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Increased Arterial Stiffness is Found in Adolescents with Obesity or Obesity-Related Type 2 Diabetes Mellitus

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Introduction

Adults with obesity or obesity-related type 2 diabetes (T2DM) are at higher risk for stroke and myocardial infarction.[1] Increased arterial stiffness is one mechanism that may explain this finding as vascular dysfunction is linked to higher rates for cardiovascular (CV) diseases[2] and arterial abnormalities are more prevalent in overweight and diabetic persons.[3] Therefore, we sought to determine if arterial stiffness is increased in youth with obesity or T2DM as compared to lean controls.

Methods

Study Population

A total of 670 youth were examined as part of an ongoing study of the cardiac and vascular effects of obesity and T2DM (62% non-Caucasian, 35% male) conducted at a single site. Youth age 10 to 24 years with a diagnosis of T2DM (N = 195) made by the primary provider, who were islet cell antibody negative (glutamic acid decarboxylase, ICA 512, insulin autoantibodies), had no evidence of other specific type of diabetes, and who were non-insulin requiring in the basal state to prevent diabetic ketoacidosis were eligible. Most were recruited from the Cincinnati Children's Hospital diabetes clinic. Average duration of diabetes was 3.6 ± 2.6 years. The majority of the T2DM subjects were overweight or obese (93% had BMI ≥ 85th percentile, 80% were actually ≥ 95th percentile for age and sex). Each diabetic subject was matched to at least one lean (L = 231, < 85th percentile for BMI) and obese control (O = 234, > 95th percentile)[4] by age, race and gender. All O subjects underwent a 2-hour oral glucose tolerance test to rule out sub-clinical T2DM according to ADA guidelines.[5] Pregnant females were excluded from the study.

Prior to enrollment in the study, written informed consent was obtained from subjects ≥18 years old or the parent or guardian for subjects < 18 years old. Written assent was also obtained for subjects < 18 years old according to the guidelines established by the Institutional Review Board at Cincinnati Children's Hospital.

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The authors have no Conflicts of Interest to report.

Data Collection

After a minimum 10 hour overnight fast, participants had questionnaire, anthropometric, blood pressure (BP), laboratory and arterial stiffness data collected. Trained personnel obtained two measures of height using a calibrated stadiometer (Veeder-Rood, Elizabethtown, NC) and two measures of weight using a Health-O-Meter electronic scale. The average of each was used in analyses. Body mass index was calculated as kilograms per meter squared. Blood pressure was measured according to the standards of the Fourth Report on BP in Children.[6]

Dual-energy X-ray Absorptiometry (DXA) was performed with a Hologic 4500A (Hologic, Bedford, Mass.). Standards correlating X-ray beam attenuation to amount of lean and fat mass have been developed and validated against the hydrodensitometry method, which has previously been established as the most valid measurement of lean body mass and fat mass.[7] Percent body fat was calculated as total body fat mass divided by total body mass times 100. To determine fat distribution, android (abdominal) to gynoid (hip) ratio was calculated as sum of fat content in the subscapular (neck to waist) plus waist area (to iliac crest), divided by the hip and thigh regions.[7] In previous studies, the coefficients of variation for regional measurements are less than 5%.

Physical activity was assessed using an Actical accelerometer (Phillips Respironics) worn on the waist during waking hours over a 7 day period. This device is an omni-directional detector that provides counts of movement in all directions.[8] Counts of activity per minute worn were calculated and averaged over the 7 days.

Fasting plasma glucose was measured using a Hitachi model 704 glucose analyzer (Roche Hitachi, Indianapolis, IN) with intra-assay and inter-assay coefficients of variation of 1.2% and 1.6% respectively.[9] Plasma insulin was measured by radio-immunoassay using an anti-insulin serum raised in guinea pegs, 125I 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- and interassay coefficients of variation of 5% and 8%.[10] Assays of fasting plasma lipid profiles were carried out in a laboratory which is NHLBI-CDC standardized with the LDL cholesterol concentration calculated using the Friedewald equation. C-reactive protein (CRP) was measured using a high sensitivity enzyme-linked immunoabsorbent assay. HbA1c was measured in red blood cells using HPLC methods. Duration of disease was measured from the date of diagnosis to the date of study.

