43.4)	<0.0001
RMSSD (ms)	51.2 (29.8; 80.4)	54.7 (32.2; 85.1)	39.0 (22.9; 66.5)	<0.0001
LF (n.u.)	45.0 (30.3; 59.3)	44.1 (30.2; 58.7)	47.9 (32.5; 61.8)	0.0675
HF (n.u.)	55.1 (40.7; 69.7)	55.9 (41.3; 69.9)	52.1 (38.2; 67.5)	0.0675
LF:HF ratio	0.8 (0.4; 1.5)	0.8 (0.4; 1.4)	0.9 (0.5; 1.6)	0.0675
HRV at follow-up assessment				
SDNN (ms)	51.5 (34.4; 73.0)	54.2 (38.8; 76.9)	35.6 (23.9; 53.3)	<0.0001
PNN50 (%)	16.5 (2.6; 40.7)	19.6 (4.5; 43.3)	4.5 (0.3; 24.9)	<0.0001
RMSSD (ms)	40.4 (22.9; 67.5)	43.3 (25.6; 70.1)	27.5 (14.2; 47.3)	<0.0001
LF (n.u.)	48.3 (35.0; 63.2)	48.1 (34.7; 62.5)	49.7 (36.6; 66.2)	0.3002
HF (n.u.)	51.7 (36.8; 65.0)	51.9 (37.5; 65.3)	50.3 (33.8; 63.4)	0.3002
LF:HF ratio	0.9 (0.5; 1.7)	0.9 (0.5; 1.7)	1.0 (0.6; 2.0)	0.2898
Change in HRV over time				
SDNN (ms)	−8.9 (27.8)	−8.2 (28.1)	−11.9 (26.3)	0.0961
PNN50 (%)	−6.4 (19.2)	−5.8 (19.3)	−9.1 (18.5)	0.0314
RMSSD (ms)	−11.3 (34.1)	−10.8 (34.5)	−13.5 (31.9)	0.3041
LF (n.u.)	3.1 (21.0)	3.3 (21.0)	2.1 (20.9)	0.4731
HF (n.u.)	−3.1 (21.0)	−3.3 (21.0)	−2.1 (20.9)	0.4731
LF:HF ratio	0.2 (1.9)	0.2 (1.9)	0.1 (2.1)	0.6648

Data are mean (SD) or median (25th percentile; 75th percentile). n.u., normalized units.

RESULTS

Demographic and metabolic characteristics of the cohort (949 participants with type 1 diabetes, 210 with type 2 diabetes) who had initial and follow-up arterial stiffness assessments are presented in Table 1. At the first arterial stiffness assessment, both groups had a mean duration of diabetes of ∼8 years. Individuals with type 2 diabetes were older (22 vs. 17 years) and more likely to be female (71% vs. 55%) and identify with racial or ethnic minority populations (76% vs, 40%, all $P < 0.0001$). Those with type 2 diabetes had a higher mean BMI (35.9 vs. 23.6 kg/m^2), BP (119/76 vs. 106/68 mmHg), and worse lipid levels than those with type 1 diabetes (all $P < 0.0001$). In addition, participants with type 2 diabetes reported more use of antihypertension (23.9% vs. 6.1%) and lipid-lowering (9.6% vs. 3.3%) medications than those with type 1 diabetes (all $P < 0.0001$).

At follow-up (arterial stiffness and HRV assessment 4.6 ± 1.1 years later), participants with type 2 diabetes continued to have higher BMI and BP, worse dyslipidemia (Table 1), and greater use of antihypertension (17.7% vs. 9.5%) and lipid-lowering (9.8% vs. 4.6%) medications than those with type 1 diabetes (all $P < 0.01$). CRP and HbA_{1c} were also higher in those with type 2 diabetes versus type 1 diabetes (9.6 vs. 9.1%, $P = 0.0021$).

Not all participants had both arterial stiffness and HRV measured. There were 864 participants with type 1 diabetes and 192 with type 2 diabetes who had only HRV measured twice. Demographic and metabolic characteristics were compared between these individuals as above. While the actual means differed from those described above, the group differences and the findings did not (Supplementary Table 1).

