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ORIGINAL RESEARCH

Accelerated Early Vascular Aging Among Adolescents With Obesity and/or Type 2 Diabetes Mellitus

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BACKGROUND: The normal rate of subclinical vascular aging from adolescence to young adulthood has not been well-characterized. We conducted a 5-year longitudinal study among adolescents with normal-weight, obesity, and/or type 2 diabetes mellitus to examine trajectories of early vascular aging.

METHODS AND RESULTS: Adolescents (mean [SD] age 17.6 [3.5]; 35.3% male) had either normal weight (n=141), obesity (n=156), or type 2 diabetes mellitus (n=151) at baseline. Primary metrics used for early vascular aging included measures of vascular structure (carotid intima-media thickness [cIMT]; common, internal, and bulb) and arterial stiffness (carotid-femoral pulse wave velocity, and augmentation index). Longitudinal (5-year) outcomes were examined using generalized estimating equations adjusting for baseline value, sex, race, and age. Compared with participants with normal weight, those with obesity had greater positive change in common cIMT (0.05 mm [0.03, 0.06]; $P<0.001$), bulb cIMT (0.02 mm [0.00, 0.05]; $P=0.033$), internal cIMT (0.03 mm [0.01, 0.05]; $P<0.001$), and pulse wave velocity carotid-femoral (0.38 m/sec [0.14, 0.61]; $P=0.001$), and those with type 2 diabetes mellitus had greater positive change in common cIMT (0.05 mm [0.04, 0.07]; $P<0.001$), bulb cIMT (0.06 mm [0.04, 0.09]; $P<0.001$), internal cIMT (0.04 mm [0.02, 0.07]; $P<0.001$), augmentation index (4.67% [2.20, 7.13]; $P<0.001$), and pulse wave velocity carotid-femoral (0.74 m/sec [0.46, 1.02]; $P<0.001$). Higher baseline systolic blood pressure was associated with greater positive change in common cIMT (0.007 mm [0.003, 0.011]; $P<0.001$), bulb cIMT (0.009 mm [0.002, 0.016]; $P=0.01$), internal cIMT (0.008 mm [0.003, 0.013]; $P=0.001$), and pulse wave velocity carotid-femoral (0.066 m/sec [0.002, 0.130]; $P=0.042$).

CONCLUSIONS: These longitudinal data support the hypothesis that the presence of obesity, type 2 diabetes mellitus, and elevated baseline systolic blood pressure in early life accelerates the progression of risk factors key in the development of early vascular aging.

Key Words: adolescent ■ cardiovascular ■ longitudinal ■ subclinical

Atherosclerosis is a progressive process beginning early in life and continuing through senescence. Longitudinal studies in adults clearly demonstrate that many cardiovascular risk factors (obesity, dyslipidemia, diabetes mellitus, hypertension) are associated with accelerated cardiovascular or early vascular aging.[1–4] The latter contributes to adverse cardiovascular outcomes and higher likelihood of early cardiovascular morbidity and mortality. While the association between risk factors and greater subclinical atherosclerosis is well-defined in adults, data in youth are limited to cross-sectional studies.

Seminal autopsy studies in children and adolescents demonstrated an association between individual cardiovascular risk factors (age, sex, race) and visible atherosclerotic development (eg, fatty streaks, lesions).[5–8] Non-invasive imaging studies in youth have shown similar cross-sectional associations

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CLINICAL PERSPECTIVE

What Is New?

- This longitudinal study examines early vascular aging among adolescents with obesity and type 2 diabetes mellitus.
- The presence of obesity and type 2 diabetes mellitus in adolescence accelerates the early vascular aging process associated with several key risk factors.
- High systolic blood pressure is also a key risk factor for accelerated early vascular aging.

What Are the Clinical Implications?

- Obesity and type 2 diabetes mellitus predispose adolescents to greater vascular disease risk and should warrant continued evaluation and treatment to reduce the associated risk.

between numerous risk factors (obesity, male sex, hypertension, insulin resistance) and higher carotid intima-media thickness (cIMT) and arterial stiffness.[9–16] Moreover, autopsy and imaging studies showed clustering of key risk factors to be associated with more extensive visual and subclinical atherosclerosis.[17,18] However, the normal trajectory of subclinical vascular aging from adolescence into young adulthood has not been well-documented because of relatively small sample sizes in longitudinal studies. Additionally, the key risk factors associated with accelerated early vascular aging are unknown, and need to be identified so that optimized prevention and treatment efforts can be initiated.

To address these gaps, we conducted a 5-year longitudinal study among adolescents with normal weight, obesity, and/or type 2 diabetes mellitus to examine trajectories of early vascular aging and identify factors associated with accelerated subclinical atherosclerosis. We examined multiple non-invasive measures of subclinical atherosclerosis and traditional cardiovascular risk factors (eg, age, sex, lipids, and blood pressure) at each time point. A priori, we hypothesized that accelerated early vascular aging, defined as a steeper slope of rise in carotid intima-media thickness and arterial stiffness over time, would occur in youth with obesity and/or type 2 diabetes mellitus as compared with normal weight. Additionally, we hypothesized that male sex and higher systolic blood pressure (SBP) would be associated with accelerated early vascular aging.

METHODS

The data that support the findings of this study are available from the corresponding author who will be responsible for maintaining availability upon reasonable request.