Arterial Stiffness Measurements

Vascular function testing was conducted after 5 minutes of rest in the supine position. Three measures of brachial artery distensibility (BrachD), systolic (SBP), diastolic (DBP), mean arterial blood pressures (MAP), pulse pressure (PP) and heart rate (HR) were obtained with a DynaPulse Pathway instrument (Pulse Metric, Inc., San Diego, CA) as previously described.[11] This device derives brachial artery pressure curves from distensibility arterial pressure signals obtained from a standard cuff sphygmomanometer assuming a straight tube brachial artery and T-tube aortic system.[11] Repeat measures in our laboratory show excellent reproducibility with coefficients of variability less than 9% (unpublished data).

Pulse Wave Velocity (PWV) was measured with a SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) according to the manufacturer's protocol. The average of three recordings of PWV for each of the arterial sites: PWV-arm (carotid-radial); PWV-trunk (carotid-femoral) and PWV-leg (femoral-foot) was used in the analyses. Repeat measures in our laboratory show excellent reproducibility with coefficients of variability less than 7% (unpublished data).

Augmentation Index (AIx), which is influenced by arterial stiffness and provides additional information concerning wave reflections[12] was also collected. The SphygmoCor tonometer was placed over the right radial artery and 3 measures of AIx were collected. The pressure waves were calibrated using MAP and DBP obtained in the same arm. The device then analyzed the pulse wave using a validated generalized transfer function.[13] Since AIx is affected by HR, values were adjusted to a standard HR of 75 beats per minute. Reproducibility studies in our laboratory demonstrated intraclass correlation coefficients between 0.7 and 0.9 for all variables (unpublished data).

Statistical Analysis

All analyses were performed with Statistical Analyses Software (SAS®, version 9.1.3)[14] Average values for demographic, anthropometric, and laboratory data were obtained by group. Variance stabilizing measures to transform non-normal values were performed as needed. Analysis of variance was performed to look for differences by group, with Bonferroni correction for multiple comparisons as appropriate. Chi square analyses were performed to determine group differences for categorical variables. Bivariate correlations were calculated between arterial stiffness outcome variables and all covariates overall and by group. General linear models were constructed using important covariates from correlation analyses to elucidate independent determinates of arterial stiffness. The full model contained demographic (group, age, race/ethnicity, sex), anthropometric (waist/height ratio, percent body fat from DXA, android/gynoid ratio from DXA), hemodynamic (MAP, HR except for the model for Aix, which is already adjusted for HR), laboratory (LDL-C, HDL-C, triglycerides, fasting glucose, fasting insulin, C-reactive protein), and physical activity (average activity counts per minute) measures. Total cholesterol was highly collinear with LDL-C, and HbA1c with fasting glucose so these covariates were omitted to ensure stability of the models. Height was added to the model for AIx since height directly influences distance of wave reflection sites from the heart. Height is used in the calculations for BrachD and PWV so it was omitted from models for those outcomes. Significance of each covariate in the initial model was assessed and non-significant terms were removed by backward elimination until all remaining covariates or their interaction (effect modifier) terms were significant. Robustness of the models was assessed with use of the maximum R^2 technique and calculation of Mallow's Cp. Each model had the most ideal Cp with no further significant increase in adjusted R^2 with addition of other variables. Other regression diagnostics were also performed including examination of eigen values, variance inflation values and condition indices. All fell within published guidelines indicating no colinearity among the covariates in the models[15]

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

There was a progressive deterioration in CV risk status from L to O to T2DM (table 1) for adiposity (percent body fat, android-gynoid ratio), lipids (total cholesterol, triglycerides, HDL-C), metabolic control (fasting insulin), BP (systolic BP, central systolic & diastolic BPs, heart rate), and physical activity (counts per minute; all $p \leq 0.05$). Groups did not differ by age or sex distribution but there was a greater proportion of non-Caucasians in the O as compared to the L or T2DM groups (Chi square $p \leq 0.05$).

