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Racial Differences in Arterial Stiffness Among Adolescents and Young Adults with Type 2 Diabetes

Amy S Shah, MD¹, Lawrence M Dolan, MD¹, Zhiqian Gao, PhD², Thomas R Kimball, MD², and Elaine M Urbina, MD.²

¹Cincinnati Children's Hospital Medical Center, Division of Endocrinology. Cincinnati Ohio 45229

²Cincinnati Children's Hospital Medical Center, Division of Cardiology. Cincinnati Ohio 45229

Structured Abstract

Background—African American adults demonstrate a higher prevalence of cardiovascular complications including myocardial infarction and stroke. Whether similar racial disparities are present to suggest African Americans adolescents are at higher risk to develop cardiovascular disease is not known. Thus, we compared arterial stiffness, an early marker of cardiovascular disease, in African American and Caucasian adolescents and young adults with type 2 diabetes.

Methods—Demographic, anthropometric, laboratory data and arterial stiffness measures including pulse wave velocity (PWV) and augmentation index (AIx) were collected in a cross sectional study of 215 adolescents (average age 18 years) with type 2 diabetes (55% African American, 65% female).

Results—Compared to Caucasians, African Americans had increased PWV (6.21 ± 0.87 vs 6.96 ± 1.30 , $p < 0.01$) and AIx (4.44 ± 11.17 vs 7.64 ± 12.02 , $p = 0.05$). Regression modeling demonstrated age, lipids, blood pressure and duration of diabetes were differently associated with arterial stiffness in each race group ($p < 0.05$).

Conclusions—African American adolescents and young adults with type 2 diabetes have worse vascular stiffness than age matched Caucasians. This process is mediated by different cardiovascular risk factors. These results suggest race specific risk factor modification may be helpful to prevent early cardiovascular disease in this high risk population.

Keywords

pediatrics; diabetes; arterial stiffness; pulse wave velocity; augmentation index

Introduction

Adults with type 2 diabetes mellitus are at increased risk to develop myocardial infarction and stroke due to accelerated atherosclerosis [1]. These complications occur more frequently and at an earlier age in African Americans compared to Caucasians [2, 3].

Adolescents with type 2 diabetes also appear to be at higher risk to develop atherosclerosis. Compared to their adolescent counterparts without diabetes, youth with type 2 diabetes demonstrated increased arterial stiffness[4, 5], a known precursor of atherosclerosis [6].

Corresponding Author or Reprints: Amy S Shah, M.D., Division of Endocrinology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7012, Cincinnati OH 45229. Phone 513-636-7033, Fax 513-636-4786, amy.shah@cchmc.org.

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Whether racial differences in arterial stiffness exist among adolescents with type 2 diabetes is not known.

To address this issue, we evaluated arterial stiffness using pulse wave velocity and augmentation index in African-American and Caucasian adolescents and young adults with type 2 diabetes. Additionally we sought to determine whether the cardiovascular risk factors that contribute to arterial stiffness are different between African-American and Caucasian adolescents with type 2 diabetes.

Methods

Subjects were recruited as part of an ongoing cross-sectional study at Cincinnati Children's Hospital Medical Center which was designed to evaluate vascular function in adolescents and young adults with type 2 diabetes, as previously described [7]. Briefly, participants were recruited from either the Diabetes clinic at Cincinnati Children's Hospital Medical Center, local physician offices, college campus, or health fairs. Eligibility criteria included: age greater than 11 years and the diagnosis of type 2 diabetes given by a health care provider. Pregnant females were excluded from this study.

The diagnosis of type 2 diabetes was based on the American Diabetes Association criteria [8]. Specifically, participants had either an elevated fasting plasma glucose levels of at least 126 mg/dl, symptoms of hyperglycemia and random plasma glucose of at least 200 mg/dl, or 2-h plasma glucose of at least 200 mg/dl during an oral glucose tolerance test. All individuals also had no evidence of another specific type of diabetes and were non-insulin requiring in the basal state to prevent diabetic ketoacidosis. A total of 178 subjects were islet cell antibody-negative (glutamic acid decarboxylase, islet cell antigen 512, insulin autoantibodies). Thirty one individuals who were recruited from local medical practices did not have islet cell antibody data available.

Prior to enrollment in the study, written informed consent was obtained from subjects ≥ 18 years old or the parent or guardian with written assent for subjects < 18 years old according to the guidelines established by the Institutional Review Board at Cincinnati Children's Hospital Medical Center and in accordance with the Declaration of Helsinki.