Study Design and Population

Adolescents with normal weight, obesity, and type 2 diabetes mellitus were identified through an existing cohort from a cross-sectional study. The original cohort (n=775) was formed first by recruiting youth with type 2 diabetes mellitus (n=244). Then controls with normal weight (n=275) and obesity (n=256) were each recruited to be frequency matched to the set of type 2 diabetes mellitus youth on characteristics of sex, race, and age (within 3 years of median). All individuals in this original cross-sectional cohort were invited to participate in a 5-year follow-up visit, regardless of their weight or disease status. These 3 baseline groups (type 2 diabetes mellitus, normal weight, obesity) were used to define adolescents at both time points. All participants with complete data at baseline and follow-up were included for this analysis (n=448 of the original 775). Written informed consent was obtained from individuals aged ≥18 years or the parent or guardian for individuals aged <18 years. Written assent was also obtained for individuals aged <18 years according to the guidelines established by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Participants who were examined as part of an ongoing study of the cardiac and vascular effects of obesity and type 2 diabetes mellitus were eligible. For the baseline examination, youth with type 2 diabetes mellitus were recruited who were islet cell antibody negative (glutamic acid decarboxylase, ICA 512, insulin autoantibodies), had no evidence of other types of diabetes mellitus, and did not require insulin in the basal state to prevent diabetic ketoacidosis. The BMI percentiles were obtained from the Centers for Disease Control and Prevention (Atlanta, GA) growth charts. All participants with obesity underwent a 2-hour oral glucose tolerance test to rule out subclinical type 2 diabetes mellitus according to American Diabetes Association guidelines.[19] Pregnant females and participants with preexisting cardiac diseases were excluded.

Anthropometrics, Diabetes Mellitus Status, Lipids, and Blood Pressure

At each assessment, height was measured on a wall-mounted stadiometer (Holtain Ltd, Great Britain) and weight on a digital scale (SECA Inc, Hanover MD) and BMI (kg/m^2) was calculated. Normal weight was defined as BMI-percentile >5th to <85th and obesity as ≥95th. Diabetes mellitus was defined by using self-reported diagnoses, medical record review, medication use for the treatment of diabetes mellitus, hemoglobin A1c (HbA1c) ≥6.5%, impaired fasting glucose (≥126 mg/dL), or 2-hour oral glucose ≥200 mg/dL. Low-density

lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, CRP (C-reactive protein) were measured from fasting blood samples. Blood samples were obtained after a minimum 10-hour fast. Plasma glucose was measured with a Hitachi glucose analyzer with intra-assay and inter-assay coefficients of variation of 1.2% and 1.6%, respectively.[20] Plasma insulin was measured by radioimmunoassay with an anti-insulin serum raised in guinea pigs, ^{125}I-labeled insulin (Linco, St Louis, MO), and a double antibody method to separate bound from free tracer. This assay has a sensitivity of 2 pmol and has intra-assay and inter-assay coefficients of variation of 5% and 8%, respectively.[6] Lipid profile assays were performed in a laboratory standardized by the National Heart, Lung, and Blood Institute and Centers for Disease Control and Prevention. The low-density lipoprotein cholesterol (LDL) concentration was calculated using the Friedewald equation. High-sensitivity CRP was measured using an enzyme-linked immunosorbent assay. Glycated hemoglobin A1c (HbA1c) was measured in red blood cells by high-performance liquid chromatography methods. Average systolic blood pressure (SBP) was taken from ≥2 separate measurements obtained using an automated cuff system.

Measurement of Vascular Structure and Arterial Stiffness

Carotid intima-media thickness (cIMT) was measured bilaterally in the common, internal, and bulb of the carotid artery. High-resolution B-mode carotid ultrasound was obtained with a linear array vascular 5.0 to 11.0 MHz probe with subjects in a supine position. Images were obtained at pre-specified angles using a Meyer's arc.[21] A continuous scan technique was used to find the maximal cIMT and the angle at which it is obtained is noted. Right and left carotid arteries in the distal 1.0 cm of the common carotid proximal to the bifurcation, the bifurcation itself ('bulb'), and the proximal 1.0 cm of the internal carotid artery are imaged digitally for off-line analyses. Depth and gain settings are adjusted to maximize resolution of the far wall lumen-intima and media-adventitia borders. M-Mode measurements of the common carotid will also be performed 1 cm proximal to beginning of the carotid bulb.[22] The maximum far wall cIMT of the 3 carotid artery segments are measured off-line on both sides using an automatic edge detection software that reduces variability in measurement with the mean R and L used in analyses.[23,24] The maximal and minimal lumen diameters from M-mode is measured for calculations of carotid stiffness including incremental elastic modulus (cIEM),[25] Peterson elastic modulus,[25,26] beta stiffness index.[25] Analyses of blind duplicate recordings from the vascular core laboratory demonstrate excellent reproducibility with coefficient of variability for automatic edge detection for all carotid segments of <4% compared with the older reading techniques such as manual trace (cardiovascular 5%) and point-to-point (cardiovascular 6%–7%) measures (Urbina, EM 2014).

Arterial stiffness was measured by carotid-femoral pulse wave velocity (PWV) and Aix (SphygmoCor system, Sydney, Australia). Radial artery waveforms are recorded with a high-fidelity micromanometer and calibrated with non-invasive Mean Arterial Pressure (MAP) and diastolic blood pressure.[27–29] A generalized transfer function validated from catheterization data is used to calculate central (ascending aortic) pressure waveforms[28,30–33] from which central aortic pressure and Aix is calculated. Aix, is the pressure difference between the primary (main outgoing wave) and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure.[34,35] The whole procedure is repeated 3 times per subject and the average value is used for the analysis. Reproducibility studies in our laboratory demonstrated intraclass correlation coefficients between 0.7 and 0.9.[13]

Statistical Analysis

Descriptive data at baseline and 5-year follow-up are presented as mean (SD) for continuous variables and n (%) for categorical variables. Measures of vascular structure and arterial stiffness are further visualized graphically at both timepoints with means and 95% CIs super-imposed on top of scatter plots. Mean change in longitudinal outcomes were examined using multiple linear regression with robust SEs for CIs and *P* values adjusting for group (normal, obesity, and type 2 diabetes mellitus), baseline value, sex, race, and age. Additional models included adjustment for several additional risk factors (LDL-C, triglycerides/HDL ratio, heart rate, CRP, SBP, and diastolic blood pressure) to examine the association of these baseline risk factors with change in measures of vascular structure and arterial stiffness. Each model was fit first with weight status (normal, obese, and type 2 diabetes mellitus) as categorical variables treating normal weight as the reference group to obtain obesity (versus normal) and type 2 diabetes mellitus (versus normal) contrasts. Models were then fit with the obesity group as the reference to obtain the type 2 diabetes mellitus (versus obesity) contrasts. Significance was set at an alpha level of $P<0.05$. All analyses were conducted using R version 3.4.0.[36]

