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Reduced brachial artery distensibility in patients with type 1 diabetes

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ABSTRACT

Background and aims: In patients with type 1 diabetes mellitus (T1D), cardiovascular disease (CVD) events are more common and occur earlier in life than in non-diabetics. Reduced brachial artery distensibility (BrachD) is an independent risk factor for development of CVD. Our aim was to determine if adults with T1D have lower BrachD compared to adults without diabetes and also to determine how age and gender affect the relationship of BrachD with T1D status.
Materials and methods: BrachD was measured using the Dynapulse instrument in 829 participants (352 with T1D, 477 non-diabetics). An ANCOVA model was used to test the association of BrachD with age, sex, and T1D, and the significance of an age*sex*T1D interaction.
Results: Mean BrachD was lower in T1D patients vs. controls (6.43 ± 1.46 vs. 7.16 ± 1.48 % change per mmHg, $p < 0.0001$). In a model adjusted for age, T1D, and sex, the interaction of age*T1D*sex was significant ($p = 0.0045$). Younger women both with and without T1D had higher BrachD than men with and without T1D, but older women with and without T1D had lower BrachD compared to older men with and without T1D. Women with T1D had a steeper decline in BrachD with age than nondiabetic women.
Conclusions: BrachD is lower in T1D patients than in non-diabetics, indicating increased vascular stiffness. Younger females have higher BrachD than males, but the decline with age in BrachD is steeper for women, particularly among those with T1D. BrachD may be an inexpensive, non-invasive method to ascertain increased CVD risk in this population.

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1. Introduction

Individuals with type 1 diabetes (T1D) are at higher risk of developing cardiovascular disease (CVD) than individuals without diabetes and CVD occurs earlier in life (Krolewski et al., 1987). The process of atherosclerosis is generally subclinical for decades prior to the clinical presentation of CVD (de Ferranti et al., 2014). One way to evaluate vascular changes before clinical signs or symptoms is by measuring arterial stiffness (Urbina et al., 2010).

Systolic blood pressure (SBP) increases with a stiffer arterial bed resulting in a wider pulse pressure (PP) and increased left ventricular work (because of a higher cardiac afterload), which leads to left ventricular hypertrophy. The clinical consequences of this may include coronary artery disease, hypertensive heart disease, and stroke. Therefore, detecting cardiovascular changes as early in the disease process as possible will allow for primary prevention of CVD (Urbina, Brinton, Elkasabany, & Berenson, 2002; Stehouwer, Henry, & Ferreira, 2008).

One method to examine vascular stiffness non-invasively is brachial artery distensibility (BrachD) (Wadwa et al., 2010). The brachial artery is a useful location to study vascular changes that are independent of aging, since stiffness in the brachial artery demonstrates less change with age compared to large elastic arteries as the aorta (van der Heijden-Spek et al., 2000). A lower BrachD indicates increased arterial stiffness. Reduced BrachD has been demonstrated to be an independent risk factor for development of coronary artery disease (Budoff et al., 2003). Data from the Bogalusa Heart Study demonstrated an association between lower BrachD and several modifiable cardiovascular risk factors, such as high blood pressure (BP) and weight (Urbina et al., 2002). Lower BrachD is also associated with an elevated level of coronary artery calcium (CAC) (Budoff et al., 2003; Urbina, Khoury, Martin, D'Alessio, & Dolan, 2009), a marker of subclinical artery atherosclerosis.

In this study, our aim was to determine if adults with T1D have lower BrachD compared to adults without diabetes and also to determine how age, gender, and other known CVD risk factors affect the relationship between BrachD by diabetes status. We also

Conflict of interest: The authors have no conflicts of interest to disclose.

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investigated the association of BrachD with CAC. We hypothesized that BrachD would be lower in adults with T1D, and decrease with age. We also hypothesized that lower BrachD would be correlated with higher CAC.

1.1. Ethics

The Colorado Multiple Institutional Review Board approved the study, and all subjects provided their informed consent.

2. Methods

The Coronary Artery Calcification in T1D (CACTI) cohort is a longitudinal study of adults with T1D designed to investigate the determinants of early and accelerated atherosclerosis in T1D. The CACTI study enrolled subjects 19–56 years of age with and without T1D who were asymptomatic for cardiovascular disease at the baseline visit in 2000–2002 as previously described (Maahs et al., 2005). The data used in this study come from the third visit (6 years after the baseline examination) and consist of data on 829 subjects, 352 with T1D, diabetes duration 29.4 ± 8.8 years, age 43 ± 9 years, range 25–63 years; 477 non-diabetics age 47 ± 9, range 26–62 years.

Height and weight were measured and BMI calculated as kg body weight divided by squared height in meters. Resting systolic blood pressure (SBP) and fifth phase diastolic blood pressure (DBP) were measured three times while the subject was seated, and the second and third measurements were averaged. Hypertension was defined as current antihypertensive therapy or untreated hypertension (blood pressure ≥ 140/90 mmHg) at the time of the study visit. Antihypertensive medication use was determined by a medication inventory as previously described (Maahs et al., 2005). Physical activity was obtained from the validated Modifiable Activity Questionnaire designed for the Pima Indian study (Kriska, Knowler, LaPorte, et al., 1990). Activities were defined as moderate, vigorous, or low intensity, and the number of minutes per week for each activity level was calculated.