Arterial stiffness significantly increased across groups (table 2 and figure) with rising AIx and PWV-trunk and declining BrachD (only trend for difference between O and T2DM)s. Diabetic subjects had a higher (stiffer) PWV-leg than L and higher PWV-arm than both L and O (all $p \leq 0.05$). PWV in the arm and leg were higher than in the trunk due to the smaller

caliber of the limb vessels. AIx adjusted for CV risk factors remained higher in T2DM than L and O. Adjusted BrachD was lower in O and T2DM as compared to L, and the graded increase in PWV-trunk from L to O to T2DM remained significant. There was no difference among groups in PWV-leg after risk factor adjustment but L continued to have a lower PWV-arm as compared to both O and T2DM youth (all $P \leq 0.05$).

In multivariate models (table 3), group (status as a L, O or T2DM participant) was an independent determinant of arterial stiffness even after adjusting for CV risk factors for all measures except PWV-leg. For PWV-trunk there was an interaction between group and waist/height ratio. A regression of waist/height ratio on PWV-leg stratified by group demonstrated no relationship for L (slope not significant) but a significant effect for O and T2DM subjects (both model $p \leq 0.0001$ with respective slopes of 0.94 and 0.60 and r^2 of 0.28 and 0.13). A similar interaction between group and age was found for PWV-arm. Again, there was no influence of age on PWV-arm for L but there was a positive linear relationship for O and T2DM (both model $p \leq 0.0001$ with respective slopes of 0.015 and 0.018 and r^2 of 0.15 and 0.16). These data suggest that adiposity and age have a greater effect on arterial stiffness in O and T2DM subjects.

Traditional risk factors were also important in explaining the variance in arterial stiffness. As seen previously, female gender was associated with lower BrachD.[16] Higher age was associated with faster PWV and non-Caucasian race/ethnicity was associated with poorer AIx and PWV. Greater adiposity was associated with stiffer BrachD and higher PWV. Higher BP was a determinant for increased stiffness in all measures except PWV-leg and adverse lipids for all but PWV. Lower physical activity was related only to higher AIx (all model and parameter $p \leq 0.05$).

Models were repeated to account for possible effects of any drug affecting vascular function, such as ADHD medications, central alpha agonists, decongestants, cholesterol lowering agents (statins), exogenous insulin, insulin sensitizing agents (usually metformin) and antihypertensive agents (mostly angiotensin converting enzyme inhibitors). Few subjects used vasoactive (5%) or cholesterol lowering agents (0.9%) and neither were significant in any of the multivariate models. Although the prevalence of use of insulin (43%) or insulin sensitizing agents (16.4%) among T2DM subjects was notable, neither agent was a significant independent determinant of any measure of vascular function. Five percent of the cohort were on anti-hypertensive drugs (T2DM = 4.7%, O = 0.5%, L = 0.2%). Use of antihypertensive medication was positively associated with PWV-trunk. If history of ever having been diagnosed with hypertension (whether on medication or not) was also added to the model, only history of hypertension was significantly associated with higher PWV. This suggests that use of antihypertensive medication is a surrogate for history of hypertension which is known to associate with higher arterial stiffness.[17]

Discussion

Our data demonstrate that arterial stiffness is increased in subjects with obesity-related T2DM compared to lean controls. We also demonstrated higher stiffness in obese diabetic as compared to non-diabetic obese subjects. These findings hold true for carotid-femoral PWV a measure of central arterial stiffness, BrachD which measures a peripheral muscular artery and AIx which is a mixed measure influenced by central stiffness and peripheral wave reflections. As expected, CV risk factor profile deteriorated from L to O to diabetic subjects, with central adiposity (android-gynoid ratio), blood pressure and metabolic control (TG, HDL-C and fasting insulin) displaying the greatest difference between T2DM subjects and the other groups. However, for most measures, status as an non-diabetic obese or obese diabetic subject remained an independent determinant of arterial stiffness even after

correcting for risk factors. These data demonstrate there is pervasive vascular dysfunction associated with obesity and diabetes above and beyond what is expected from the contribution of traditional risk factors.