RESULTS

Four hundred and forty-eight adolescents (mean [SD] age 17.6 [3.5]; 35.3% male; 36.4% white) completed a

Table 1. Baseline Demographics, Clinical, and Vascular Characteristics of the Cohort

Measure	Normal-Weight (n=141)	Obesity (n=156)	Type 2 Diabetes Mellitus (n=151)
Sex, Male	60 (42.6%)	43 (27.6%)	52 (34.4%)
Race, non-white	78 (55.3%)	108 (69.2%)	99 (65.6%)
Age, y	17.2 (3.7)	17.6 (3.3)	18.0 (3.4)
Height, cm	165 (12.1)	166 (10.4)	168 (10.5)
Weight, kg	57.5 (12.4)	103 (21.5)	106 (28.1)
BMI, kg/m^2	20.8 (2.5)	37.2 (6.9)	37.0 (8.8)
SBP, mm Hg	108 (10.4)	116 (11.6)	122 (12.6)
DBP, mm Hg	58.8 (14.5)	65.0 (13.0)	68.0 (13.2)
HR, bpm	62.9 (10.0)	65.5 (9.9)	71.0 (11.9)
Total cholesterol, mg/dL	160 (26.6)	171 (33.0)	179 (38.8)
Triglycerides, mg/dL	70.2 (31.3)	102 (69.4)	136 (93.6)
LDL-C, mg/dL	90.5 (22.9)	104 (29.2)	107 (31.8)
HDL-C, mg/dL	55.2 (12.3)	47.1 (9.9)	44.9 (11.0)
Glucose, mg/dL	89.1 (6.7)	91.6 (7.7)	148 (76.2)
Insulin, µIU/mL	10.6 (5.0)	22.8 (11.6)	27.3 (16.1)
HbA1c, %	5.4 (0.51)	5.5 (0.4)	7.9 (2.6)
CRP, mg/L	1.1 (2.0)	4.5 (4.4)	4.6 (4.0)
Common cIMT, mm	0.5 (0.08)	0.48 (0.07)	0.53 (0.09)
Bulb cIMT, mm	0.48 (0.09)	0.49 (0.1)	0.53 (0.11)
Internal cIMT, mm	0.38 (0.08)	0.4 (0.09)	0.43 (0.1)
Augmentation Index, %	–1.2 (11.0)	2.6 (11.6)	6.6 (13.0)
PWV carotid femoral, m/sec	5.3 (0.66)	6.2 (1.1)	6.7 (1.3)

Values presented are mean (SD) or frequency (%) where indicated. BMI indicates body mass index; cIEM, carotid incremental elastic modulus; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; and SBP, systolic blood pressure.

baseline and 5-year follow-up visit (Table 1). Baseline (Table 1) and 5-year follow-up (Table 2) visit demographics, clinical characteristics, and measures of vascular structure and arterial stiffness are presented without adjustment. At baseline, adolescents with obesity and type 2 diabetes mellitus were more likely to be female, non-white, have higher SBP, and diastolic blood pressure, and higher lipids (total cholesterol, triglycerides, and LDL-C) compared with adolescents with normal weight. Figure 1 displays change in common cIMT (A), bulb cIMT (B), and internal cIMT (C) in each group (normal weight, obesity, type 2 diabetes mellitus) over the 5-year time period. Figure 2 displays changes in Aix (A), cIEM (B), and PWV carotid-femoral (C) in each group (normal weight, obesity, type 2 diabetes mellitus) over the 5-year time period.

Male sex was associated with greater positive change in bulb cIMT (0.05 mm [0.02, 0.08]; P<0.001) and cIEM (128.94 mm Hg [49.98, 207.91]; P=0.001) and reduced Aix (–3.40% [–5.42, –1.39]; P<0.001) compared with females (Table 3). Non-white race was associated with greater positive change in bulb cIMT (0.03 mm [0.01, 0.05]; P=0.013) compared with whites. Age was associated with greater positive change in common cIMT (0.02 mm [0.00, 0.03]; P=0.007), bulb cIMT (0.04 mm [0.02, 0.06]; P<0.001), internal cIMT (0.03 mm [0.02, 0.05]; P<0.001), and Aix (3.94% [2.54, 5.34]; P<0.001). Participants with obesity had greater positive change in each of the following measures than normal weight: common cIMT (0.05 mm [0.03, 0.06]; P<0.001), bulb cIMT (0.02 mm [0.00, 0.05]; P=0.033), internal cIMT (0.03 mm [0.01, 0.05]; P<0.001), and PWV carotid-femoral (0.38 m/sec [0.14, 0.61]; P=0.001). Participants with type 2 diabetes mellitus had greater positive change in each of the following measures than normal weight : common cIMT (0.05 mm [0.04, 0.07]; P<0.001), bulb cIMT (0.06 mm [0.04, 0.09]; P<0.001), internal cIMT (0.04 mm [0.02, 0.07]; P<0.001), Aix (4.67% [2.20, 7.13]; P<0.001), and PWV carotid-femoral (0.74 m/sec [0.46, 1.02]; P<0.001). Participants with type 2 diabetes mellitus had greater change in each of the following measures than obesity: bulb cIMT (0.04 mm [0.01, 0.07]; P=0.007), Aix (4.83% [2.29, 7.36]; P<0.001), and PWV carotid-femoral (0.36 m/sec [0.09, 0.63]; P=0.009).

