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Smoking and Arterial Stiffness in Youth with Type 1 Diabetes: The SEARCH Cardiovascular Disease Study

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Objective To evaluate the effects of smoking on early markers of cardiovascular disease (arterial stiffness) in adolescents with and without type 1 diabetes (T1D) in the SEARCH Cardiovascular Disease Study.

Study design Participants included 606 youth (18.9 $\pm$ 3.3 years, 83% non-Hispanic white; 50% male). Six groups were defined: (1) smokers with T1D (n = 80); (2) former smokers with T1D (n = 88); (3) nonsmokers with T1D (n = 232); (4) smokers without T1D (n = 40); (5) former smokers without T1D former (n = 51); and (6) nonsmokers without T1D (n = 115). Arterial stiffness measurements included pulse wave velocity (PWV), augmentation index, and brachial distensibility. Multivariate linear regression was used to assess the independent and joint effects of T1D and smoking on arterial stiffness.

Results Nearly 20% of both youth with and without T1D and T1D were smokers. In youth without T1D, smokers had higher trunk and arm PWV. After adjustment for potential confounders, T1D, but not smoking, was an independent predictor of PWV ($P < .05$). Moreover, smoking status did not modify the association between T1D and increased arterial stiffness.

Conclusions We found a high prevalence of smoking among youth with and without T1D; however, smoking status was not independently associated with increased arterial stiffness in youth with T1D. *(J Pediatr 2014;165:110-6)*.

Cross-sectional and prospective studies in adults with type 1 diabetes (T1D) have shown that cigarette smoking increases the risk of micro[1-4] and macrovascular complications[5,6] and premature mortality.[7] Although cigarette smoking is harmful at all ages, adolescents with T1D stand out as a particularly high-risk group given their increased risk to develop cardiovascular disease.[8]

Prior work from has shown that adolescents with T1D have evidence of early arterial disease compared with their healthy counterparts.[9-11] However, studies documenting the association between cigarette smoking and early arterial disease in adolescents with T1D are lacking. The purpose of this study was to evaluate the effects of smoking on early markers of arterial disease as measured by arterial stiffness.

Methods

Data for these analyses come from SEARCH Cardiovascular Disease Study, an ancillary study to the SEARCH for Diabetes in Youth Study, conducted at 2 clinical sites in Ohio and Colorado. A detailed description of the SEARCH for Diabetes in Youth study has been previously published.[12] Participants with T1D that were included in this analysis were age 11-26 years at the time of the study visit, diagnosed with T1D by a health care provider, and had T1D for at least 5 years. Control participants without T1D (fasting glucose <100 mg/dL) were recruited from primary care clinics in Colorado and Ohio and frequency-matched to participants with T1D by age, race/ethnicity, and sex.

Participants were seen at an in-person study visit where fasting blood samples were collected, processed, and sent to the SEARCH Central Laboratory at the University of Washington for analysis of total, low density lipoprotein (LDL),

AIx	Augmentation index
BMI	Body mass index
BP	Blood pressure
BrachD	Brachial distensibility
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
LDL	Low density lipoprotein
PWV	Pulse wave velocity
T1D	Type 1 diabetes

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and high density lipoprotein (HDL) cholesterol, triglycerides, glucose, and hemoglobin A1c (HbA1c) as previously described.[12]

Weight and height were measured in light clothing without shoes. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. The average of the 2 anthropometric measures was used in the analyses. Weight and height were compared with 2000 Centers for Disease Control and Prevention standards for the US to calculate body mass index (BMI) z-scores. Blood pressure (BP) was measured using a standardized protocol. Participants were seated with feet resting flat on a surface and right arm resting at heart level. The first appearance of 2 consecutive beats determined the first Korotkoff phase; the point at which a sound becomes muffled determined the fourth Korotkoff phase; and when the sound disappeared determined fifth Korotkoff phase. The fifth Korotkoff phase was used to define the diastolic BP measurement. BP was measured 3 times with the average used to calculate the mean systolic, diastolic, and mean arterial BP.

