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Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors

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Abstract

Aims: We aimed to determine the prevalence of arterial stiffness in young adults with youth-onset type 2 diabetes who previously participated in the TODAY clinical trial and whether arterial stiffness is influenced by their prior diabetes treatment assignment or glycemic control.

Methods: We measured arterial stiffness by femoral, radial, and foot pulse wave velocity (PWV), augmentation index (AIx), and brachial distensibility (BrachD) in 453 TODAY participants (age

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Author contributions

AS and EMU conceived and designed the study, wrote, edited and reviewed the manuscript. FB, SSG, DEH, LELK, NL, KJN, and JT researched data, contributed to the discussion and interpretation of data, and edited and reviewed the manuscript. LE performed the statistical analysis, edited and reviewed the manuscript. AS, EMU, and LE take full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript. All authors gave final approval for publication.

Duality of interest: There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jdiacomp.2018.05.013>.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) NCT00081328.

Data available in NIDDK repository under the name "TODAY".

A complete list of the members of the TODAY/TODAY2 Study Group can be found in the online appendix.

20.8 ± 2.5 years, diabetes duration 7.6 ± 1.5 years, 36.4% male, BMI 36.7 ± 8.2 kg/m²) at a mean of 7.6 years post-randomization. Increased arterial stiffness in TODAY youth was defined compared with data from lean controls. We assessed whether glycemic control over time or diabetes treatment in TODAY was associated with arterial stiffness.

Results: Arterial stiffness was identified in up to 50% of TODAY participants. Prior diabetes treatment assignment was not associated with higher arterial stiffness. Glycemic control over time was associated with PWV radial and foot only. Age, race-ethnicity, sex, higher blood pressure and BMI were also associated with higher arterial stiffness.

Conclusions: Nearly half of TODAY youth have increased arterial stiffness. Targeting blood pressure and perhaps obesity and glycemic control may positively impact arterial health in adolescents with type 2 diabetes.

Keywords

Arterial stiffness; Vascular disease; Pediatrics; Type 2 diabetes; Glycemic control

1. Introduction

Youth-onset type 2 diabetes is a high-risk condition associated with an accelerated rate of atherosclerosis and the potential to develop early micro and macrovascular complications importantly myocardial infarction, stroke and cardiomyopathy.^{1–7} Stiffness of the arteries can be measured non-invasively and reflects an increased risk to develop atherosclerosis.^{8–10} Prior cross-sectional work has shown that, compared with their lean and obese non-diabetic peers, adolescents with type 2 diabetes have greater arterial stiffness measured by a higher pulse wave velocity (PWV) and augmentation index (AIx) and lower brachial distensibility (BrachD).^{11–13} Additionally, risk factors such as age, sex, race-ethnicity, blood pressure, adiposity and lipids have been shown to be associated with higher stiffness.^{11–13} However, the number of studies in adolescents with type 2 diabetes is limited, and data on the impact of diabetes control over time or prior diabetes treatment on arterial stiffness at follow-up are lacking.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) randomized clinical trial assembled the largest group of children and adolescents with type 2 diabetes to date.¹⁴ Arterial stiffness measures were assessed in those TODAY participants who participated in TODAY2, the observational follow-up study. The goals of this study were to: 1) establish the prevalence of arterial stiffness in young adults with youth-onset type 2 diabetes who previously participated in the TODAY clinical trial based on criteria established in healthy lean and obese adolescents, 2) evaluate whether prior type 2 diabetes treatment assignment in TODAY or glycemic control is an independent predictor of arterial stiffness in young adults with youth-onset type 2 diabetes, and 3) identify additional risk factors associated with arterial stiffness in this cohort.

2. Subjects, materials and methods

2.1. TODAY participants

Details of the TODAY study design have previously been reported.¹⁴ Briefly, 699 youth with recent onset type 2 diabetes were recruited. Inclusion criteria included: age 10–17 years, BMI ≥ 85th percentile for age and sex, diagnosis of type 2 diabetes for ≥ 2 years, and negative for islet cell autoantibodies. Participants were then randomized to one of 3 treatment arms (metformin alone, metformin + intensive lifestyle intervention or metformin + rosiglitazone) and followed for 2–6.5 years. The primary endpoint of the TODAY clinical trial was time to treatment failure, defined as hemoglobin A1c ≥ 8% [≥ 64 mmol/mol] for 6 months or metabolic decompensation requiring insulin therapy.¹⁵

The TODAY follow-up study, TODAY2, lasted 3 years and began immediately after the TODAY clinical trial was completed. One objective of the follow-up study was to examine the persistence of effects of the TODAY randomized treatment assignment on long-term glycemic control following discontinuation of randomized treatment.