After adjusting for baseline factors (baseline value, race, age, obesity, type 2 diabetes mellitus, LDL-C, triglycerides/HDL ratio, heart rate, CRP, SBP, and diastolic blood pressure) male sex remained

Table 2. Participant 5-Year Follow-Up Demographics, Clinical, and Vascular Characteristics of the Cohort

Measure	Normal-Weight (n=141)	Obesity (n=156)	Type 2 Diabetes Mellitus (n=151)
Sex, Male	60 (42.6%)	43 (27.6%)	52 (34.4%)
Race, non-white	78 (55.3%)	108 (69.2%)	99 (65.6%)
Age, y	22.5 (4.1)	23.1 (3.6)	23.4 (4.1)
Height, cm	170 (9.6)	169 (10.0)	170 (10.2)
Weight, kg	67.3 (11.3)	113 (26.8)	107 (29.6)
BMI, kg/m^2	23.1 (3.1)	39.5 (9.2)	36.6 (9.0)
SBP, mm Hg	111 (11.3)	117 (13.0)	121 (15.4)
DBP, mm Hg	69.1 (8.5)	74.8 (10.6)	76.3 (10.7)
HR, bpm	64.5 (10.0)	67.2 (10.8)	76.4 (13.4)
Total cholesterol, mg/dL	166 (33.3)	168 (30.7)	178 (41.4)
Triglycerides, mg/dL	81.2 (38.6)	102 (63.9)	132 (80.5)
LDL-C, mg/dL	97.0 (28.2)	105 (27.4)	111 (36.2)
HDL-C, mg/dL	58.8 (16.0)	49.7 (12.7)	46.6 (13.4)
Glucose, mg/dL	90.7 (7.9)	92.4 (11.4)	205 (118.4)
Insulin, μIU/mL	8.9 (10.0)	17.8 (8.3)	22.2 (14.9)
HbA1c, %	4.9 (0.55)	5.1 (0.53)	8.7 (3.1)
CRP, mg/L	1.5 (2.2)	4.5 (4.7)	5.2 (4.7)
Common cIMT, mm	0.47 (0.07)	0.51 (0.09)	0.53 (0.1)
Bulb cIMT, mm	0.5 (0.1)	0.53 (0.12)	0.59 (0.16)
Internal cIMT, mm	0.39 (0.09)	0.43 (0.1)	0.46 (0.13)
Augmentation Index, %	−3.1 (10.9)	−0.5 (12.1)	17 (11.3%)
PWV carotid femoral, m/sec	5.5 (0.81)	6.4 (1.2)	7.1 (1.4)

Values presented are mean (SD) or frequency (%) where indicated. BMI indicates body mass index; cIEM, carotid incremental elastic modulus; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; and SBP, systolic blood pressure.

significantly associated with greater positive change in bulb cIMT (0.038 mm [0.010, 0.065]; *P*=0.008), and cIEM (188.16 mm Hg [100.97, 275.35]; *P*<0.001) and reduced Aix (–2.76% [–5.27, –0.25; *P*=0.031) compared with females (Table 4). Non-white race was associated with greater positive change in common cIMT (0.018 mm [0.001, 0.034]; *P*=0.036), bulb cIMT (0.034 mm [0.007, 0.060]; *P*=0.013), and Aix (2.756% [0.534, 4.978; *P*=0.015) compared with whites. Age was associated with greater change in bulb cIMT (0.028 mm [0.007, 0.049]; *P*=0.009), internal cIMT (0.029 mm [0.014, 0.044]; *P*<0.001), and Aix (3.680% [1.932, 5.429]; *P*<0.001). Adjusting for all risk factors in the model, participants with obesity had greater positive change in common cIMT (0.024 mm [0.004, 0.043]; *P*=0.016) than normal weight. Participants with type 2 diabetes mellitus had greater positive change in each of the following measures than normal weight: common cIMT (0.032 mm [0.009, 0.055]; *P*=0.006), Aix (3.756% [0.221, 7.292]; *P*=0.037), and PWV carotid-femoral (0.43 m/sec [0.107, 0.754]; *P*=0.009). Participants with type 2 diabetes mellitus had greater change in Aix (5.649% [2.751, 8.547]; *P*<0.001) and bulb cIMT (0.034 mm [0.002, 0.066]; *P*=0.039) than those with obesity. Higher baseline SBP was associated with greater positive change in common cIMT (0.007 mm [0.003, 0.011]; *P*<0.001), bulb cIMT (0.009 mm [0.002, 0.016]; *P*=0.010), internal cIMT (0.008 mm [0.003, 0.013]; *P*=0.001), and PWV carotid-femoral (0.066 m/sec [0.002, 0.130]; *P*=0.042). Higher baseline LDL-C was associated with greater positive change in PWV carotid-femoral (0.069 m/sec [0.016, 0.122]; *P*=0.011) but reduced cIEM (–27.76 mm Hg [–51.24, –4.29]; *P*=0.02). No statistically significant associations were observed for heart rate, HDL-C, triglycerides, or CRP with measures of early vascular aging.

