Published in final edited form as:

J Diabetes Complications. 2016 July ; 30(5): 893–897. doi:10.1016/j.jdiacomp.2016.03.004.

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

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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.

Keywords

Brachial Artery Distensibility; Arterial Stiffness; Type 1 diabetes; Coronary Artery Calcium; Cardiovascular Disease

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 (1). The process of atherosclerosis is generally subclinical for decades prior to the clinical presentation of CVD (2). One way to evaluate vascular changes before clinical signs or symptoms is by measuring arterial stiffness (3).

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 (4,5).

One method to examine vascular stiffness non-invasively is brachial artery distensibility (BrachD) (6). 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 (7). A lower BrachD indicates increased arterial stiffness. Reduced BrachD has been demonstrated to be an independent risk factor for development of coronary artery disease (8). 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 (4). Lower BrachD is also associated with an elevated level of coronary artery calcium (CAC) (8,9), 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 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(10). 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 was 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 $\geq 140/90$ mmHg) at the time of the study visit. Antihypertensive medication use was determined by a medication inventory as previously described (10). Physical activity was obtained from the validated Modifiable Activity Questionnaire designed for the Pima Indian study (11). 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 minutes, 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 (8). 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:

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

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_0) is estimated using an empirically derived model based on sex, height, weight, and mean arterial BP, and is validated using B-mode ultrasound (12) BA distensibility is then calculated as the percent volume change per pressure change using the formula:

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

Validation studies of BP determinations and the method to derive arterial compliance have been previously published (13,14). 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 (15). 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 were 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 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 (Figure 1).

Comparison 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: (1) The parameter estimate for the age*sex*T1D interaction in T1D females was still negative, but was significantly different from zero after adjusting for smoking and medication use and (2) the parameter estimate for the age*sex*T1D interaction in T1D males was negative instead of positive after adjusting for smoking and medication use, although in both cases, the parameter estimate was not significantly different from zero.

Table 3 shows spearman correlation coefficients for BrachD and known risk factors in the diabetic and control groups respectively. In the participants with T1D and non-diabetic controls, significant positive correlations were found between BrachD and kcal of physical activity per week. Significant negative correlations in the adults with T1D were found between BrachD and BMI, SBP, age, and duration of diabetes. In the non-diabetic adults, significant negative correlations were found between BrachD and BMI, HbA1c, triglycerides, SBP, DBP, and age. In a model with Spearman correlation coefficients adjusted for lipid lowering medication use in all subjects, the correlation between BrachD and LDL was not statistically significant ($p=0.43$).

Results of linear regression models with BrachD as the outcome and known risk factors as covariates in diabetics and control population are shown in Table 4. There was a significant negative association between BrachD and BMI, age and SBP in adults both with and without T1D.

In the T1D adults, there was a significant negative association between BrachD and the use of hypertension medication and diabetes duration. In the control subjects there was also a significant positive association between BrachD and DBP. There was a significant age*sex interaction, which resulted in a smaller negative slope in BrachD across age for men compared to women, such that younger women had higher BrachD compared to men of the same age, but older women had lower BrachD than men of the same age.

Ever smokers had lower BrachD in both adults with and without T1D, although this did not reach significance in the multivariable model. BrachD was significantly negatively correlated with CAC score (Spearman correlation= -0.17 , $p<0.0001$) and CAC volume square root transformed (CVS) (Spearman correlation= -0.17 , $p<0.0001$). In a linear model, a one-unit increase in BrachD was associated with a 16.9 ± 8.1 decrease in CAC score ($p=0.037$). A one-unit increase in BrachD was associated with a 0.74 ± 0.19 unit decrease in CVS ($p<0.0001$). However, after adjusting for age and sex, neither CAC score nor CVS were significantly associated with BrachD ($p=0.95$ and $p=0.23$, respectively).

In logistic regression models, the presence of CAC (any score greater than zero) was significantly associated with BrachD ($p=0.002$). A one-unit increase in BrachD was associated with an odds ratio of 0.86 (95% CI 0.78-0.94) for the presence of CAC. However, after adjusting for age, sex, and diabetes status, BrachD was no longer significantly associated with CAC presence ($p=0.21$, OR=0.93, 95% CI 0.84-1.04).