Of the 699 participants who participated in the TODAY clinical trial, 453 who chose to participate in TODAY2 had arterial stiffness measurements performed. Arterial stiffness measurements were collected in the last year of the follow-up study (median time from randomization 7.0 ± 1.3 years). Comparison of the 453 with arterial stiffness measurements to the 246 who did not participate in TODAY2 showed that those who continued participation were older at baseline (14.4 years vs. 13.8 years, $p = 0.0002$) but not different in sex, race-ethnicity, baseline BMI or baseline hemoglobin A1c. The study was approved by the Institutional Review Boards for the Protection of Human Subjects of each participating institution. All participants provided informed consent and minor children confirmed assent according to local guidelines.

2.2. Study variables for TODAY participants

The demographics, anthropometrics and laboratory data reported here were obtained within one month of the arterial stiffness measurements. Study visits were conducted after a 10–14 hour overnight fast. Race-ethnicity was self-reported using 2000 U.S. Census-based questions. Participants checked Hispanic/Latino ethnicity yes-or-no and then checked as many racial categories as needed. All physical measurements were made by trained staff according to a study-wide protocol.¹⁴ Height was measured without shoes using a stadiometer. Weight was measured twice using a Seca scale (model 882, Seca USA, Hanover, MA), with a third measurement taken if the first two differed by >0.2 kg, and measurements were averaged. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the iliac crest using a non-stretch, non-tension fiberglass Gulick II tape measure. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a CAS 740 monitor with standardized oscillometric cuff sizes while the participant was seated. Mean arterial pressure (MAP) was calculated as $[(2 * DBP) + SBP] / 3$. Information on cigarette smoking and tobacco use in the past month (yes/no) was obtained from the participants.

All laboratory tests including assessments of hemoglobin A1c, fasting lipids, and high-sensitivity C-reactive protein (hs-CRP) were performed in a central laboratory as previously described.¹⁴ Hemoglobin A1c was measured with a dedicated high-performance liquid chromatography method (TOSOH Biosciences Inc., South San Francisco, CA) every 2 months during year 1 of TODAY and then quarterly. Insulin sensitivity was calculated as 1/fasting insulin. Lipid lowering and anti-hypertensive medications were initiated as needed per study protocol.¹⁴

2.3. Control participants

While a control population was not part of the TODAY2 follow-up study design, we compared data from lean and obese individuals who were recruited between 2005 and 2010 in Cincinnati, Ohio as part of the Type 2 Diabetes and Cardiovascular Disease Study. Extensive details of this control cohort have previously been published.¹³ Briefly, this study recruited 241 lean adolescents who were defined as healthy with a BMI of <85th percentile for age and sex and 234 obese adolescents defined as a BMI ≥95th percentile for age and sex and without evidence of type 2 diabetes by fasting and post-prandial blood glucose levels based on oral glucose tolerance testing. Arterial stiffness measurements in lean and obese individuals were obtained using the same protocol, training procedures and underwent the same data editing procedures as in TODAY2.

2.4. Outcome measures

Arterial stiffness measurements included PWV and AIx using the SphygmoCorCPVH (AtCor Medical, Lisle, IL) and BrachD using the DynaPulse 2000 (PulseMetric, San Diego, CA). All measurements were conducted after the participant rested for >10 min.

PWV calculates the speed of pressure waves generated by cardiac ejection to reach the periphery, with a higher PWV indicating a *higher* arterial stiffness. PWV was assessed in three locations, between the carotid and femoral artery (PWV carotid femoral), the carotid and radial artery (PWV carotid radial), and the femoral and dorsalis pedis artery (PWV femoral foot). The same procedure was used for all three measurements. ECG leads are applied to the torso of each participant. The distances from the two arterial sites were measured to the nearest 0.1 cm three times using a specialized caliper and averaged. A pressure waveform was recorded from the proximal site (carotid artery) followed by a second arterial waveform recorded from the distal site (femoral, radial or dorsalis pedis) using a tonometer. Waveforms were also recorded on a simultaneous electrocardiogram. PWV was then calculated as the difference in the proximal and distal artery divided by the time delay measured between the feet of the two waveforms reported in meters per second. The average of at least 10 beats was used in the analysis to cover a complete respiratory cycle. Three PWV recordings were obtained per participant and averaged.