DISCUSSION

These longitudinal data collected over a 5-year time period support the hypothesis that adolescents and young adults with obesity and/or type 2 diabetes mellitus experience accelerated early vascular aging evidenced by changes in subclinical vascular markers compared with normal weight. Accelerated early vascular aging is more prominent among youth with type 2 diabetes mellitus versus obesity. Importantly, risk factors for accelerated early vascular aging include SBP, age, male sex, and non-white race, each appearing to

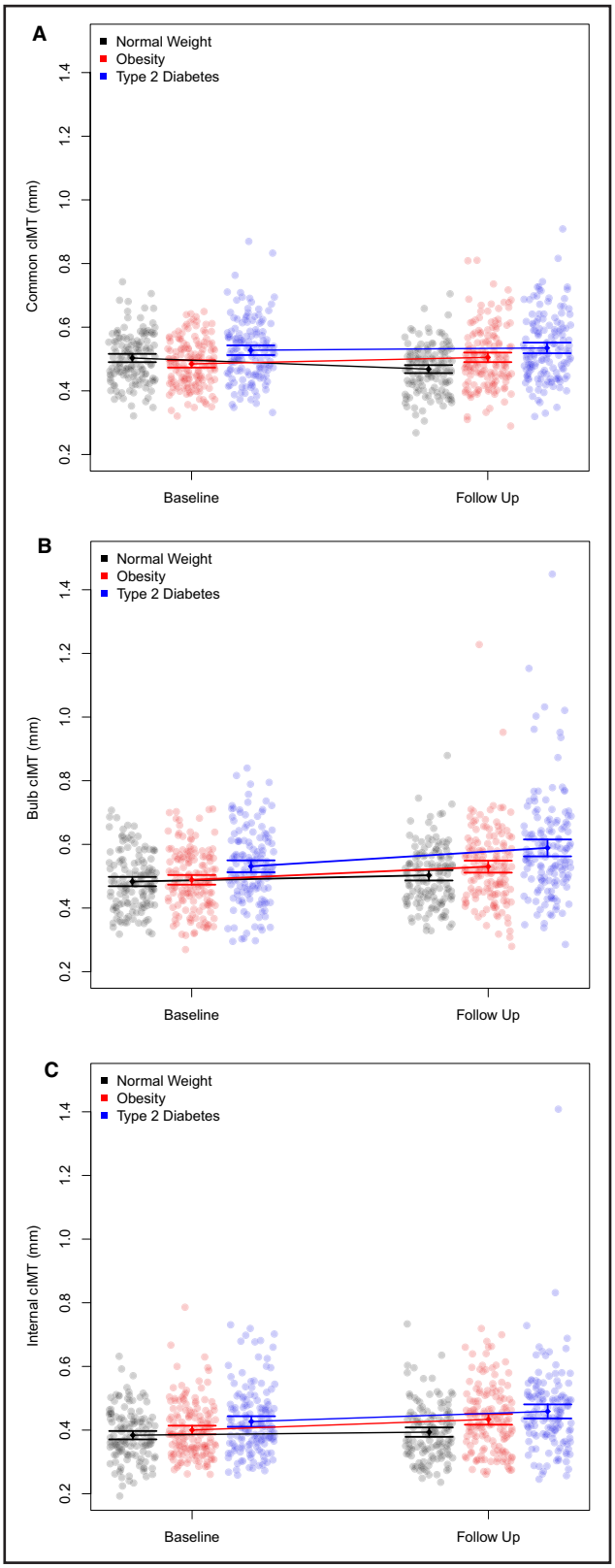

Figure 1. Change in common (A), bulb (B), and internal (C) carotid intima-media thickness among adolescents with normal weight, obesity, and type 2 diabetes mellitus over 5 years.
cIMT indicates carotid intima-media thickness.

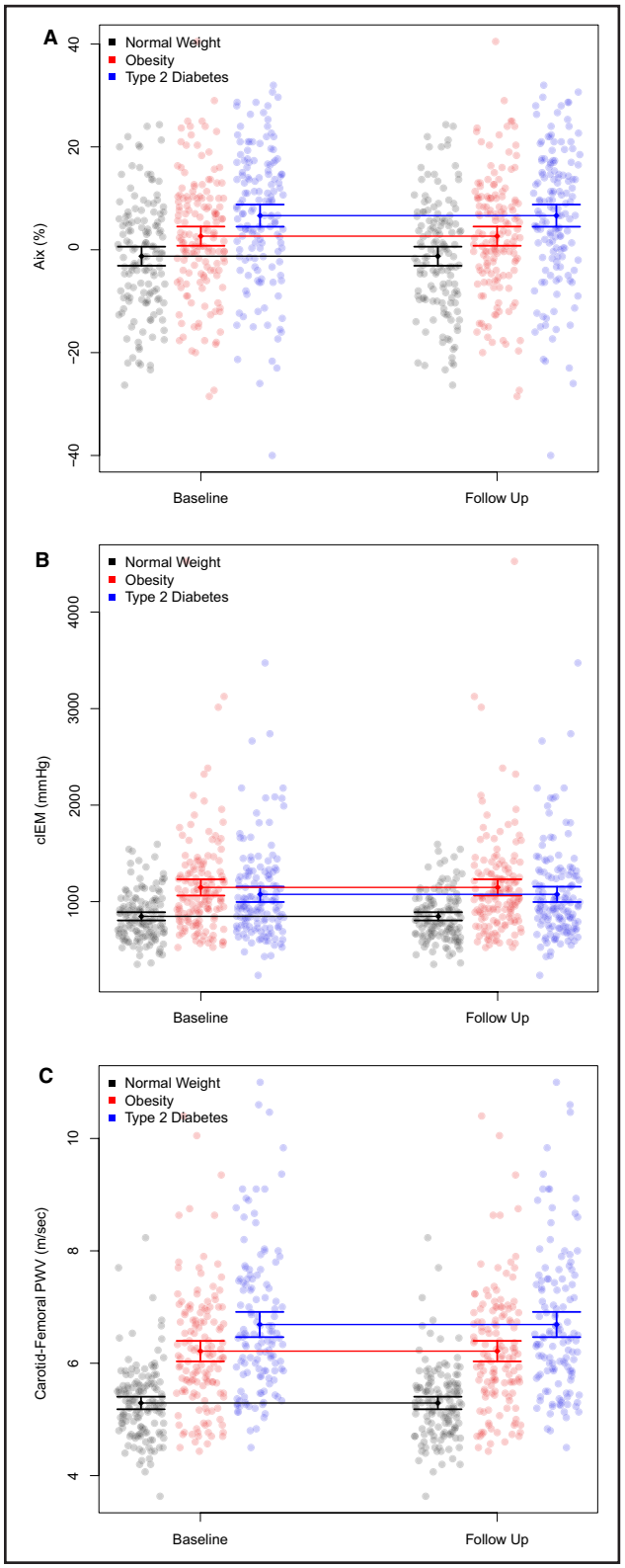

Figure 2. Change in augmentation index (A), carotid stiffness including incremental elastic modulus (B), and carotid-femoral pulse wave velocity (C) among adolescents with normal weight, obesity, and type 2 diabetes mellitus over 5 years.
Aix indicates augmentation index; cIEM, carotid stiffness including incremental elastic modulus; and PWV, pulse wave velocity.