Data Collection

After a minimum 10 hour overnight fast, participants came to the Clinical Research Center for an in-person study visit where demographic, anthropometric data, and laboratory data was collected and vascular function testing was performed. Trained personnel obtained two measurements of height and weight as previously described [7]. The average of each was used in analyses. Body mass index (BMI) was calculated as kilograms per meter squared. Blood pressure (BP) was obtained manually with sphygmomanometer (Baum Desktop Model with V-Lok cuffs) according to the Fourth Report [9] with the average of 3 measurements used in the analysis.

Laboratory

Assays of fasting plasma lipid profiles were carried out in a laboratory which is National Heart Lung Blood Institute-Centers for Disease Control and Prevention standardized with the LDL cholesterol concentration calculated using the Friedewald equation. Fasting plasma glucose was measured using a Hitachi model 704 glucose analyzer (Roche Hitachi, Indianapolis, IN). Fasting plasma insulin was measured by radioimmunoassay using an anti-insulin serum raised in guinea pigs, 125I labeled insulin (Linco, St. Louis, MO) and a double antibody method to separate bound from free tracer. Glycosylated hemoglobin (HbA1c) was measured in red blood cells using high performance liquid chromatography

methods. To convert glucose to mmol/L divide by 18. To convert LDL or HDL cholesterol and triglycerides to mmol/L divide by 39 and 89, respectively. To convert insulin to pmol/L multiply by 6.945.

Arterial Function Testing

Arterial function testing was conducted on each subject after 5 minutes of rest in the supine position. Pulse wave velocity (PWV) was measured with a SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia). The distance from a proximal artery (carotid) to distal artery recording site (femoral artery), was measured to the nearest 0.1 cm, twice, averaged and entered into the software. 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 carotid-to-distal path length divided by the time delay measured between the feet of the two waveforms reported in m/sec [6]. Three recordings of PWV were obtained on each subject and averaged. Repeat measures in our laboratory show coefficients of variability less than 7% [5].

Augmentation Index (AIx), which provides information about arterial stiffness and pulse wave reflections [6] was also collected. AIx was collected when the SphygmoCor tonometer was placed over the right radial artery. The device analyzes pulse waves using a generalized transfer function validated in catheterization laboratory to calculate a central aortic pressure wave [10]. 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. Since AIx is affected by heart rate, values were adjusted to a standard heart rate of 75 beats per minute. Reproducibility studies in our laboratory demonstrated intraclass correlation coefficients between 0.7 and 0.9 [5].

Statistical Analysis

All analyses were performed with Statistical Analysis Software (SAS®, version 9.1.3)[11]. First, group differences were assessed using T-tests, Chi square tests or Wilcoxon rank sum tests using a p value of <0.05 to indicate significance. Non-normal values of vascular stiffness were log transformed, as needed. The number of cardiovascular risk factors (0–3) for each subject was also evaluated. The following were used to define the presence of a cardiovascular risk factor: 1) body mass index (BMI) $\geq$ 95th percentile based on Centers for Disease Control and Prevention National Centers for Health Statistics growth charts (13), 2) blood pressure (systolic or diastolic) $\geq$ 95th percentile based on gender, age and height (8), 3) the presence of dyslipidemia (either a total cholesterol $\geq$ 200mg/dL, low density lipoprotein (LDL) $\geq$ 130mg/dL, triglycerides $\geq$ 150mg/dL, or high density lipoprotein (HDL) $\leq$ 35mg/dl). Lipid cutoffs were generated from the American Heart Association guidelines for high risk adolescents [12].

Correlation analysis was performed to examine the unadjusted effect of race on PWV and AIx. Subsequently, multiple linear regression models were constructed to elucidate independent determinates of arterial function measures, initially in all subjects and then separately by race group. Full models included age, sex, mean arterial pressure, total, LDL and HDL cholesterol, triglycerides, BMI and diabetes risk factors including fasting glucose, HbA1c and duration of diabetes. Height was included in the full model of AIx as height influences the distance of reflection sites to the heart which in turn affects AIx. P values of < 0.05 were deemed significant. Robustness of all models was assessed using the maximum R square (R^2) technique.

Results

Demographic, anthropometric and laboratory data are shown as mean $\pm$ standard deviation in Table 1. Groups were similar in age and sex distribution. Cardiovascular risk profiles were similar between groups with the exception of triglycerides, HDL-cholesterol, and HbA1c values. Specifically, Caucasian adolescents demonstrated higher triglycerides and lower HDL cholesterol levels, while African Americans adolescents were found to have increased HbA1c values ($p < 0.01$). Compared to Caucasian adolescents, African Americans had significantly higher PWV ($p < 0.05$) and marginally significantly higher AIx ($p = 0.05$), both indicating increased arterial stiffness.

Table 2 demonstrates the number of subjects who had 0, 1, 2 or 3 cardiovascular risk factors by race group. The numbers of cardiovascular risk factors were similar in African American and Caucasian adolescents indicating no differences by race group. Also, there were no differences in number of smokers between groups.