AIx is a measure of wave reflections and systemic arterial stiffness.⁸ A *higher* AIx suggests higher arterial stiffness. For measurement of AIx, the SphygmoCor tonometer was placed over the right radial artery and pressure waves were recorded. The device then calculated an aortic pressure curve from the measured radial pressure curve using a generalized transfer function validated in the cardiac catheterization laboratory.¹⁶ The transfer function is valid

in those with normal cardiac anatomy. Waveforms collected over a 10-second period are averaged to produce peripheral and corresponding central (ascending aortic) pressure waveforms. AIx is calculated as the difference between the main outgoing peripheral wave and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure. Because AIx is affected by heart rate, all values are adjusted to a standard heart rate of 75 beats per minute. The average of three AIx measurements was used in the analysis.

BrachD was obtained with the DynaPulse Pathway instrument. This instrument uses pulse dynamic analysis of arterial pressure signals obtained from a standard cuff sphygmomanometer.¹⁷ The pressure waveform obtained is incorporated into a physical model of the cardiovascular system, assuming a straight tube brachial artery and T-tube aortic system. Brachial artery compliance is then derived from waveform parameters and brachial artery distensibility is calculated using an empirical model to estimate baseline brachial artery diameter from sex, height, weight and MAP. Off-line analyses of brachial artery pressure curve data were then performed by Pulse Metric, Inc., using an automated system to derive parameters from the pulse curves to calculate BrachD. Three measurements of BrachD were obtained per participant and averaged. A *lower* BrachD indicates greater stiffness.

Vascular measurements were defined as increased in TODAY participants if PWV and AIx values were >90th percentile for lean controls. For BrachD, since a lower value indicates greater stiffness, a value of <10% in TODAY participants compared to lean controls was defined as abnormal. Similar cutoffs have been used to define increased arterial stiffness in adolescent studies.¹⁸

2.5. Statistics

Statistical analyses were performed using SAS for Windows (version 9.4; SAS Institute Inc., Cary, NC). All analyses were considered exploratory, with statistical significance defined as *p*-values of <0.05 and no adjustment for multiple testing. Data are mean and SD or percent. Variables with a skewed distribution were log transformed (triglycerides and hs-CRP). Paired *t*-tests were used to test for differences in demographic and laboratory data between the baseline and follow-up visit. Due to varying time measures of hemoglobin A1c during the study (values collected every 2 months during the first year and quarterly thereafter), a time-weighted hemoglobin A1c average was computed that included all values from the start of TODAY until the time of the vascular assessment. General linear models were used to compare arterial stiffness measurements in TODAY youth to published control groups,¹³ after adjustment for age, sex, and race-ethnicity.

Multivariate general linear regression models were constructed to assess the relationship between glycemic control (designated as either a time weighted hemoglobin A1c or failure to maintain glycemic control (defined as two consecutive hemoglobin A1c measurements of 8% [64 mmol/mol]) or randomized type of diabetes treatment and our dependent variables, arterial stiffness measurements. Height was included in the AIx model and heart rate (beats per minute) in all others by default. In addition, the following covariates were entered in the model: baseline age, sex, race-ethnicity, and the following values from the

time of the arterial stiffness assessment: BMI, MAP, LDL cholesterol, triglyceride/ HDL cholesterol ratio (representing small dense LDL particles), insulin sensitivity, hs-CRP, and cigarette smoking (in the past month yes/no). Significance of each covariate in the full model was assessed and non-significant terms were removed using a backward elimination approach with a removal criterion of $p > 0.10$ until all remaining covariates or their interaction (effect modifier) were significant. R-square (R^2) and p -value of the models was evaluated to assess the robustness of the models. Additional models including both the baseline and change from baseline to follow-up visit in BMI, MAP, LDL cholesterol, triglycerides/HDL cholesterol ratio and hs-CRP were also considered. Sensitivity analyses were conducted using models excluding participants prescribed blood pressure and/or lipid lowering medication at the time of the arterial stiffness measurements.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 453 TODAY participants who had arterial stiffness measurements performed in TODAY2 are shown in Table 1. At the baseline visit, these adolescents were a mean age of 13.8 ± 2.0 years and had an average duration of type 2 diabetes of 0.6 ± 0.5 years. A total of 39.7% were Hispanic, 32.9% were non-Hispanic black, 20.0% were non-Hispanic white, 7.4% were classified as Other (mainly American Indian or Asian) and 63.6% were female. Five percent ($n = 23$) were taking an ACE inhibitor for hypertension and 1.1% ($n = 5$) reported taking lipid lowering medication. At baseline for these 453 TODAY participants, randomized treatment group was as follows: metformin (32.7%), metformin + lifestyle (33.8%) and metformin + rosiglitazone (33.5%).