Table 3. Demographic and Weight Status Predictors of Change in Vascular Structure and Arterial Stiffness Over 5 Years

Outcome	Covariate	Difference in 5-Y Change (95% CI)	*P* Value
Common cIMT, mm	Male (vs female)	0.01 (0.00, 0.03)	0.094
	Non-white (vs white)	0.01 (0.00, 0.03)	0.078
	Age (5 y)	0.02 (0.00, 0.03)	0.007
	Obesity (vs normal)	0.05 (0.03, 0.06)	<0.001
	Type 2 diabetes mellitus (vs normal)	0.05 (0.04, 0.07)	<0.001
	Type 2 diabetes mellitus (vs obesity)	0.01 (–0.01, 0.03)	0.384
Bulb cIMT, mm	Baseline cIMT (per mm)	–0.66 (–0.79, –0.54)	<0.001
	Male (vs female)	0.05 (0.02, 0.08)	<0.001
	Non-white (vs white)	0.03 (0.01, 0.05)	0.013
	Age (5 y)	0.04 (0.02, 0.06)	<0.001
	Obesity (vs normal)	0.02 (0.00, 0.05)	0.033
	Type 2 diabetes mellitus (vs normal)	0.06 (0.04, 0.09)	<0.001
	Type 2 diabetes mellitus (vs obesity)	0.04 (0.01, 0.07)	0.007
Internal cIMT, mm	Baseline cIMT (per mm)	–0.55 (–0.65, –0.44)	<0.001
	Male (vs female)	0.02 (0.00, 0.04)	0.060
	Non-white (vs white)	0.00 (–0.02, 0.02)	0.911
	Age (5 y)	0.03 (0.02, 0.05)	<0.001
	Obesity (vs normal)	0.03 (0.01, 0.05)	<0.001
	Type 2 diabetes mellitus (vs normal)	0.04 (0.02, 0.07)	<0.001
	Type 2 diabetes mellitus (vs obesity)	0.01 (–0.01, 0.03)	0.440
Aix, %	Baseline AiX	–0.52 (–0.61, –0.44)	<0.001
	Male (vs female)	–3.40 (–5.42, –1.39)	<0.001
	Non-white (vs white)	1.81 (–0.21, 3.82)	0.079
	Age (5 y)	3.94 (2.54, 5.34)	<0.001
	Obesity (vs normal)	–0.16 (–2.50, 2.18)	0.892
	Type 2 diabetes mellitus (vs normal)	4.67 (2.20, 7.13)	<0.001
	Type 2 diabetes mellitus (vs obesity)	4.83 (2.29, 7.36)	<0.001
PWV carotid-femoral, m/sec	Baseline PWV	–0.42 (–0.59, –0.24)	<0.001
	Male (vs female)	–0.16 (–0.34, 0.02)	0.087
	Non-white (vs white)	–0.01 (–0.22, 0.19)	0.899
	Age (5 y)	0.17 (0.00, 0.34)	0.057
	Obesity (vs normal)	0.38 (0.14, 0.61)	0.001
	Type 2 diabetes mellitus (vs normal)	0.74 (0.46, 1.02)	<0.001
	Type 2 diabetes mellitus (vs obesity)	0.36 (0.09, 0.63)	0.009
	Baseline cIEM	–0.70 (–0.80, –0.60)	<0.001
	Male (vs female)	128.94 (49.98, 207.91)	0.001
	Non-white (vs white)	–3.04 (–79.38, 73.31)	0.938
cIEM, mm Hg	Age (5 y)	–7.51 (–66.40, 51.38)	0.803
	Obesity (vs normal)	–23.49 (–117.40, 70.41)	0.624
	Type 2 diabetes mellitus (vs normal)	3.61 (–88.70, 95.93)	0.939
	Type 2 diabetes mellitus (vs obesity)	27.11 (–65.44, 119.65)	0.566

Each model adjusted for weight status, baseline value of measure, sex, and age. BMI indicates body mass index; cIEM, carotid incremental elastic modulus; cIMT, carotid intima-media thickness; and PWV, pulse wave velocity.

be key independent risk factors for changes in cIMT and arterial stiffness. The influence of SBP at baseline was present in both obesity and type 2 diabetes mellitus. Of interest, the effects of different risk factors appeared to be location-specific for cIMT. SBP was associated with adverse thickening in the common, bulb and internal carotid, while the effects of obesity and type 2 diabetes mellitus were only associated with higher cIMT in the common carotid after accounting for the effects of SBP.