4. Discussion

Our findings confirm earlier reports that BrachD is lower in patients with T1D compared to the general population (16). We report that females have a steeper decline in BrachD with age compared to males, both in the general and type 1 diabetic population, but the decrease in women with T1D is greater than in non-diabetic women. Previous studies have shown that men have a lower BrachD than women, and that healthy young women have decreasing BrachD with age (17,18). An important observation in this study is that women started with a higher BrachD than men but the decline was steeper with age in women than in men, resulting in lower BrachD among older women than men of the same age. BrachD could be a non-invasive, inexpensive, and useful method to ascertain increased CVD risk in this population. The underlying causes for the steeper decline in BrachD for women need further investigation. An interesting hypothesis to test is the role of menopause in the greater decline in BrachD, since it is suggested that menopausal women are more susceptible to CVD, especially in women with T1D (19). Currently, the CACTI study does not have a sufficient sample size in this sub-group to investigate this hypothesis.

In contrast, the significant correlation between CAC volume and BrachD as well as CVS and BrachD was attenuated after adjusting for age and sex. The same applies for the association between presence of CAC and BrachD after adjusting for age and sex. An association between CAC and BrachD has previously been shown in a non-diabetic population (8). However, after adjusting for T1D, that association is no longer significant. Our data suggest that these markers of subclinical atherosclerosis (BrachD and CAC) may have different pathophysiologic pathways and measurement of each may provide complementary information on early atherosclerosis. Most young people, even with T1D, don't have measurable CAC (20, 21, 22). The BrachD may therefore be telling us additional information about the younger populations cardiovascular complications through a separate pathway.

Studies on healthy young adults have shown an association between higher lipid values and lower BrachD (18). However in this study the lipid levels were lower among adults with T1D, although the BrachD was lower. It is well known that people with well-controlled T1D have better lipid profiles than non-diabetic peers, but that within T1D more atherogenic lipid profiles are associated with more cardiovascular disease (23). Also, the association of LDL with BrachD was not significant once lipid lowering treatment (increased in the T1D patients) was accounted for. As these data are cross-sectional, any inferences concerning causality await confirmation during prospective follow-up of the cohort. An advantage for this study is that the study sample is larger than other studies investigating similar areas in people with T1D.

4.1. Conclusion

In summary, BrachD is lower in T1D patients and the decline with age in BrachD is steeper for women, particularly among women with T1D. The greater change in BrachD with age seen in women with T1D is consistent with the increased rate of CVD in women with T1D compared to non-diabetic women and suggests that BrachD may be an inexpensive, noninvasive method to ascertain increased CVD risk in this population. CAC was not associated with BrachD after adjusting for age and sex, suggesting that these markers of subclinical atherosclerosis may have different pathophysiologic pathways.

Acknowledgements

I want to thank the CACTI study team for all their help during this project. I also want to thank NHLBI, JDRF and Blekinge Diabetesförening. The study was performed at the Barbara Davis Center for Childhood Diabetes in Denver, CO, and at the Clinical Translational Research Centers (CTRC) at the University of Colorado and Children's Hospital Colorado supported by the NIH M01 RR000051 and CTSI UL1 TR000154. Support was provided by the NIH National Heart, Lung and Blood Institute grants R01 HL61753, R01 HL079611 and HL113029, JDRF grant 17-2013-313, American Diabetes Association Junior Faculty Award 1-10-JF-50 (JSB) and Career Development Award 7-13-CD-10, and Diabetes Endocrinology Research Center Clinical Investigation Core P30 DK57516. The study was performed at the Clinical Translational Research Center at the University of Colorado Denver.

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Figure 1.

Younger females have higher BrachD than males, but the decline with age in BrachD is steeper for women, particularly among those with T1D.