Arterial stiffness measurements were obtained at a mean of 7.0 ± 1.3 years after randomization, when average duration of type 2 diabetes was 7.6 ± 1.5 years. BMI, waist circumference, blood pressure, lipids, hs-CRP, percent smoking and hemoglobin A1c were significantly worse at follow-up (all $p < 0.0001$) compared with baseline. The percent of participants who reported taking an ACE inhibitor or lipid lowering drug was 41.0% and 14.3%, respectively. In sum, participants had a total of 27 ± 6 hemoglobin A1c values collected (range 7–40) between baseline and the follow-up visit and the mean time weighted hemoglobin A1c for the group was $7.7 \pm 2.0\%$.

3.2. Multivariate models

In multivariate models (Table 2), hemoglobin A1c over time was independently associated with PWV carotid radial and PWV femoral foot. Other risk factors associated with worse arterial stiffness were older age for PWV carotid femoral, PWV carotid radial and AIx and higher MAP for all measures. Female sex was associated with a worse AIx and race-ethnicity was associated with both AIx and BrachD. Higher BMI values and lower LDL-C at the time of the arterial stiffness measurement related to lower BrachD only (higher stiffness). Models that included both the baseline and change in metabolic variables (BMI, MAP, LDL cholesterol, triglycerides/HDL cholesterol ratio, insulin sensitivity, and hs-CRP) provided similar results. Lipid lowering medication and current cigarette smoking were not associated with any of the outcomes. Blood pressure medication was associated with PWV carotid

radial only ($p = 0.0003$). Those on blood pressure medication at the time of the arterial stiffness measure had a lower PWV radial compared with those not taking blood pressure medication (7.7 ± 1.2 vs. 7.8 ± 1.3 m/s). When we excluded participants on blood pressure medication from the multivariate PWV carotid radial model, all variables, except age, remained significant in the model including time-weighted hemoglobin A1c ($p = 0.0108$) and the model R^2 increased from 0.12 to 0.18 ($p < 0.0001$).

There were no significant differences in arterial stiffness measurements by randomized diabetes treatment in the TODAY clinical trial for any of the arterial stiffness measures. Additionally, arterial stiffness measurements did not differ in adolescents who failed to maintain glycemic control vs. those that maintained glycemic control (hemoglobin A1c $\geq 8\%$ [≥ 64 mmol/mol]) up to the time of the arterial stiffness assessment and no effect modification of the covariates with glycemic control was found for any of the arterial stiffness measures.

3.3. Comparison with lean and obese controls

The p values in Table 3 represent differences between TODAY participants and lean and obese controls for demographics and arterial stiffness measurements adjusted for differences in age, race-ethnicity, and sex. Compared with lean controls, TODAY participants had worse arterial stiffness for nearly all measurements except PWV femoral foot (worse meaning higher values for PWV carotid femoral, carotid radial, AIx, and lower values for BrachD). Compared with obese controls, TODAY youth had higher PWV carotid radial and AIx but also higher BrachD. The percent of TODAY participants with increased arterial stiffness defined as >90 th percentile for PWV and AIx and less than the 10th percentile compared to lean was between 22 and 50%, depending on the measure obtained when compared to lean controls (Fig. 1).

4. Discussion

We report novel data in the largest cohort of adolescents and young adults with type 2 diabetes to date demonstrating 1) a high percent of increased arterial stiffness; 2) an independent association between prior glycemic control and PWV carotid radial and femoral foot; and 3) no differences in arterial stiffness by prior treatment group in the TODAY clinical trial. Furthermore, we found the most consistent risk factor associated with arterial stiffness in this cohort was blood pressure.

