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Lean Body Mass May Explain Apparent Racial Differences in Carotid Intima-Media Thickness in Obese Children

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Abstract

Background—Racial differences in carotid intima-media thickness (cIMT) have been suggested to be associated with the disproportionally high prevalence of cardiovascular disease in black adults. The objective of this study was to evaluate the effects of cardiovascular risk factors on the racial differences seen in cIMT in obese children.

Methods—Obese subjects ages 4 to 21 were recruited prospectively. Height, weight, blood pressure, fasting insulin, glucose, lipid panel, high-sensitivity c-reactive protein, and body composition by dual-energy x-ray absorptiometry were obtained. B-Mode carotid imaging was analyzed by a single blinded physician.

Results—A total of 120 subjects (46 white and 74 black) were enrolled. Blacks exhibited greater cIMT (0.45 ± 0.03cm vs. 0.43 ± 0.02cm, $p < 0.01$) and higher lean body mass (LBM) index (19.3 ± 3.4kg/m^2 vs. 17.3 ± 3.2kg/m^2, $p = 0.02$) than whites. Simple linear regression revealed modest associations between mean cIMT and race ($R = 0.52$, $p < 0.01$), systolic blood pressure ($R = 0.47$, $p < 0.01$), and LBM ($R = 0.51$, $p < 0.01$). Upon multiple variable regression, LBM remained the only measure to maintain a statistically significant relationship with mean cIMT ($p < 0.01$).

Conclusions—Black subjects demonstrated greater cIMTs than white subjects. The relationship between race and cIMT disappeared when lean body mass was accounted for. Future studies

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assessing the association of cardiovascular disease risk factors to cIMT in obese children should include lean body mass in the analysis.

Introduction

In the United States, adults of black African descent have a higher prevalence of obesity and an increased risk of cardiovascular disease than whites of European origin.[1-3] Carotid intima-media thickness (cIMT) is a strong predictor of cardiovascular disease; it has been shown to be higher in black vs. white healthy adults.[4-10] Traditional risk factors for cardiovascular disease, such as hypertension, contribute to higher cIMT and increased risk of cardiovascular disease in black adults.[11,12]

Similar to adults, cardiovascular disease risk factors in childhood and adolescence also show racial differences.[13,14] In fact, racial differences in cIMT have been reported in healthy non-obese children.[15] The etiology behind the racial differences in cIMT in children is not clear, and, no studies have examined whether such differences persist in obese children – a group at high risk for future cardiovascular disease. If racial differences are found in cIMT in obese patients, the cardiovascular risk factors associated with these differences may provide targets for intervention in future studies. The primary objectives of this study were to 1) determine if racial differences exist in cIMT between white and black obese children and, 2) if such differences are present, to identify measures of body composition and markers of cardiovascular risk that contribute to these differences. We hypothesized that black obese children would have higher cIMT than whites and that blood pressure, race, and lean body mass would be associated with cIMT.

Methods

This was a prospective, cross-sectional study. All tests were conducted during a single assessment using a standardized protocol. The protocol was approved by the institutional review board. Informed consent was obtained from the parent or legal guardian of minors or from the participants of age 18 or older.

Subject Population

Patients were recruited from the Medical University of South Carolina's childhood obesity management clinic. Inclusion criteria included: 1) BMI > 95th percentile, 2) ages 4 to 21 years old, and 3) white or black race. Patients of Hispanic ethnicity were not included in the analysis. Subjects who were pregnant, taking insulin, or were on oral steroids were excluded. Patients were enrolled consecutively so long as they were not of Hispanic ethnicity and did not have one of the three exclusion factors listed. Study visits were rescheduled if the patient had experienced a febrile illness within 72 hours of the planned study date.