Adult studies consistently demonstrate increased PWV along the trunk in subjects with T2DM as compared to controls[18,19] regardless of level of systolic blood pressure.[2] This increase in central stiffness affects hard outcomes as demonstrated by the hazard ratio shown for all-cause and CV mortality of 1.08 (95% CI 1.03 to 1.14) for each 1 m/sec increase in PWV.[2] Peripheral stiffness is also higher in diabetic patients, as demonstrated by lower brachial compliance, than controls even when measured at isobaric conditions controlling for baseline distending pressure.[20] The mixed measure, AIx, is higher (stiffer) in diabetic versus control subjects[21] with diabetes emerging as an independent determinant of AIx in multivariate analyses in adult men.[22] Although Scuteri demonstrated higher PWV in insulin-resistant first-degree relatives of diabetic subjects (average age of 33 ± 7 years)[23] and Haller found higher AIx in adolescents with type 1 diabetes mellitus,[24] our data are the first to demonstrate increased arterial stiffness in young subjects with T2DM. Furthermore, our findings of increased PWV in the arm and leg of diabetic subjects as compared to non-diabetic controls suggests that early peripheral vascular disease may be identified in youth with T2DM.

Adiposity correlates strongly with PWV in adult diabetics.[25] In non-diabetic adults, both BMI, a measure of overall adiposity, and waist-hip ratio, a measure of central adiposity, are strong independent determinants of PWV, explaining similar amounts of variance in arterial stiffness.[26] Obesity has also been associated with brachial artery stiffness. Zebekakis et al[27] studied over 1300 subjects aged 10 to 86 years (average 44 years) with an ultrasound-based wall-tracker technique. Consistently, a lower brachial distensibility was seen with increasing BMI across ages, even after adjusting for BP, lipids and blood glucose.[27] The relationship between adiposity and AIx appears to be more complex. In one study of indigenous Australians, weight, waist circumference, BMI and fat mass were all determinants of AIx in multivariate analyses.[28] However, the investigators did not find a difference in AIx by diabetic status which may relate to genetic differences in this population, limiting generalizability to our Caucasian and African-American cohort. In contrast, Greenfield et al[29] found that only central fat, not total body fat measured by DXA was an independent determinant for AIx in females. In our data, height was a significant determinant, not central adiposity. Shorter individuals have wave reflection sites closer to the heart resulting in earlier arrival of reflected waves even at the same mean blood pressure[30] thus it is important to include height in modeling. Differences among our data and the reports by Maple-Brown[28] and Greenfield[29] may be related to the inclusion of height in our models.

Previous work demonstrated correlations between obesity and arterial stiffness in youth. Gungor et al[3] studied adolescents and found a higher BMI to correlate (correlation coefficient = 0.5) with PWV after controlling for SBP. A recent paper studying younger children (average age 10.1 ± 0.3 years) compared anthropometric measures of adiposity to those obtained with DXA to determine the strength of their relationship to arterial stiffness. The investigators found that all measures (BMI, waist circumference, percent body fat by DXA) were independently associated with PWV with similar strength (total R^2) after adjustment for other CV risk factors.[31] However, in both of these studies, android-gynoid ratio, a measure of central adiposity, which we found to be more consistently and strongly correlated with PWV, was not evaluated.

Other measures of arterial stiffness, such as resting brachial artery distensibility are also correlated with adiposity. Whincup used a wall-tracker technique and found BMI,

percentage body fat (estimated from bio-electrical impedance), sum of skinfolds, waist circumference and waist-hip ratio all to be correlated with brachial artery function.[32] As in our data, the strength of the relationship was greater between BrachD and adiposity than for other CV risk factors (BP, lipids). Singhal also measured fat mass with bioelectrical impedance and found this measure of adiposity, but not BMI, skinfolds or waist-hip ratio, to be independently related to brachial distensibility after adjustment for CV risk factors.[33] This relationship was only found in boys[33] but these findings in a predominantly pre-term cohort may not be directly applicable to our study group. Our data, which include a variety of methods for measuring obesity extend the observations regarding the importance of central adiposity in determining arterial stiffness.