Multiple arterial stiffness measurements were utilized in this study because atherosclerosis develops in a non-uniform fashion¹⁹ and each measurement assesses different properties of the arterial tree.⁸ For example, PWV carotid femoral is a measure of central arterial stiffness^{20, 21} while PWV carotid radial and femoral foot provide a means to assess the vasculature in peripheral sites.^{22, 23} AIx, on the other hand, is an indirect mixed measure of arterial stiffness that is influenced by central stiffness and peripheral wave reflections.⁸ Lastly, BrachD is a non-ultrasound measure of stiffness (arterial compliance) in a medium muscular artery.¹⁷ Though not interchangeable, each measure is a non-invasive surrogate end point for cardiovascular disease and PWV carotid-femoral and AIx have been shown in adult studies to predict cardiovascular events.^{8, 9, 24–26} There is no data on the most sensitive

measure to detect arterial stiffness youth with type 2 diabetes so we have explored multiple parameters including PWV carotid radial, PWV femoral foot and BrachD in addition to PWV carotid femoral and AIx.

Prior work suggests adolescents with type 2 diabetes are at high risk for cardiovascular disease.¹⁻⁷ Therefore, we sought to determine if youth who participated in the TODAY clinical trial had greater arterial stiffness, using surrogate markers for atherosclerosis, compared to lean and obese controls who had vascular measurements obtained by the same methods.¹³ Compared to lean youth, TODAY youth had higher mean values for nearly all vascular assessments. TODAY youth had also higher arterial stiffness compared to obese youth but not for all measures. TODAY participants had less stiffness in the brachial artery. The latter is inconsistent with previous data published in a cohort of adolescents with type 2 diabetes from Cincinnati where adolescents with type 2 diabetes had greater stiffness, lower BrachD, compared to obese controls.¹³ Reasons for this less severe phenotype in TODAY youth vs. the Cincinnati type 2 cohort are not clear but lower hemoglobin A1c (Cincinnati mean A1c $8.2 \pm 3.0\%$ single measurement vs. TODAY time weighted A1c $7.7 \pm 2.0\%$), consistent medication use in TODAY (Cincinnati cohort provider treated 57% on metformin and 45% on insulin without adherence assessed),²⁷ and unmeasured cohort characteristics at the time of the arterial stiffness measure including diet and physical activity may all play a role.

Despite this apparent less severe phenotype, a high percent of TODAY youth had increased arterial stiffness. Nearly half of the cohort had a mean PWV carotid femoral greater than the 90th percentile for lean. For the other vascular measurements, the percent abnormal ranged from a quarter to a third of the cohort. To put this in perspective, each 1 SD increase in PWV carotid femoral among adults studied in the Framingham Heart Study was associated with a 48% increase in incident cardiovascular events over 7.8 years of follow-up.²⁸ Similar degrees of abnormal arterial stiffness have been published by the SEARCH for Diabetes in Youth study¹⁸ suggesting youth with type 2 diabetes are at high risk for subsequent cardiovascular events.

Prior cross sectional studies have shown a higher hemoglobin A1c is associated with higher vascular thickness.^{27, 29} However, the association between glycemic control over time and arterial stiffness in youth onset type 2 diabetes had not been explored. We show independent effects of hemoglobin A1c overtime with PWV carotid radial and PWV femoral foot. However, PWV carotid radial and femoral foot have been less explored in adults, therefore the impact of these results on cardiovascular risk is unclear. We found no differences in arterial stiffness at follow-up by prior treatment modalities used in the TODAY clinical trial (metformin alone, metformin and lifestyle, and metformin and rosiglitazone) but we cannot exclude a treatment modifying effect on our vascular measures independent of glycemia. It is also possible longer follow-up of the cohort is needed to see the effects of diabetes treatments (metabolic memory) or that medication effects do not persist after their discontinuation.

We identified several other risk factors associated with arterial stiffness in TODAY youth. Older age was associated with higher stiffness as measured by PWV carotid femoral, PWV

carotid radial, and AIx. Higher blood pressure was associated with worse stiffness in all measures while higher BMI was associated with worse stiffness when measured by BrachD. We also found compared to non-Hispanic white, Hispanic ethnicity was associated with lower AIx whereas female sex was associated with a higher AIx. Unexpectedly, we also found higher LDL is associated with lower stiffness in the brachial artery. These results concur with prior cross-sectional work in youth that demonstrates differential associations between risk factors and arterial stiffness suggest arterial stiffness is influenced by more than one risk factor.^{12, 13, 30} It should be noted though cause and effect cannot be established given the cross sectional nature of this study.