Race was significantly correlated with PWV ($r = 0.30$, $p < 0.01$) and AIx ($r = 0.14$, $p < 0.05$). In linear regression models adjusted for cardiovascular risk factors, including age, sex, BMI, and BP, race was also found to be a significant independent determinant of both PWV and AIx ($p < 0.05$, data not shown). The models for PWV and AIx produced R^2 values of 0.49 and 0.28, respectively.

Subsequently, race specific linear regression models were constructed to identify which cardiovascular risk factors contribute to arterial stiffness by race group. Table 3 displays the β coefficients $\pm$ SEM for the independent determinants of PWV and AIx. In Caucasians, age, obesity, blood pressure and lipids (HDL and triglycerides) and diabetes duration were independently associated with increased vascular stiffness. In African-Americans, only age, blood pressure and obesity were significant. Closer examination of the regression models demonstrated a higher mean β coefficient for blood pressure in Caucasians compared to African Americans. In contrast, in African Americans age appeared to make a greater contribution to arterial stiffness. Although BMI-Z was an independent risk factor of arterial stiffness in both groups, the equivalent β coefficient indicates a similar contribution from obesity to arterial stiffness in both races.

Discussion

Our data demonstrate that African American adolescents and young adults with type 2 diabetes have increased arterial stiffness compared to Caucasians after controlling for age, sex, BMI and BP. Our race specific regression models suggest this process is mediated by age, obesity and blood pressure. However, compared to Caucasians blood pressure appears to have less of an effect on arterial stiffness in African Americans while the effects of obesity appear equal between the two groups. In addition, we found an independent effect of HDL-cholesterol and duration of diabetes on arterial stiffness in Caucasians which was not observed in African Americans. Thus, our data demonstrate arterial stiffness in adolescents with type 2 diabetes is mediated by different cardiovascular risk factors. Moreover, these data suggest while weight reduction and blood pressure management may improve arterial stiffness in both ethnic groups, improvement in lipid profile and diabetes prevention may only reduce arterial stiffness in Caucasians.

Cross sectional studies in pediatrics have reported racial differences in arterial stiffness but these studies have not been conducted in adolescents with type 2 diabetes. Thurston et al demonstrated significantly increased pulse wave velocity in overweight (average body mass index $24.4 \pm 0.4 \text{ kg/m}^2$) African Americans adolescents without diabetes compared to their age and body mass index matched Caucasian counterparts [13]. In a study of normal weight

youth, Collins et al described increased brachial pulse wave velocity in African Americans compared to Caucasians, $p < 0.05$ [14]. Hlaing et al conducted the only longitudinal study in children and found that African-Americans demonstrated increased arterial stiffness at age 7 compared to Caucasians, but these differences in arterial stiffness did not persist after age 12 [15]. However, their findings were observed in a younger population without diabetes. Our study is the first to examine racial differences in arterial stiffness in adolescents with type 2 diabetes. We demonstrate early in the course of type 2 diabetes (average duration of 3.6 ± 2.7 years) African American adolescents with type 2 diabetes have increased arterial stiffness compared to their age-matched Caucasian counterparts.

In adults, many theories have been proposed as to why African Americans demonstrate higher rates of morbidity and mortality from type 2 diabetes. This process is thought to be mediated by a higher prevalence of cardiovascular risk factors including hypertension, obesity and insulin resistance [16]. The Insulin Resistance Atherosclerosis Study (IRIS), a large observational cohort study in adults, suggested this process may not only be mediated by higher blood pressure but also higher hemoglobin A1c levels [17]. Additional information from the Atherosclerosis Risk in Community (ARIC) study has suggested increased arterial stiffness in African Americans is likely due to independent contributions of hypertension, the presence of diabetes and socioeconomic status [18]. To date, potential mediators which may contribute to differences in arterial stiffness among African American and Caucasians in adolescents with type 2 diabetes have not been studied.

In contrast to adult studies, we demonstrate that the increased arterial stiffness observed in African Americans is not explained by differences in traditional risk factors alone, as the degree of BMI, lipid and blood pressure elevation observed among the African American and Caucasian adolescents and young adults in our study was not different. Our regression models suggest increased arterial stiffness in African Americans is partially mediated by age, blood pressure and obesity but compared to Caucasians the contribution from obesity is similar and that from blood pressure appears less. Additionally diabetes risk factors and lipids do not appear to contribute to increased stiffness in African Americans. These findings suggest other mechanisms are likely involved.