Procedures

Patients' anthropomorphic assessments were performed at the Clinical and Translational Research Center. Blood pressure was measured (DINAMAP automatic cuff, GE Healthcare) with an appropriate sized cuff after seated for 5 minutes. The average of two blood pressure

measurements was used in the analysis – taken once at the beginning of the visit and once at the end. Patients' fasting status was confirmed prior to phlebotomy. Labs obtained included serum insulin, glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and high sensitivity c-reactive protein (hsCRP). Body composition (total body fat, % body fat, and lean body mass) was quantified using dual-energy x-ray absorptiometry (DXA).

Carotid arteries were studied with a duplex scanner using a 7.5 MHz linear array transducer (Philips IE33 4-8 MHz). All B-Mode carotid imaging was performed by a single sonographer. Participants were positioned supine with their neck rotated at 45° to expose an area from the clavicle to the angle of the jaw. Recommendations from the American Society of Echocardiography's consensus statement on cIMT were followed, that is, measurements from both carotid arteries were used and that cIMT was only measured from the far wall of the artery.[16] Measurements from the near wall were not used, as recommendations from the METEOR study group were not published prior to the start of the study.[17] Right and left common carotid intima-media thicknesses were imaged longitudinally 1 cm proximal to the carotid bifurcation with the transducer placed both in the lateral and anterior-posterior windows. Three five-second acquisitions were recorded and three magnified end-diastolic frames of the far wall were selected and analyzed at each position (Figure 2). All studies were read offline by a single physician blinded to the clinical and laboratory data using QLAB version 8.1 (Phillips Medical Systems, Bothell, WA) with automatic detection of cIMT by the software (Figure 3). For each subject, the mean cIMT was calculated as the average of the twelve measurements from the left and right common carotid arteries (3 frames for each position x 2 positions x 2 carotid arteries = 12 measurements). A subgroup of thirty studies (the initial 15 and the final 15) was reanalyzed at a four week time interval to assess for intraobserver and interobserver variability. All twelve measurements were repeated and averaged. Observers were free to choose the image and frame to re-measure.

Calculations

Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Lean body mass index was calculated as lean body mass (kg)/height^2 (m^2) and fat mass index as fat mass (kg)/height^2 (m^2). Body surface area (BSA) was calculated by method of Haycock[18]: BSA = $0.024265 \times \text{height}^{0.3964} \times \text{weight}^{0.5378}$. Quantitative insulin sensitivity check index (QUICKI) was calculated as 1/[log(fasting insulin μU/mL) + log(fasting glucose mg/dL)].[19] Insulin level was divided dichotomously as normal (< 20 μIU/mL) or abnormal (≥ 20 μIU/mL).

Statistical Analysis

To assess for differences between white and black patients two-group t-tests were used for parametric data while Mann-Whitney U tests were used for non-parametric data. Simple linear regression was used to assess the individual effects of cardiovascular risk factors on cIMT. Multiple variable regression was used to model the relationship between two or more independent variables and cIMT. Intraobserver and interobserver variability were assessed using intraclass correlation coefficient using a random effects model measuring absolute agreement. Based on clinical relevance and previous studies investigating the correlation of

LBM to cIMT, an effect size of r = 0.25 was chosen to base sample size calculation. [20] This resulted in a sample size of 120 subjects giving a power of 80% with alpha = 0.05 to detect the chosen effect size. All statistics were performed using IBM® SPSS® Statistics software v. 20.

Results

From September 2009 to December 2011, 142 patients were eligible for inclusion. Nineteen declined participation and three met exclusion criteria. Therefore, 120 obese children [46 white (72% female) and 74 black (64% female)] were enrolled. Figure 1 demonstrates the age distribution of subjects. Differences by race in clinically derived anthropometrics and laboratory data can be found in Table 1. Five patients were on anti-hypertensive medicines. Eight other patients had blood pressure >95th percentile for age, sex and height at the time of the visit without the diagnosis of hypertension. No patients were diagnosed with diabetes mellitus. Two patients were smokers. Black patients had higher insulin levels and evidence of insulin resistance by QUICKI than white patients, while whites had increased triglycerides when compared to blacks. Body composition and cIMT results are summarized in Table 2. Intraobserver and interobserver variability for cIMT measures had an intraclass correlation coefficient of r = 0.92 and r = 0.86, respectively. While body mass index was higher in blacks than whites by ~13%, fat mass index and % body fat were not significantly different between groups. This was consistent with the finding that lean body mass was significantly higher in blacks by almost 16%. Also, black patients demonstrated higher cIMT when compared with white patients. There were no statistically significant differences in anthropomorphic, laboratory, or imaging data between males and females.