Limitations

The cross-sectional nature of this study does not allow determination of the time course for the development of the vascular changes seen. Therefore, we can not determine which arterial sites are influenced first by CV risk factors and whether obesity or obesity-related diabetes has a more profound effect. Our O group also had a greater proportion of non-Caucasian subjects which may have influenced our results. Furthermore, the predominance of non-Caucasian subjects in all groups may limit application of our findings to other races/ethnicities. Finally, use of arterial stiffness measurements for risk-stratification in children is limited by lack of normal values across ages, sexes and race/ethnicities. Additional large studies in healthy youth are needed before inferences linking arterial stiffness measured in youth and future CV outcomes can be made.

Conclusions

Adolescents and young adults with obesity-related T2DM and those with obesity without diabetes have increased arterial stiffness. These abnormalities persist after controlling for factors such as BP and lipids, implying an augmented risk for development of target organ damage which is predisposing to future CV events. Heightened awareness of the adverse consequences of obesity and obesity-related T2DM should prompt health care providers to institute early and aggressive life-style interventions in adolescents with or at risk for overweight.

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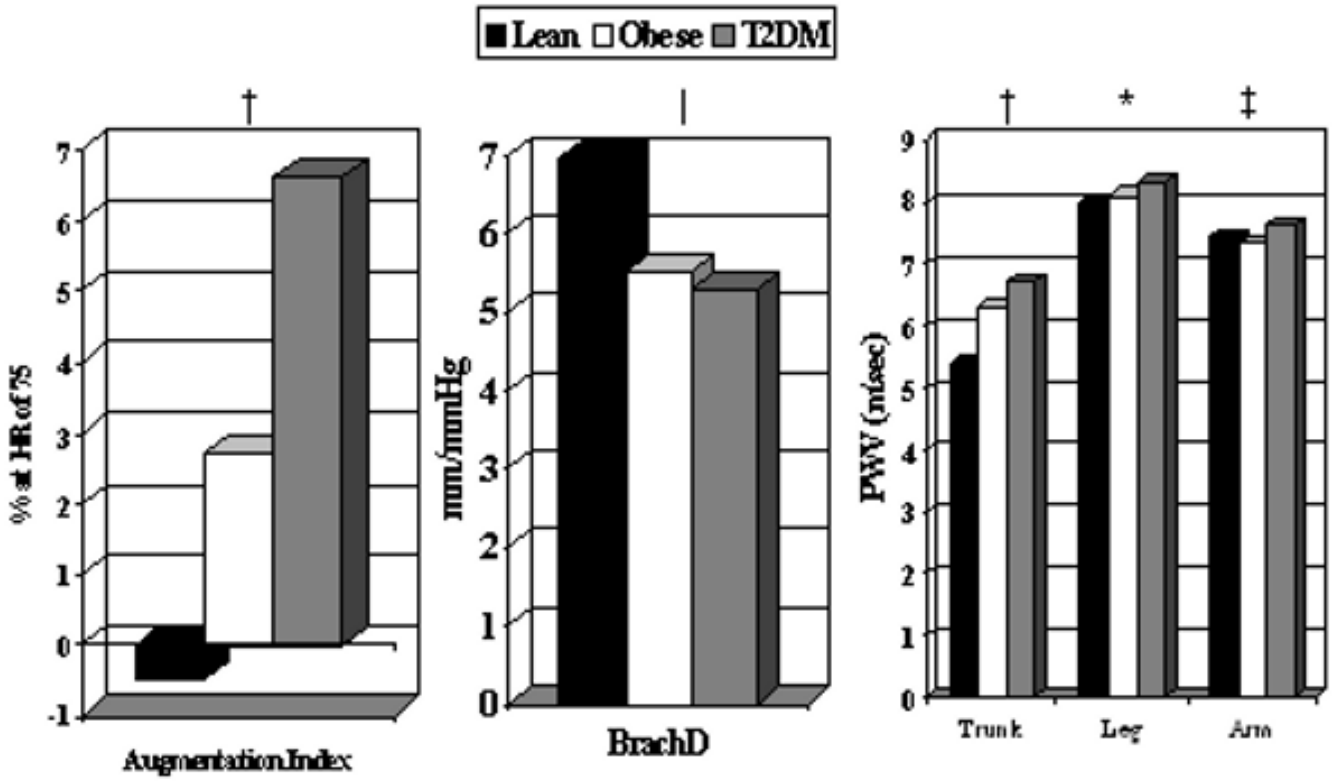