Table 4. Association of Baseline Risk Factors and Change in Vascular Structure and Arterial Stiffness Over 5 Years

Outcome	Covariate	Difference in 5-Y Change (95% CI)	*P* Value
Common cIMT, mm	Baseline cIMT (per mm)	−0.522 (−0.630, −0.414)	<0.001
	Male (vs female)	0.004 (−0.014, 0.023)	0.643
	Non-white (vs white)	0.018 (0.001, 0.034)	0.036
	Age (per 5 y)	0.008 (−0.005, 0.021)	0.218
	Obese (vs normal)	0.024 (0.004, 0.043)	0.016
	Type 2 diabetes mellitus (vs normal)	0.032 (0.009, 0.055)	0.006
	Type 2 diabetes mellitus (vs obese)	0.008 (−0.013, 0.029)	0.440
	LDL-C (per 15 mg/dL)	0.004 (0.000, 0.009)	0.068
	Triglycerides/HDL ratio (per 0.25)	0.001 (−0.001, 0.003)	0.422
	HR (10 bpm)	−0.002 (−0.010, 0.006)	0.589
	CRP (per 1 mg/L)	0.002 (0.000, 0.004)	0.056
	SBP (per 5 mm Hg)	0.007 (0.003, 0.011)	<0.001
	DBP (per 5 mm Hg)	−0.001 (−0.005, 0.002)	0.420
m	Baseline cIMT (per mm)	−0.735 (−0.879, −0.592)	<0.001
	Male (vs female)	0.038 (0.010, 0.065)	0.008
	Non-white (vs white)	0.034 (0.007, 0.060)	0.013
	Age (per 5 y)	0.028 (0.007, 0.049)	0.009
	Obese (vs normal)	−0.014 (−0.043, 0.014)	0.329
	Type 2 diabetes mellitus (vs normal)	0.020 (−0.014, 0.054)	0.258
	Type 2 diabetes mellitus (vs obese)	0.034 (0.002, 0.066)	0.039
	LDL-C (per 15 mg/dL)	0.008 (0.000, 0.015)	0.052
	Triglycerides/HDL ratio (per 0.25)	0.001 (−0.001, 0.004)	0.317
	HR (10 bpm)	0.003 (−0.009, 0.015)	0.638
	CRP (per 1 mg/L)	0.003 (−0.001, 0.006)	0.111
	SBP (per 5 mm Hg)	0.009 (0.002, 0.016)	0.010
	DBP (per 5 mm Hg)	0.002 (−0.004, 0.007)	0.586
Internal cIMT, mm	Baseline cIMT (per mm)	−0.578 (−0.703, −0.452)	<0.001
	Male (vs female)	0.008 (−0.013, 0.028)	0.471
	Non-white (vs white)	−0.005 (−0.028, 0.017)	0.655
	Age (per 5 y)	0.029 (0.014, 0.044)	<0.001
	Obese (vs normal)	0.018 (−0.007, 0.043)	0.154
	Type 2 diabetes mellitus (vs normal)	0.020 (−0.004, 0.044)	0.099
	Type 2 diabetes mellitus (vs obese)	0.002 (−0.023, 0.026)	0.894
	LDL-C (per 15 mg/dL)	0.003 (−0.005, 0.010)	0.442
	Triglycerides/HDL ratio (per 0.25)	0.000 (−0.002, 0.001)	0.759
	HR (10 bpm)	0.006 (−0.005, 0.018)	0.269
	CRP (per 1 mg/L)	0.001 (−0.002, 0.003)	0.637
	SBP (per 5 mm Hg)	0.008 (0.003, 0.013)	0.001
	DBP (per 5 mm Hg)	−0.002 (−0.006, 0.002)	0.333
Aix, %	Baseline Aix	−0.564 (−0.659, −0.470)	<0.001
	Male (vs female)	−2.762 (−5.271, −0.253)	0.031
	Non-white (vs white)	2.756 (0.534, 4.978)	0.015
	Age (per 5 y)	3.680 (1.932, 5.429)	<0.001
	Obese (vs normal)	−1.892 (−4.816, 1.031)	0.205
	Type 2 diabetes mellitus (vs normal)	3.756 (0.221, 7.292)	0.037
	Type 2 diabetes mellitus (vs obese)	5.649 (2.751, 8.547)	<0.001
	LDL-C (per 15 mg/dL)	0.156 (−0.467, 0.779)	0.624

(Continued)

Table 4. Continued

Outcome	Covariate	Difference in 5-Y Change (95% CI)	*P* Value
	Triglycerides/HDL ratio (per 0.25)	0.087 (–0.098, 0.273)	0.356
	HR (10 bpm)	0.419 (–0.658, 1.496)	0.446
	CRP (per 1 mg/L)	0.055 (–0.244, 0.354)	0.716
	SBP (per 5 mm Hg)	0.307 (–0.256, 0.870)	0.286
	DBP (per 5 mm Hg)	0.283 (–0.101, 0.666)	0.148
PWV carotid-femoral, m/sec	Baseline PWV	–0.378 (–0.526, –0.231)	<0.001
	Male (vs female)	–0.216 (–0.439, 0.006)	0.056
	Non-white (vs white)	0.015 (–0.212, 0.242)	0.896
	Age (per 5 y)	0.031 (–0.165, 0.226)	0.759
	Obese (vs normal)	0.150 (–0.102, 0.403)	0.244
	Type 2 diabetes mellitus (vs normal)	0.430 (0.107, 0.754)	0.009
	Type 2 diabetes mellitus (vs obese)	0.280 (–0.011, 0.571)	0.059
	LDL-C (per 15 mg/dL)	0.069 (0.016, 0.122)	0.011
	Triglycerides/HDL ratio (per 0.25)	0.007 (–0.010, 0.025)	0.407
	HR (10 bpm)	–0.018 (–0.141, 0.106)	0.776
	CRP (per 1 mg/L)	0.007 (–0.024, 0.037)	0.666
	SBP (per 5 mm Hg)	0.066 (0.002, 0.130)	0.042
	DBP (per 5 mm Hg)	–0.013 (–0.055, 0.029)	0.538
	Baseline cIEM	–0.69 (–0.79, –0.59)	<0.001
	Male (vs female)	188.16 (100.97, 275.35)	<0.001
	Non-white (vs white)	–23.89 (–105.89, 58.12)	0.568
cIEM, mm Hg	Age (per 5 y)	19.35 (–52.21, 90.91)	0.596
	Obese (vs normal)	40.62 (–62.12, 143.35)	0.438
	Type 2 diabetes mellitus (vs normal)	54.24 (–72.36, 180.84)	0.401
	Type 2 diabetes mellitus (vs obese)	13.62 (–94.47, 121.72)	0.805
	LDL-C (per 15 mg/dL)	–27.76 (–51.24, –4.29)	0.020
	Triglycerides/HDL ratio (per 0.25)	–4.13 (–9.67, 1.43)	0.145
	HR (10 bpm)	41.46 (–0.001, 82.92)	0.050
	CRP (per 1 mg/L)	–2.70 (–14.62, 9.21)	0.657
	SBP (per 5 mm Hg)	–16.59 (–36.03, 2.84)	0.094
	DBP (per 5 mm Hg)	8.08 (–6.96, 23.12)	0.293