Simple linear regression revealed modest associations between mean cIMT and race ($r = 0.52$, $p < 0.01$), systolic blood pressure ($r = 0.46$, $p < 0.01$), and lean body mass ($r = 0.51$, $p < 0.01$) (Figure 4). Age, height, diastolic blood pressure, LDL level, total cholesterol to HDL ratio, hsCRP, QUICKI, total body fat, and % body fat did not demonstrate any association with mean cIMT. Variables which showed a statistically significant relationship with cIMT after simple linear regression and variables that have been associated with cIMT in previous studies were included in a multiple variable regression analysis.[21,22] These variables included race, age, hsCRP, QUICKI, LDL, systolic blood pressure, and lean body mass. Then, a second multiple variable regression analysis was performed with only those variables which showed a statistically significant relationship with cIMT (race, systolic blood pressure, and lean body mass). Lean body mass remained the only measure to have a statistically significant relationship with mean cIMT in both analyses ($p < 0.01$ and < 0.01, respectively). Another reduced model with only race and lean body mass was then created. Again, only lean body mass had a statistically significant relationship with cIMT ($p < 0.01$). No variables showed collinearity with race (Variance Inflation Factors of all variables and interaction terms < 5). Comprehensive results of the simple and multiple variable linear regression are presented in Table 3.

Discussion

There are two primary findings from this study. First, black obese children exhibit higher cIMT compared to whites. Second, higher cIMT in black obese children is associated with the differences in lean body mass between groups.

Black adults have higher cIMT than white adults.[7-10] Healthy non-obese children exhibit similar racial differences.[15] The current study shows that similar racial differences in cIMT exist in obese children. Obese black participants had a higher cIMT when compared to whites. Studies have shown that blood pressure, race, BMI, and body fat are associated with increased cIMT in children.[21,22] Some have hypothesized that the racial differences in these cardiovascular risk factors contribute to the differences seen in cIMT, and hence, contribute to the racial differences in cardiovascular outcomes.[15] However, in the current study, groups did not differ in age, height, blood pressure, HDL, LDL, or % body fat. While the groups did differ in insulin level and insulin resistance, these risk factors did not appear to be associated with cIMT.

We found an association between lean body mass and cIMT in obese children. This is similar to what has been found in healthy adults and in obese women with polycystic ovarian syndrome.[20,23] The proposed explanation behind this association is based on the linear relationship between the size of cardiovascular structures and cardiac output. As the amount of metabolically active tissue (lean body mass) increases, oxygen demand increases. This leads to an increase in cardiac output and, thus, an increase in cIMT. Therefore, increases in cIMT may be in part reflective of increased somatic growth. For example, one group found a linear relationship between common carotid diameter and cIMT with normal shear-stress relationships indicating, at specific cIMT ranges, an increased cIMT reflects an adaptive response to increased flow instead of atherosclerosis.[24] Our finding that race and blood pressure do not independently associate with cIMT may be because both are related to lean body mass. For example, black patients are known to have a higher lean body mass than whites at similar levels of body mass index.[21,25] Also, lean body mass has been proposed as a more significant predictor of blood pressure than traditional cardiovascular risk factors.[26] Thus, while recognizing that cross-sectional associations do not amount to causality, it is conceivable that the differences in cIMT between obese white and black children may be in part due to the differences seen in lean body mass between the groups and may not necessarily represent increased atherosclerotic burden. In fact, in adults, black patients have been shown to have higher cIMT despite showing lower coronary calcium levels than whites.[27]