Figure 1*A* and Table 2 show median values for carotid-femoral PWV and AIx at initial and follow-up assessment stratified by diabetes type. Carotid-femoral

Table 3—Risk factors associated with arterial stiffness and HRV outcomes

		P
Carotid-femoral PWV (m/s) (higher is worse)		
Intercept	−2.34 (0.46)	<0.0001
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	−0.22 (0.11)	0.0428
Age (years)	0.02 (0.01)	0.0216
Diabetes duration (years)	0.06 (0.01)	<0.0001
Time-weighted waist circumference (cm)	0.02 (0)	<0.0001
Time-weighted MAP (mmHg)	0.03 (0)	<0.0001
Time-weighted HbA_{1c} (%)	0.07 (0.02)	0.0001
Heart rate (beats/min)	0.02 (0)	<0.0001
Initial carotid-femoral PWV	0.29 (0.03)	<0.0001
Femoral-foot PWV (m/s) (higher is worse)		
Intercept	1.35 (0.71)	0.0573
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	−0.19 (0.16)	0.2321
Age (years)	0.05 (0.01)	<0.0001
Diabetes duration (years)	0.05 (0.02)	0.0092
Sex: male (REF = female)	0.22 (0.08)	0.0089
Time-weighted waist circumference (cm)	−0.01 (0)	0.0013
Time-weighted MAP (mmHg)	0.04 (0.01)	<0.0001
Time-weighted HbA_{1c} (%)	0.07 (0.03)	0.0074
Ln(time-weighted triglycerides) (mg/dL)	0.27 (0.09)	0.0044
Initial femoral-foot PWV	0.21 (0.03)	<0.0001
Carotid-radial PWV (m/s) (higher is worse)		
Intercept	1.1 (0.61)	0.0740
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	−0.27 (0.13)	0.0348
Age (years)	0.04 (0.01)	<0.0001
Diabetes duration (years)	0.04 (0.02)	0.0497
Race/ethnicity: non-Hispanic White	−0.38 (0.09)	<0.0001
Sex: male (REF = female)	0.28 (0.08)	0.0008
Time-weighted MAP (mmHg)	0.03 (0.01)	<0.0001
Time-weighted HbA_{1c} (%)	0.07 (0.03)	0.0065
Heart rate (beats/min)	0.02 (0)	<0.0001
Initial carotid-radial PWV	0.26 (0.03)	<0.0001
AIx (%) (higher is worse)		
Intercept	4.92 (7.18)	0.4938
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	−3.28 (1.01)	0.0012
Age (years)	0.68 (0.09)	<0.0001
Diabetes duration (years)	0.51 (0.15)	0.0008
Time-weighted MAP (mmHg)	0.24 (0.05)	<0.0001
Time-weighted HbA_{1c} (%)	1.22 (0.05)	<0.0001
Physically active: yes (REF = no)	−2.93 (0.64)	<0.0001
Height (cm)	−30.75 (3.73)	<0.0001
Initial AIx	0.51 (0.03)	<0.0001
Ln(SDNN) (lower is worse)		
Intercept	3.55 (0.29)	<0.0001
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	0.08 (0.04)	0.0724
Diabetes duration (years)	−0.02 (0.01)	0.0146
Sex: male (REF: female)	0.12 (0.03)	<0.0001
Time-weighted MAP (mmHg)	−0.01 (0)	0.0006
Time-weighted HbA_{1c} (%)	−0.08 (0.01)	<0.0001
Ln(time-weighted triglycerides) (mg/dL)	−0.11 (0.03)	0.0005
Physically active: yes (REF = no)	0.09 (0.03)	0.0011
Initial Ln(SDNN)	0.56 (0.03)	<0.0001
PNN50 (lower is worse)		
Intercept	72.42 (8.88)	<0.0001
Etiologic type 1: type 1 diabetes (REF = type 2 diabetes)	1.5 (1.67)	0.3698
Diabetes duration (years)	−0.91 (0.24)	0.0002
Time-weighted MAP (mmHg)	−0.23 (0.08)	0.0029
Time-weighted HbA_{1c} (%)	−2.34 (0.34)	<0.0001
Ln(time-weighted triglycerides) (mg/dL)	−2.9 (1.17)	0.0136
Physically active: yes (REF = no)	4.05 (1.08)	0.0002
Initial PNN50	0.51 (0.02)	<0.0001