Other investigators have suggested arterial stiffening may be mediated by increased insulin resistance or central adiposity [19, 20]. Additionally, hypoadiponectinemia may contribute to arterial stiffness by reducing endothelial activation [21]. Finally, adult studies have suggested increased endothelin-1 levels, a potent vasoconstrictor released from the endothelium which impairs blood flow in large arteries may be higher in African Americans compared to Caucasians [22]. In this study, these parameters were not measured. Thus, further investigation is needed to examine the role of potential mediators which may explain increased arterial stiffness in type 2 diabetes.

This study is limited in our cross-sectional design as it can not identify causality and it provides only a single measurement in time. In addition, we were unable to assess other “non-traditional risk factors” which may contribute to increased vascular stiffness in both race groups such as increased small LDL particles, increased lipoprotein (a), increased serum homocysteine levels and as mentioned, endothelin-1 levels. Also, socioeconomic variables were not considered in the current analysis.

Despite these limitations, this is the first study to provide evidence that racial discrepancies in vascular stiffness exist in adolescents and young adults with type 2 diabetes while identifying cardiovascular risk factors which contribute to arterial stiffness by race group. Beginning in the fourth decade African American adults are known to have higher rates of diabetes and cardiovascular complications including myocardial infarction [3] and stroke

[2]. Our findings suggest given the increased prevalence of type 2 diabetes in the adolescent population, these complications may be seen earlier. Thus aggressive approaches to prevent the development of type 2 diabetes should be taken in the pediatric population.

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Abbreviations

AIx	augmentation index
PWV	pulse wave velocity
T2DM	type 2 diabetes mellitus
BMI	body mass index
BP	blood pressure
LDL	low density lipoprotein
HbA1c	glycosylated HbA1c
HDL	high density lipoprotein

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Table 1

Characteristics of the Patient Population by Race Group

Variable	Caucasians n= 96	African Americans n=119
Age (years)	17.9 ± 3.1	18.5 ± 3.2
Female (%)	59 (61%)	81 (68%)
Height (cm)	169.5 ± 10.4	169.0 ± 9.9
Weight (kg)	104.6 ± 26.1	108.8 ± 30.6
BMI (kg/m ²)	36.2 ± 7.6	37.9 ± 9.8
Systolic BP (mmHg)	121 ± 12	123 ± 13
Diastolic BP (mmHg)	66 ± 12	68 ± 13
Mean Arterial Pressure	85 ± 9	87 ± 10
Total cholesterol (mg/dl)	182 ± 43	180 ± 39
LDL cholesterol (mg/dl)	103 ± 37	110 ± 31
Triglycerides (mg/dl)	173 ± 111	116 ± 67 [*]
HDL cholesterol (mg/dl)	43 ± 13	46 ± 10 [*]
Fasting insulin (mIU/ml)	24.9 ± 16.4	28.7 ± 23.3
Fasting glucose (mg/dl)	148 ± 71	162 ± 87
HbA1c %	7.7 ± 2.6	8.6 ± 3.2 [*]
Duration of Diabetes (years)	3.4 ± 2.5	3.5 ± 2.7
PWV (m/sec)	6.21 ± 0.87	6.96 ± 1.30 [*]
AIx (%)	4.44 ± 11.17	7.64 ± 12.02 [†]

Variables reported as mean ± standard deviation

^{*} denotes a group difference of p< 0.05[†] denotes p=0.05.

Table 2

Number of Cardiovascular Risk Factors by Race Group

Number of Risk Factors	Caucasian *	African American
N (% of total race group)	N=96	N=119
0	7 (7%)	7 (6%)
1	31 (32%)	51 (43%)
2	43 (45%)	45 (38%)
3	15 (16%)	16 (13%)
Smokers	3 (3%)	6 (5%)

Risk factors account for: BMI $\geq 95^{\text{th}}$ percentile, BP $\geq 95^{\text{th}}$ percentile, cholesterol (either total, LDL or HDL) or triglycerides $\geq 95^{\text{th}}$ percentile.

* denotes no difference in % by race group, $p=0.47$.

Table 3

Determinants of Arterial Stiffness from Multiple Linear Regression by Race Group

Variable	PWV	PWV	PWV	AIx	AIx
	Caucasian	African American		Caucasian	African American
Age (years)	0.018 ± 0.004	0.023 ± 0.005			
Height (cm)				-0.434±0.110	-0.430±0.110
HDL cholesterol (mg/dl)				-8.789±4.380	
Triglycerides (mg/dl)	0.079±0.021				
BMI (kg/m ²)	0.008 ± 0.002	0.008 ± 0.002			
Mean Arterial Pressure (mmHg)		0.004±0.001		0.363±0.115	0.284±0.104
Duration of diabetes (years)				1.046±0.432	
R ²	0.48	0.39		0.29	0.15

Data are β coefficients $\pm$ SEM. Only significant ($p < 0.05$) values listed.