After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4 °C until assayed. Total plasma cholesterol and triglyceride levels were measured by standard enzymatic methods, HDL cholesterol was separated with the use of dextran sulfate (Adult Clinical and Translational Research Center, University of Colorado Anschutz Medical Campus), and LDL cholesterol was calculated by the Friedewald equation. High-performance liquid chromatography (Bio-Rad variant) was used to measure HbA_{1c}, (University of Colorado Hospital Clinical Laboratory).

For BrachD measures, study participants were seated for 5 min, and then had a special BP cuff placed around their upper arm. Subject data were entered into a personal computer interfaced to the DynaPulse 2000A noninvasive BP and hemodynamic monitoring instrument (Pulse Metric, Inc., San Diego, CA). This noninvasive instrument derives BrachD using waveform analysis of the arterial pressure signals obtained from a standard cuff sphygmomanometer (Budoff et al., 2003). Three recordings were performed sequentially, and measurements were obtained for systolic, diastolic, and mean arterial BP as well as heart rate. The pressure waveform is calibrated and incorporated into a physical model of the cardiovascular system assuming a straight tube BA and T-tube aortic system. BA compliance is derived from waveform parameters as:

$$\text{Arterial Distensibility (D)} = Cp/\left[\pi\left(D_0{}^2/4\right)\cdot L_c\right] \approx 4\pi/\left(dP/dt_{pp}\cdot t_{pp}\right)$$

where dP/dt_{pp} is the amplitude from the peak positive pressure derivative to the peak negative pressure derivative, and t_{pp} is the time interval between the peak positive and peak negative pressure derivatives. The effective cuff width (L_c) is defined as the cuff width divided by the square root of 2. BA diameter (D_o) is estimated using an empirically derived model based on sex, height, weight, and mean arterial BP, and is validated using B-mode ultrasound (Tsai et al., 2000) BA distensibility is then calculated as the percent volume change per pressure change using the formula:

$$\text{Arterial Compliance (Cp)} = \frac{\pi^2 \cdot D_0{}^2 \cdot [D_0 + L_c]}{dP/dt_{pp} \cdot t_{pp}}$$

Validation studies of BP determinations and the method to derive arterial compliance have been previously published (Brinton et al., 1997; Brinton, Walls, & Chio, 1998). Correlation between compliance measurements obtained during cardiac catheterization and brachial artery compliance measurements derived with the noninvasive method was high (r = 0.83).

CAC was measured using an Imatron C-150 Ultrafast computed tomography scanner as described previously (Dabelea et al., 2003). All participants underwent two electron beam computed tomography scans without contrast within 5 min at baseline and two scans using the standard acquisition protocol at the six year examination.

2.1. Biostatistical methods

The distribution of all variables was examined prior to analysis. BrachD in control and T1D participants was compared with a t-test. An ANCOVA model was used to test the association of BrachD with age, sex, and T1D, and the significance of an age*sex*T1D interaction, in models with and without adjustment for ever having smoked and medication use (lipid and hypertension), to determine whether BrachD differed by sex and T1D over the age span included in the study. Spearman correlation coefficients, linear models, and logistic regression were used to examine the correlation and association between CAC and BrachD. Multivariable logistic regression and linear models were used to examine the association between CAC and BrachD, after adjusting for age, sex, and T1D. Spearman correlation coefficients and linear regression models were used to test the association between BD and known risk factors. Analyses were performed using SAS 4 version 9.4 for Windows; SAS Institute, Cary, NC.

3. Results

The clinical characteristics of the study population are shown in Table 1. The BrachD was lower among the T1D population, both in men and in women. Diabetic and non-diabetic women had a lower BrachD compared to men. The lipid values were lower in the male and female T1D population compared to the controls.

The mean BrachD was significantly lower in T1D patients vs. controls (6.43 ± 1.46 vs. 7.16 ± 1.48, respectively, $p < 0.0001$). In a model adjusted for age, T1D, and sex, the interaction of age*T1D*sex was significant ($p = 0.0045$). This means that the four groups formed by crossing sex*T1D have different slopes of BrachD versus age, indicating that the association of age with BrachD differs by diabetes status and sex. Younger women, both with and without T1D, had a higher BrachD than men with and without T1D, but older women, both with and without T1D, had lower BrachD compared to older men. The decline in BrachD with age was steeper for females, with or without diabetes, compared to males. Control participants had a higher BrachD than the T1D participants at all ages (Fig. 1).

Comparisons of p-values and parameter estimates for full and reduced models are shown in Table 2. Both models have mean BrachD as the outcome, as well as age, T1D, sex, and the interaction of age*T1D*sex. The full model also contained adjustment for ever having smoked, lipid lowering medication, and antihypertension medication. There were two differences between the full and reduced models in terms of the interaction effects: (Krolewski et al., 1987) The parameter estimate for the age*sex*T1D interaction in T1D females was still negative, but was significantly different from zero after

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