Clinical characteristics of the study population

Table 1

Variable	Male (N=407 ^{***})		P-value	Female (N=422 ^{***})		P-value
	T1D (N=166)	Non-T1D (N=241)		T1D (N=186)	Non-T1D (N=236)	
Age, yr [*]	46 (37-52)	48 (42-55)	0.0003	42 (36-50)	48 (40-53)	<.0001
Race, % NHW	95	88	0.03	94	81	<.0001
T1D Duration, yr	30.1 ± 9.16	N/A	N/A	28.8 ± 8.4	N/A	N/A
Insulin Dose, units/kg [*]	0.59 (0.48-0.75)	N/A	N/A	0.54 (0.43-0.66)	N/A	N/A
On Hypertension Meds, % yes	99 (60%)	41 (17%)	<.0001	79 (42%)	35 (15%)	<.0001
SBP, mmHg [*]	119 (112-127)	120 (112-126)	0.93	113 (106-120)	111 (103-120)	0.08
DBP, mmHg	78 ± 9	82 ± 8	<.0001	72 ± 9	76 ± 8	<.0001
MAP, mmHg	93 ± 10	94 ± 9	0.07	87 ± 9	87 ± 10	0.89
HbA1c, % [*]	7.6 (7.0-8.1)	5.5 (5.3-5.8)	<.0001	7.9 (7.2-8.8)	5.5 (5.2-5.8)	<.0001
HDL, mg/dl [*]	53 (44-64)	46 (37-55)	<.0001	66 (53-77)	61 (52-72)	0.06
LDL, mg/dl [*]	89 (69-108)	113 (92-138)	<.0001	81 (64 - 99)	101 (81-123)	<.0001
Cholesterol, mg/dl	162 ± 34	189 ± 36	<.0001	166 ± 31	186 ± 32	<.0001
Triglycerides, mg/dl [*]	66 (48-94)	115 (73-163)	<.0001	63 (51-84)	80 (61-116)	<.0001
On Lipid Meds, % yes	97 (58%)	65 (27%)	<.0001	73 (39%)	26 (11%)	<.0001
On Statins, % yes	88 (53%)	57 (24%)	<.0001	69 (37%)	26 (11%)	<.0001
BMI, kg/m ² [*]	26.6 (24.3-28.8)	27.0 (24.4-30.0)	0.15	25.3 (23.1-29.2)	24.1 (21.7-28.2)	0.02
Current Smoker, %yes	12 (7%)	8	0.80	9	6	0.21
BrachD, %/mmHg	6.5 ± 1.4	7.3 ± 1.2	<.0001	6.4 ± 1.5	7.1 ± 1.7	<.0001
CAC Present, % yes	113 (68%)	140 (58%)	0.05	86 (46%)	70 (30%)	0.0006
CAC Score (Agatston units) [*]	5.2 (0.0-99.3)	1.6 (0.0-20.8)	0.004	0.0 (0.0-13.0)	0.0 (0.0-0.7)	<.0001
CAC Score Category, %						
0	47 (28.3%)	90 (37.3%)		94 (50.5%)	155 (65.7%)	
>0-99	73 (44.0%)	110 (45.6%)		59 (31.7%)	67 (28.4%)	

Variable	Male (N=407)		Female (N=422)		P-value
	T1D (N=166)	Non-DM (N=241)	T1D (N=186)	Non-DM (N=236)	
100-299	11 (6.6%)	10 (4.2%)	12 (6.5%)	1 (0.4%)	
300	29 (17.5%)	20 (8.3%)	15 (8.1%)	2 (0.9%)	<.0001
Square Root Calcium Volume *	3.3 (0.0-10.6)	1.9 (0.0-6.3)	0.0 (0.0-4.7)	0.0 (0.0-0.7)	<.0001
Kcal of Activity Per Week	1960 (784-3352)	2131 (956-3444)	1432 (616-2800)	1665 (825-3197)	0.11

* Median and IQR

** N=166 for the T1D males and N=241 for the non-DM males, except for insulin dose (T1D=163), HbA1c (T1D=165, non-DM=238), HDL (T1D=166, non-DM=240), LDL (T1D=166, non-DM=236), Cholesterol (T1D=166, non-DM=240), Triglycerides (T1D=166, non-DM=240), CAC Score T1D=160, non-DM=230), Square root calcium volume (T1D=160, non-DM=231), Kcal of activity per week (T1D=165, non-DM=239)

*** N=186 for the T1D females and N=236 for the non-DM females, except for insulin dose (T1D=183), HbA1c (T1D=185, non-DM=236), HDL (T1D=186, non-DM=235), Cholesterol (T1D=186, non-DM=235), Triglycerides (T1D=186, non-DM=235), CAC Score (T1D=180, non-DM=225), Square root calcium volume (T1D=181, non-DM=225), Kcal of activity per week (T1D=182, non-DM=234).