Figure.
Arterial Stiffness by Group. P<0.005 for †Lean<Obese<T2DM; |Lean > Obese > T2DM; *Lean < T2DM; ‡Lean and Obese < T2DM.

Table 1

Demographic, anthropometric and laboratory values by group (means ± SD)

Variable	Lean N = 241		Obese N = 234		T2DM N = 195		P values		
	Mean	SD	Mean	SD	Mean	SD	Lean vs Obese	Lean vs T2DM	Obese vs T2DM
Age (years)	17.8	3.5	18.1	3.3	18.3	3.2	0.3893	0.1615	0.5642
Sex (% Male)	38.6	X	29.9	X	35.4	X	0.0472	0.4843	0.2358
Race (% Non-Caucasian)	58.1	X	70.5	X	64.6	X	0.0051*	0.8878	0.0053*
Height (cm)	165.3	11.1	166.6	10.0	168.8	10.2	0.1967	0.0007*	0.0322†
Weight (kg)	59.2	12.0	103.4	21.0	106.7	29.0	0.0001*	0.0001*	0.1159
Body Mass Index (kg/m^2)	21.4	2.5	37.2	6.9	37.3	9.2	0.0001*	0.0001*	0.9291
Waist Circumference (mm)	76.1	7.5	113.7	15.9	117.0	19.9	0.0001*	0.0001*	0.0231†
Waist/height ratio	0.46	0.04	0.68	0.10	0.69	0.12	0.0001*	0.0001*	0.2613
Body Fat (% from DXA)	21.8	7.3	39.0	7.2	36.7	8.0	0.0001*	0.0001*	0.0034*
Android-Gynoid Ratio (ratio of DXA counts)	0.52	0.16	1.03	0.27	1.26	0.40	0.0001*	0.0001*	0.0001*
Total Cholesterol (mg/dl)	162.0	28.2	171.1	32.5	181.0	40.3	0.0051*	0.0001*	0.0096*
LDL-Cholesterol (mg/dl)	90.3	23.7	104.6	28.3	107.7	33.2	0.0001*	0.0001*	0.6035
HDL-Cholesterol (mg/dl)	57.0	13.3	47.3	10.0	44.6	11.7	0.0001*	0.0001*	0.0014*
Triglycerides (mg/dl)	72.7	34.4	97.0	59.3	139.1	92.2	0.0001*	0.0001*	0.0001*
Fasting Glucose (mg/dl)	89.2	6.3	92.1	7.5	154.2	81.2	0.1920	0.0001*	0.0001*
Fasting Insulin (microUnits/ml)	11.2	4.5	21.7	15.3	26.7	20.2	0.0001*	0.0001*	0.0145*
HbA1c (%)	5.3	0.5	5.5	0.4	8.2	3.0	0.2014	0.0001*	0.0001*
C-Reactive Protein (mg/L)	0.9	1.5	5.4	6.1	6.3	7.0	0.0001*	0.0001*	0.2740
Interleukin-6 (pg/ml)	1.2	1.2	2.8	2.1	2.7	1.9	0.0001*	0.0001*	0.4519
TNF-a (pg/ml)	2.1	1.7	2.6	2.3	2.0	1.7	0.0009*	0.6841	0.0077*

P values calculated on normalized variables.

*P values significant after correction for multiple comparisons except as indicated by † where only a trend was found after correction.