Limitations of the current study include a single assessment of arterial stiffness, so we cannot comment on change in arterial stiffness over time or how glycemic control or prior diabetes treatment may have influenced the progression of stiffness, but follow-up arterial stiffness measurements for this cohort are planned. Additionally, though physical activity was collected in the parent TODAY study, the information was not obtained during the TODAY2 follow-up phase. Alcohol consumption was obtained for participants of legal age only. For those reasons, we were unable to account for the effect of physical activity and alcohol in the analyses. Finally, the lean and obese controls were recruited from a different study. Although vascular assessments were obtained using the same protocol and data were age, race/ethnicity and sex adjusted, there were likely additional characteristics that differed between the cohorts that were not accounted for.

In conclusion, youth with type 2 diabetes in TODAY demonstrate a high prevalence of arterial stiffness. We found higher blood pressure was associated with higher arterial stiffness and higher BMI was associated with worse BrachD. Prior diabetes treatments used in the TODAY trial do not appear to differentially influence arterial stiffness and hemoglobin A1c overtime was associated with arterial stiffness in the arm and foot only. These results suggest that targeting blood pressure and perhaps obesity and glycemic control may positively impact arterial health in adolescents with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at <https://today.bsc.gwu.edu/>.

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Fig. 1.

The percent of TODAY participants with abnormal stiffness compared with published data lean controls. Abnormal stiffness was defined as the percent of TODAY participants with a PWV or AIx > 90th percentile or <10th percentile for BrachD compared to lean.

Table 1

Characteristics of the TODAY participants (mean $\pm$ SD or percent) at baseline and at the time of arterial stiffness measurements in TODAY, $n = 453$.

Variable	Baseline	Vascular assessment	<i>p</i> -value ^a
Age (years)	13.8 $\pm$ 2.0	20.8 $\pm$ 2.5	<0.0001
Male (%)	36.4%	-	-
Race-ethnicity (%)			
Black non-Hispanic	32.9%	-	-
Hispanic	39.7%	-	-
White non-Hispanic	20.1%	-	-
Other	7.3%	-	-
Cigarette smoking in the past month (%)	3.1%	21.5%	<0.0001
Waist circumference (cm)	108.7 $\pm$ 17.1	113.8 $\pm$ 17.1	<0.0001
BMI (kg/m ²)	34.9 $\pm$ 7.9	36.7 $\pm$ 8.2	<0.0001
SBP (mm Hg)	112.5 $\pm$ 10.7	118.7 $\pm$ 12.2	<0.0001
DBP (mm Hg)	66.4 $\pm$ 8.0	73.2 $\pm$ 9.8	<0.0001
Total cholesterol (mg/dL)	144.9 $\pm$ 29.5	166.5 $\pm$ 37.0	<0.0001
LDL cholesterol (mg/dL)	84.0 $\pm$ 24.8	97.3 $\pm$ 30.9	<0.0001
HDL cholesterol (mg/dL)	38.9 $\pm$ 8.8	42.6 $\pm$ 12.2	<0.0001
Triglycerides (mg/dL)	111.7 $\pm$ 76.9	139.2 $\pm$ 128.6	<0.0001
Hs-CRP (mg/dL)	0.46 $\pm$ 0.97	0.67 $\pm$ 0.82	<0.0001
Hemoglobin A1c (%)	6.0 $\pm$ 0.8	8.8 $\pm$ 2.9	<0.0001
Hemoglobin A1c group			
6.5%	79.3%	30.4%	<0.0001
6.6–7.9%	20.5%	12.2%	
8.0%	0.2%	57.4%	

^a *p*-Values from paired *t*-tests and Bowker's test of symmetry testing for differences between the baseline and follow-up visit. Triglyceride and Hs-CRP values were log-transformed prior to testing due to skewed distributions.