Each model adjusted for weight status, baseline value of measure, sex, age, low-density lipoprotein cholesterol, triglycerides/high-density lipoprotein cholesterol ratio, heart rate, CRP, systolic blood pressure, and diastolic blood pressure. BMI indicates body mass index; cIEM, carotid incremental elastic modulus; cIMT, carotid intima-media thickness; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; and SBP, systolic blood pressure.

Aging, even in our study of adolescents and young adults, was associated with adverse changes in cIMT and arterial stiffness. In adult cross-sectional studies, age is a well-established risk factor for increased IMT of both carotid and femoral arteries.[37,38] Furthermore, the effect of obesity/excess adiposity also appears to play an important role, even after accounting immutable cardiovascular risk factors (eg, age, sex, and race).[39,40] Our finding of male sex being associated with greater changes in cIMT and arterial stiffness was not unexpected, as males have a higher prevalence of cardiovascular disease than premenopausal women and cIMT increases more rapidly in age-matched males before menopause.[9,41,42] However, cross-sectional data from the Young Finn's Study has shown that the sex difference in common cIMT in young and middle-aged adults (aged 24–39 years) can be explained by differences in cardiovascular disease risk factors between sexes.[43] When LDL-C, smoking, SBP, carotid diameter (Note: our study did not adjust for this in analysis), and waist circumference were accounted for in the models, sex differences in common carotid cIMT were no longer present. In contrast, in our study male sex in younger individuals remained significantly associated with most cIMT and arterial stiffness measures. Our data support the concept that male sex is an independent and primary risk factor for accelerated early vascular aging.

We observed 3 consistent, potentially modifiable risk factors for adverse longitudinal changes in cIMT and arterial stiffness in adolescents and young adults: obesity, type 2 diabetes mellitus, and SBP. The role of obesity has been described previously;[11,12,16,44] however, our results meaningfully extend these findings by demonstrating that obesity and/or type 2 diabetes mellitus is associated with adverse changes in multiple cIMT vascular beds (common, bulb, internal) over a 5-year time course. Previously,[12] cross-sectional data supported this accelerated process being most pronounced among adolescents with type 2 diabetes mellitus and our longitudinal data confirm these findings. Moreover, once accounted for in modeling, a 5 mm Hg change in SBP surfaces as a significant risk factor exhibiting potentially differential and additive effects beyond that of obesity and/or type 2 diabetes mellitus. The vascular consequences of pre-hypertension and SBP are well-documented among youth.[9,10,45–47] However, our finding that the contribution of SBP is associated with longitudinal vascular bed changes after accounting for other cardiovascular risk factors, obesity, and/or type 2 diabetes mellitus is new. While each risk factor (obesity, type 2 diabetes mellitus, and SBP) is associated with significant longitudinal changes in common cIMT and carotid-femoral PWV, once SBP and other cardiovascular disease risk factors are added to the modeling, only SBP is associated with changes in bulb and internal cIMT. In contrast, obesity and type 2 diabetes mellitus are associated with greater changes in Aix while SBP is not. Although these differences require further study, we hypothesize that SBP may promote vessel remodeling to reduce wall stress.

Our unique presentation of individual data points to accompany group statistics yield important additional findings. The heterogeneity among each of the subclinical vascular measures is substantial. This heterogeneity is present within each group and is consistent across time points. Heterogeneity could be explained by heritability with significant heritability estimates for carotid lumen diameter (range: 44%–55%) and common cIMT (21%–34%) found in multiple studies.[48–50] This heterogeneity needs to be better understood in order for clinicians to identify high-risk individuals, as these data clearly demonstrate, people at low and high cardiovascular disease risk are present within each of the 3 unique phenotypes studied.

Study Limitations

The strengths of this study include a relatively large sample size, particularly among adolescents with type 2 diabetes mellitus, a longitudinal design over a sufficient period of time to observe significant changes, and a robust panel of non-invasive measures of subclinical cardiovascular risk. Despite these strengths this paper has the following limitations. We used non-invasive measures rather than hard cardiovascular outcomes by virtue of our focus on a pediatric population. However, studies in adults demonstrate that both arterial stiffness and cIMT are strong predictors of cardiovascular disease mortality.[4,51,52] The relatively low frequency of follow-up visits (eg, only 2 visits over 5 years) limited our ability to evaluate intermediate changes, which may have been associated with or influenced by the trajectory of cardiovascular risk factors. It should also be noted that many of the youth with type 2 diabetes mellitus were on medications for glycemic control, lipids, and/or blood pressure regulation, despite this the vascular profiles worsened overtime.

CONCLUSIONS

The presence of obesity and especially type 2 diabetes mellitus in adolescence accelerates the early vascular aging process associated with several key risk factors. SBP is associated with changes in cIMT and arterial stiffness, which are comparable with the effects of obesity and/or type 2 diabetes mellitus. Immutable risk factors such as male sex, age, and race also hasten vascular aging independent of obesity and type 2 diabetes mellitus status. These data add further evidence underscoring the importance of efforts targeting prevention and treatment of obesity, type 2 diabetes mellitus, and elevated BP among youth with a goal of delaying and/or preventing the progression of early vascular aging.

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