Table 2

Hemodynamics by group (means ± SD)

Variable	Lean N = 241		Obese N = 234		T2DM N = 195		P values*		
	Mean	SD	Mean	SD	Mean	SD	Lean vs Obese	Lean vs T2DM	Obese vs T2DM
SBP (mmHg)	108.1	10.3	116.7	11.0	122.0	12.3	0.0001*	0.0001*	0.0001*
DBP (mmHg)	60.1	12.0	65.8	12.4	67.3	13.1	0.0001*	0.0001*	0.2139
Mean Arterial Pressure (mmHg)	77.5	6.9	84.2	7.8	88.6	10.0	0.0001*	0.0001*	0.0001*
Pulse Pressure (mmHg)	47.7	11.4	50.8	11.8	54.2	14.7	0.0085*	0.0001*	0.0062*
Central SBP (mmHg)	96.8	8.7	105.5	9.6	109.1	10.8	0.0001*	0.0001*	0.0003*
Central DBP (mmHg)	67.0	6.6	70.7	7.8	74.4	9.5	0.0001*	0.0001*	0.0001*
Heart Rate (beats/min)	62.8	9.9	65.5	9.6	70.7	11.8	0.0041*	0.0001*	0.0001*
Augmentation Index @ HR 75 (%)	-0.5	10.8	2.7	11.6	6.6	11.3	0.0022*	0.0001*	0.0006*
Brachial Artery Distensibility (mm/mmHg)	6.97	1.19	5.51	1.04	5.28	1.00	0.0001*	0.0001*	0.0224†
PWV-trunk (m/sec)	5.4	0.7	6.3	1.1	6.7	1.2	0.0001*	0.0001*	0.0007*
PWV-leg (m/sec)	8.0	1.2	8.1	1.4	8.3	1.6	0.8434	0.0625	0.0984
PWV-arm (m/sec)	7.4	1.1	7.3	1.0	7.6	1.1	0.3886	0.0136*	0.0010*

P values calculated on normalized variables.

*P values significant after correction for multiple comparisons except as indicated by † where only a trend was found after correction.

Table 3

Independent determinants of arterial stiffness*

Variable		AIx-75 (higher = stiffer)	BrachD (lower = stiffer)	PWV-trunk (higher = stiffer)	PWV-leg (higher = stiffer)	PWV-arm (higher = stiffer)
Intercept		49.66 (<0.0001)	2.42 (<0.0001)	0.35	1.61	1.06
Group	**Lean**	0 (reference group)	0 (reference group)	0 (reference group)		0 (reference group)
	Obese	-0.040 (NS)	-0.09 (0.0001)	-0.33 (0.003)		-0.2 (0.004)
	T2DM	3.08 (0.02)	-0.11 (<0.0001)	-0.35*(0.001)		-0.2 (0.005)
Group*Waist/ Height Interaction	**Lean**			0 (reference group)		
	Obese			0.74 (0.0006)		
	T2DM			0.73 (0.0007)		
Group*Age Interaction	**Lean**					0 (reference group)
	Obese					0.008 (0.03)
	T2DM					0.011 (0.006)
Age				0.018 (0.0001)	0.011 (0.0001)	0.0049 (NS)
Female			0.11 (<0.0001)			
Non-Caucasian		2.46 (0.01)		0.077 (0.0001)	0.031 (0.003)	0.053 (0.0001)
Height		-0.33 (<0.0001)				
Waist/Height Ratio			-0.52 (<0.0001)	-0.13 (NS)		
Android/Gynoid Ratio					0.053 (0.01)	
MAP		0.21 (<0.0001)	-0.0019 (0.008)	0.0036 (0.0001)	0.0024 (0.001)	0.0029 (0.0001)
Heart Rate			-0.15 (0.0009)	0.16 (0.0001)		0.13 (0.0001)
Triglycerides		3.05 (0.003)				
HDL-C			0.084 (0.008)			
Average Activity Counts/min		-4.52 (0.0001)				
C-Reactive Protein					-0.014 (0.02)	
Use of anti-hypertensive medication				0.07 (0.02)		
R^2 (model p values)		***0.21 (0.0001)***	***0.44 (0.0001)***	***0.6 (0.0001)***	***0.1 (0.0001)***	***0.21 (0.0001)***

*Values are beta coefficients for significant covariates left in the model after stepwise regression (and unadjusted p values).