Continued on p. 1653

Table 3—Continued

		P
Ln(RMSSD) (lower is worse)		
Intercept	4.35 (0.35)	<0.0001
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	0.04 (0.06)	0.4452
Diabetes duration (years)	−0.03 (0.01)	0.0005
Sex: male (REF: female)	0.11 (0.04)	0.0025
Time-weighted MAP (mmHg)	−0.01 (0)	0.0002
Time-weighted HbA_{1c} (%)	−0.11 (0.01)	<0.0001
Ln(time-weighted triglycerides) (mg/dL)	−0.16 (0.04)	<0.0001
Physically active: yes (REF = no)	0.11 (0.04)	0.0028
Initial Ln(RMSSD)	0.56 (0.03)	<0.0001
Ln(LF:HF ratio) (higher is worse)		
Intercept	−1.09 (0.22)	<0.0001
Etiologic type: type 1 diabetes (REF = type 2 diabetes)	0.05 (0.08)	0.5459
Age (years)	0.03 (0.01)	<0.0001
Race/ethnicity: non-Hispanic White	0.17 (0.06)	0.0036
Sex: male (REF = female)	0.16 (0.05)	0.0021
Time-weighted HbA_{1c} (%)	0.06 (0.02)	0.0004
Initial Ln(LF:HF ratio)	0.36 (0.03)	<0.0001

Data are parameter estimates (SE).

PWV and AIx were higher in participants with type 2 diabetes versus type 1 diabetes at initial assessment ($P < 0.001$). This difference persisted at follow-up ($P < 0.001$). Femoral-foot and carotid-radial PWVs were also higher in the participants with type 2 diabetes versus type 1 diabetes at initial assessment and follow-up (Table 2). The change over time was higher for carotid-radial PWV and AIx in those with type 2 diabetes versus type 1 diabetes ($P < 0.0001$) (Table 2).

Figure 1*B* shows lower overall HRV (SDNN) and parasympathetic loss (lower PNN50) in participants with type 2 diabetes at initial assessment ($P < 0.0001$), with differences persisting at follow-up ($P < 0.0001$). Table 2 shows worse RMSSD at initial and follow-up assessment ($P < 0.001$). The change over time in PNN50 was greater in those with type 2 diabetes versus type 1 diabetes ($P = 0.0314$) and approached significance for SDNN ($P = 0.10$). There was no difference in LF:HF at initial or follow-up assessment by diabetes type and no difference in change over time by diabetes type.

Risk factors associated with the three PWV outcomes at follow-up included initial arterial stiffness value, older age, longer duration of diabetes, BP, and HbA_{1c} over time (time-weighted values, all $P < 0.05$) (Table 3). Higher waist circumference over time was also associated with worse carotid-femoral and femoral-foot PWV outcomes, while increases in triglycerides over time was associated with higher femoral-foot PWV only. Male sex was associated with higher femoral-foot and carotid-radial PWVs, while non-Hispanic White race and ethnicity were associated with lower carotid-radial PWV (all $P < 0.05$). Type 2 diabetes was significantly associated with higher carotid-femoral PWV ($P = 0.0428$), higher carotid-radial PWV ($P = 0.0348$), and higher AIx ($P = 0.0014$). Other factors associated with higher AIx were older age, longer diabetes duration, less physical activity, and higher BP and HbA_{1c} over time (all $P < 0.05$).

Lower initial HRV value, longer duration of diabetes, higher triglycerides, BP and HbA_{1c} over time, and less physical activity were associated with overall worse HRV (lower SDNN, PNN50, and RMSSD). Female sex was also associated with worse PNN50 and RMSSD. Older age and higher HbA_{1c} were also associated with worse LF:HF ratio. Diabetes type was not associated with any of the HRV indices.

In secondary analyses, all arterial stiffness and HRV models were repeated for only the participants with type 1 diabetes. Higher triglycerides, waist circumference, BP, and HbA_{1c} were associated with higher arterial stiffness and lower HRV in those with type 1 diabetes (data not shown).

CONCLUSIONS

This first longitudinal study is the to compare the change over time of arterial stiffness and HRV in young adults with youth-onset type 1 and type 2 diabetes. The major findings of this study are that youth and young adults with type 2 diabetes have worse arterial stiffness and HRV than those with type 1 diabetes at initial and follow-up assessment 4.5 years later, there is a steeper trajectory of worsening arterial stiffness and HRV in those with type 2 diabetes versus type 1 diabetes, and features of the metabolic syndrome appear to worsen arterial stiffness and HRV regardless of type of diabetes.

The majority of data documenting longitudinal changes in subclinical cardiovascular disease come from participants with adult-onset diabetes. However, since youth-onset diabetes differs from adult-onset diabetes, applying conclusions from adult data is problematic (33–35).