During the study visit, participants also completed a questionnaire that included several questions regarding cigarette smoking behaviors. Two questions were used to classify participants into "never," "former," and "current" smokers. If the participant answered "no" to the question "Have you ever tried cigarette smoking, even one or two puffs?" then the participant was classified as a "never" smoker. If the participant answered "yes" to the above question, they were asked "During the past 30 days, on how many days did you smoke cigarettes?" If the participant answered "none" then they were classified as a "former" smoker. If the participant answered "yes" to ever smoking a cigarette and said they had smoked at least 1 day in the past 30 days then they were classified as a "current" smoker.

Arterial stiffness was assessed by pulse wave velocity (PWV) using the SphygmoCor System (Atcor Medical, Sydney, Australia). A tonometer was used to collect proximal and distal arterial waveforms gated by the R-wave on a simultaneously recorded electrocardiogram. PWV was then calculated as the distance from the proximal artery to distal artery rounded to the nearest 0.1 cm divided by the time delay measured between the feet of the 2 waveforms. Measurements were taken from the carotid artery to femoral artery (PWV trunk), the carotid artery to the radial artery (PWV arm), and the femoral artery to dorsalis pedis (PWV leg). Three separate recordings were taken at each site, averaged, and are reported in m/s.[13] A higher PWV indicates stiffer vessels. Repeated measures of PWV have shown a coefficient of variability of <7%.[11]

Augmentation index (AIx), which is a mixed measure of central and peripheral stiffness was also collected using the SphygmoCor device. Pulse waves generated from the tonometer placed over the right radial artery were analyzed using a generalized transfer function that has been validated in the catheterization laboratory in adults to calculate a central aortic pressure wave.[14] AIx is derived from the central pressure waveform by calculating 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 per minute. A higher AIx implies stiffer vessels. Reproducibility studies have previously demonstrated intraclass correlation coefficients between 0.7 and 0.9.[11]

Three measures of brachial distensibility (BrachD), also a measure of peripheral arterial stiffness, were obtained with a DynaPulse Pathway instrument (PulseMetric, Inc, San Diego, California). This device derives brachial artery pressure curves from arterial pressure distensibility signals obtained from a standard cuff sphygmomanometer. A lower BrachD indicates stiffer vessels. Repeated measures show coefficient of variability of <9%.[11]

The SEARCH Cardiovascular Disease Study was reviewed and approved by local institutional review boards. Written informed consent and assent, where applicable, were obtained from all participants and their parent/guardian if aged <18 years at the time of the visit.

Descriptive statistics (mean [SD], median [IQR], n [%] as appropriate) were calculated for the arterial stiffness measures and participant characteristics within each of the 6 groups (T1D smokers, T1D former smokers, T1D nonsmokers, control smokers, control former smokers, and control nonsmokers). General linear models were used to test for differences between the groups for each of the population characteristics and arterial stiffness measures; variables not normally distributed were transformed as needed. To examine the impact of smoking status on arterial stiffness in presence of T1D, we tested the interaction of smoking and T1D status on each of the arterial stiffness measures. Because the interaction was not significant, we looked at the main effects of T1D and smoking status using multivariate generalized linear models with adjustments made for age, race, sex, BP, and heart rate, variables known to be highly associated with arterial stiffness, as well as the clinics to account for any differences due to measurements being obtained at different sites (Ohio vs Colorado). All analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina) and P values of <.05 were considered statistically significant.

Results

Table I presents the characteristics of the study participants by T1D and smoking status. Approximately 20% of adolescents with and without T1D were current smokers. P values in Table I represent differences across smoking groups among T1D and controls. Among youth with T1D, the 3 smoking groups differed in age, height, BMI z-score, systolic BP, triglycerides, and HbA1c ($P < .05$). Pairwise comparisons (data not shown) for youth with T1D revealed that compared with T1D nonsmokers, T1D former smokers were older, taller, and had higher systolic BP and T1D current smokers were older, taller, with lower BMI z-score and higher triglycerides and HbA1c values (all $P <$