Table 2

Determinante of arterial stiffness.^a

Variable	PWV carotid femoral (m/s)		PWV carotid radial (m/s)		PWV femoral foot (m/s)		AIx (%)		BrachD (mm/mm Hg)	
	Higher = worse		Higher = worse		Higher = worse		Higher = worse		Lower = worse	
	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value
Intercept	0.37	$p = \text{ns}$	3.13	$p < 0.0001$	2.94	$p = 0.0248$	38.1	$p = 0.0040$	8.82	$p < 0.0001$
Time-weighted A1c	-	-	0.09	$p = 0.0108$	0.19	$p = 0.0081$	-	-	-	-
Age (years)	0.14	$p = 0.0006$	0.07	$p = 0.0416$	-	-	0.97	$p = 0.0003$	0.08	$p = 0.0030$
Female	-	-	-	-	-	-	3.34	$p = 0.0158$	-	-
Race-ethnicity										
Non-Hispanic Black	-	-	-	-	-	-	0.31	$p = \text{ns}$	-0.07	$p = \text{ns}$
Hispanic	-	-	-	-	-	-	-3.40	$p = 0.0155$	-0.06	$p = \text{ns}$
Other	-	-	-	-	-	-	-6.81	$p = 0.0018$	0.53	$p = 0.0227$
MAP (mm Hg)	0.04	$p < 0.0001$	0.03	$p < 0.0001$	0.04	$p = 0.0015$	0.28	$p < 0.0001$	-0.02	$p < 0.0001$
BMI (kg/m ²)	-	-	-	-	-	-	-	-	-0.06	$p < 0.0001$
LDL cholesterol (mg/dL)	-	-	-	-	-	-	-	-	0.004	$p = 0.0166$
Model R ²	0.14	($p < 0.0001$)	0.12	($p < 0.0001$)	0.07	($p < 0.0001$)	0.27	($p < 0.0001$)	0.26	($p < 0.0001$)

^aFull model included a measure of glycemic control (time-weighted hemoglobin A1c or failure to maintain glycemic control over a sustained period), treatment group, baseline age, sex (referent group = 'Male'), race-ethnicity (referent group = 'Non-Hispanic White'), and the following variables from the time of the arterial stiffness assessment: BMI, MAP, LDL cholesterol, triglycerides/HDL cholesterol ratio, insulin sensitivity, insulin sensitivity, hs-CRP, and cigarette smoking (in the past month yes/no). Height was included for the AIx model and heart rate (beats per minute) in all others by default. Only factors that remained significant after backward elimination in at least one of the arterial stiffness measures are shown in the table. Parameter estimates for each covariate included in the model and the full model R² are given.

Table 3

Arterial stiffness measurements, in TODAY youth vs. lean and obese controls.^a

Arterial stiffness	Lean controls, n = 241	Obese controls, n = 234	TODAY youth, n = 453	p value, TODAY vs. lean	p value, TODAY vs. obese
Age (years)	17.8 (3.5)	18.1 (3.3)	20.8 (2.5)	p < 0.0001	p < 0.0001
Non-Caucasian (%)	58.1	70.5	80.0	p < 0.0001	p = 0.0052
Male (%)	38.6	29.9	36.4	p = ns	p = ns
BMI (kg/m ²)	21.4(2.5)	37.2 (6.9)	36.7 (8.2)	p < 0.0001	p = ns
BMI z-score	0.04 (0.69)	2.17 (0.35)	2.07 (0.67)	p < 0.0001	p = 0.0330
PWV carotid femoral (m/s)	5.5 (0.1)	6.4 (0.1)	6.2 (0.7)	p < 0.0001	p = ns
PWV carotid radial (m/s)	7.3 (0.1)	7.2 (0.1)	7.6 (0.1)	p = 0.0052	p = 0.0005
PWV femoral foot (m/s)	8.1 (0.2)	8.2 (0.2)	8.4 (0.1)	p = ns	p = ns
AIx (%)	-3.3 (0.9)	-0.4 (0.9)	6.8 (0.7)	p < 0.0001	p < 0.0001
BrachD (mm/mm Hg)	7.0 (0.1)	5.6 (0.1)	6.1 (0.1)	p < 0.0001	p = 0.0001

^a p-Value from general linear model comparing mean of the lean or obese controls to the mean of the TODAY sample. Unadjusted means/standard deviations, and p-values are given for the non-arterial stiffness measures. Adjusted means/standard errors, and p-values for age, sex, race-ethnicity are given for the 5 arterial stiffness measures.