Cross-sectional work from the SEARCH study and others have documented that many individuals with youth-onset diabetes have risk factors for or evidence of diabetes complications by young adulthood (1,36). However, when compared by diabetes type, there appears to be excess burden of comorbidities and complications in young adults with type 2 diabetes versus type 1 diabetes, even after

accounting for age, race and ethnicity, sex, and other potential confounders (1,36). The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study investigators recently showed that 60% of their cohort of young adults with youth-onset type 2 diabetes had at least one microvascular complication by age 26 years (36). The reasons for higher rates of vascular disease in type 2 diabetes versus type 1 diabetes are not clear but may be due to insulin resistance, inflammation, advanced glycation end products, endothelial dysfunction, or dietary factors, all areas of ongoing study.

Arterial stiffness and abnormalities in HRV are associated with future risk of cardiovascular target organ damage and future cardiovascular events in adults (8–12). We and others have shown in cross-sectional work that arterial stiffness and abnormalities in HRV are present in youth with type 1 diabetes (37) and type 2 diabetes (3,5,14) by their teenage years, with comparison studies showing greater arterial stiffness and lower HRV in type 2 diabetes versus type 1 diabetes (15). Recent work has begun to explore the changes over time in arterial stiffness and HRV. Young adults with youth-onset type 2 diabetes show continued changes over time in arterial stiffness and HRV (38) and accelerated changes in arterial stiffness compared with age-similar healthy peers and those who are obese and do not have diabetes (39).

Until now, a comparison of trajectories of these complications between type 1 and type 2 diabetes has not been conducted, although cross-sectional studies suggest earlier and more severe diabetes-related complications in individuals with type 2 diabetes versus type 1 diabetes (1,39,40). We observed that by young adulthood, despite similar diabetes duration, there is a greater worsening of arterial stiffness and HRV over time, with a steeper trajectory in those with youth-onset type 2 diabetes versus type 1 diabetes. It is important to note that we also observed an increase in arterial stiffness and declines in HRV in participants with type 1 diabetes over time, although these were less severe.

Risk factors over time, including higher waist circumference, BP, and triglycerides and worse glycemic control, were evaluated along with the follow-up arterial stiffness and HRV outcomes to assess their cumulative burden (15–20). Cross-sectional data have shown a relationship between worse glycemic control and higher BP with worse HRV and higher arterial stiffness (5,41). Now, we show the cumulative effect of not only glycemic control and BP but also triglycerides and waist circumference (time-weighted values), features of the metabolic syndrome. These risk factors were also significant in our sensitivity analyses of young adults with type 1 diabetes. Duration of diabetes was identified as an important risk factor, suggesting that preventing or delaying the onset of diabetes is imperative, and in both forms of diabetes, prevention of obesity and its associated comorbidities (hypertension, dyslipidemia) is critical. Other characteristics associated with follow-up arterial stiffness and HRV include minority race and ethnicity and female sex, suggesting that these groups carry a disproportionate burden of impaired arterial stiffness and HRV and may warrant closer monitoring or early intervention to reduce health disparities. Finally, it is important to note that age was associated with follow-up arterial stiffness and HRV; thus, older age may account for some of the differences in these measures between individuals with type 2 and type 1 diabetes.

No differences in the frequency measures of HRV (LF power, HF power, and LF:HF ratio) were found at baseline or over time by diabetes type, which may be a result of methodology. We postulate that analyses of HRV variability for $>$10 min is required to detect differences in these frequency domains. Assessment of HRV of 24 h has been used to predict future risk of heart attack (42). In addition, previous work has suggested that frequency measures as opposed to the time domains (SDNN, PNN50, and RMSDD) may be less sensitive to the detection of HRV and may be influenced by respiratory sinus arrhythmia, posture/movement, and other vagal components (32).

This study had several limitations. HRV was limited to a relatively short length of recording (10 min). Although this method is considered standard clinical and research practice by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, the short measurement period may limit the ability to detect differences between groups and over time compared with time domains (43). It should also be noted that although we assessed the racial and ethnic differences in arterial stiffness and HRV in our models, our analyses were limited to non-Hispanic White individuals versus others of all races and ethnicities because of sample sizes. Strengths of this study are the longitudinal follow-up of a large cohort of multiethnic youth with both type 1 and type 2 diabetes and the ability to compare the trajectory of arterial stiffness and HRV over time in young adults with type 1 versus type 2 diabetes and to assess the impact of a cumulative burden of risk factors over time.

In summary, this study demonstrates that in adolescents and young adults with youth-onset diabetes, arterial stiffness and HRV were worse among those with type 2 diabetes compared with type 1 diabetes. Furthermore, arterial stiffness over time had a worse trajectory in those with type 2 diabetes. The risk profile for progression of arterial stiffness informs potential interventions to prevent or limit future individual cardiovascular burden and reduce the public health implications.

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