Table 2

Effect of covariate adjustment on the associations between BrachD and age, sex, and diabetes status.

Parameter	Full model			Reduced model		
	Parameter Estimate	Std Err	P-value	Parameter Estimate	Std Err	P-value
Intercept	7.70	0.46	<.0001	7.92	0.46	<.0001
Age	−0.01	0.01	0.55	−0.03	0.01	0.002
T1D	−0.10	0.51	0.85	0.08	0.52	0.87
Control	0.00	-	-	0.00	-	-
Female	1.64	0.52	0.002	1.41	0.52	0.007
Male	0.00	-	-	0.00	-	-
Age*T1D*Sex in T1D Female	−0.06	0.02	0.0004	−0.02	0.02	0.22
Age*T1D*Sex in T1D Male	−0.01	0.01	0.23	0.02	0.01	0.14
Age*T1D*Sex in Control Female	−0.04	0.01	0.0002	−0.04	0.01	0.002
Age*T1D*Sex in Control Male	0.00	-	-	0.00	-	-
Ever Smoker Yes	−0.22	0.11	0.04	-	-	-
Ever Smoker No	0.00	-	-	-	-	-
On Hypertension Medication Yes	−0.24	0.12	0.05	-	-	-
On Hypertension Medication No	0.00	-	-	-	-	-
On Lipid Medication Yes	−0.14	0.12	0.25	-	-	-
On Lipid Medication No	0.00	-	-	-	-	-

Table 3

Spearman correlation coefficients for BrachD and known risk factors in diabetics and non-diabetics.

Spearman Correlation Coefficients Prob > r under H0: Rho=0 Number of Observations		
	BrachD in diabetics	BrachD in non-diabetics
BMI (kg/m2)	−0.18855 0.0004 352	−0.26902 <.0001 477
HbA1c (%)	−0.04536 0.3975 350	−0.09068 0.0485 474
Triglycerides (mg/dl)	−0.00795 0.8819 352	−0.12672 0.0057 475
LDL (mg/dl)	0.05522 0.3016 352	−0.06674 0.1481 471
HDL (mg/dl)	0.00787 0.8831 352	0.04721 0.3046 475
Cholesterol (mg/dl)	0.01679 0.7536 352	−0.07939 0.0839 475
Systolic BP (mm/Hg)	−0.42499 <.0001 352	−0.31079 <.0001 477
Diastolic BP (mm/Hg)	−0.03375 0.5279 352	−0.15426 0.0007 477
Insulin dose (units/kg)	0.01762 0.7440 346	. . 0
Age (yr)	−0.32210 <.0001 352	−0.21615 <.0001 477
Duration of diabetes (yr)	−0.35385 <.0001 352	. . N/A
Kcal of activity per week	0.14327 0.0075 347	0.14284 0.0018 473

Table 4

Results of linear models with BrachD as the outcome and known risk factors as covariates.

Variable name	Estimate	Lower 95% CI	Upper 95% CI	P-value
Diabetics				
BMI, <i>kg/m²</i>	−0.05	−0.08	−0.02	0.0007
Hypertension medication, <i>yes</i>	−0.24	−0.51	0.04	0.009
Age, <i>yr</i>	−0.02	−0.04	0.01	<.0001
Systolic BP, <i>mmHg</i>	−0.04	−0.05	−0.03	<.0001
Diabetes Duration, <i>yr</i>	−0.03	−0.05	−0.01	0.0008
Lipid Medication, <i>Yes</i>	−0.01	−0.29	0.28	0.58
Sex, <i>Male</i>	0.48	0.21	0.74	0.19
Ever Smoker, <i>Yes</i>	−0.31	−0.59	−0.03	0.09
Control subjects				
BMI, <i>kg/m²</i>	−0.07	−0.10	−0.04	<.0001
Age, <i>yr</i>	−0.03	−0.05	−0.02	<.0001
age*sex Male	0.05	0.02	0.07	0.002
Diastolic BP, <i>mmHg</i>	0.04	0.02	0.06	0.0008
Systolic BP, <i>mmHg</i>	−0.05	−0.07	−0.04	<.0001
Sex, <i>Male</i>	−1.56	−2.94	−0.19	0.04
Ever Smoker, <i>Yes</i>	−0.21	−0.47	0.06	0.13