In similar fashion, multiple studies have associated obesity (as defined by elevated BMI percentiles) with higher cIMT values in children.[28-31] These studies are limited by their inability analyze the body composition of their subjects. In the present study, fat mass as measured by DXA had no relationship to cIMT. This may be secondary to fat mass' metabolically inert nature, requiring little changes in cardiac output, and thus, having an insignificant relationship to the size of cardiovascular structures such as cIMT. It is well known that obese children have a higher fat mass than their normal weight counterparts, but they also exhibit a higher lean body mass.[25] Hence, lean body mass may have contributed

more to the increased cIMT than fat mass in these previous studies. It may be useful for future studies to compare cIMT in children with similar LBM but different levels of adiposity to further quantify adiposity's influence on atherosclerotic burden.

Carotid IMT is a surrogate for cardiovascular disease risk.[4] Groups have investigated racial differences in cIMT in adults and healthy children in an attempt to identify modifiable risk factors that may predispose black patients to a higher incidence of cardiovascular disease.[4,15] The utility of performing this analysis in the pediatric population is unknown because prospective studies establishing pediatric cIMT as a useful predictor of cardiovascular outcomes have not been performed. It is probably fair to observe that the likelihood of significant "atherosclerotic burden" in healthy children is small. Therefore, we studied obese pediatric patients – those with a theoretically higher risk for atherosclerosis. Even so, we found no relationship between cIMT and cardiovascular risk factors, such as race, after lean body mass was accounted for. We feel this study neither supports nor detracts from the use of cIMT in the obese pediatric population when assessing for racial differences in cardiovascular disease risk. However, despite scatter in the relationship between cIMT and lean body mass, we feel this study supports the inclusion of measures of body composition in future studies assessing the association of cardiovascular disease risk factors, including race, to cIMT in obese children.

Normal values for cIMT in non-obese children may not be appropriate standards for which to compare cIMT values in obese patients due to their increased lean body mass. However, the development of cIMT reference values based on an obese population is unappealing due to the possibility of underestimating cardiovascular risk. Alternatively, it may be prudent to index cIMT to lean body mass to make comparisons between obese vs. non-obese patients viable, as has been suggested for other cardiovascular structures such as left ventricular mass.[32] Further investigation of validated sex-specific formulae to calculate lean body mass may aid in accounting for lean body mass in future studies.[33]

Black subjects did demonstrate small but statistically significant elevations in insulin levels and insulin resistance than white subjects. This is consistent with previous studies in adults and children.[15,34-36] These findings were not associated with increased cIMT; however, they may be contributors to the racial differences that are encountered in cardiovascular disease outcomes in adults.[37,38] Further investigations aimed at identifying the etiologic factors contributing to the racial differences in these pediatric cardiovascular risk factors are warranted.

There are limitations to this study. The lack of a control group and cross-sectional nature of this study does not allow extrapolation of this data to other populations, such as non-obese children. Further, it is difficult to compare the cIMT values in this obese population to other studies attempting to establish reference cIMT values in normal children due to the wide variability in methods and results. For example, the mean cIMT values in this study population are, as expected, greater than the reference values produced by Jourdan et al but are smaller than those reported by Sass et al.[39,40] The patient sample included subjects over a wide age range who have varying cardiovascular risk factor exposure time. The ability to account for the effect of risk factor exposure time on cIMT is inhibited by the cross-

sectional nature of this study. It is conceivable that the effect of lean body mass becomes less significant and the effects of cardiovascular risk factors become more significant over time as the atherosclerotic process advances. The relationship of cardiovascular risk factors to cIMT may be more evident with a larger, more balanced sample size.

Conclusion

Black subjects demonstrated greater cIMTs than white subjects. The relationship between race and cIMT disappeared when lean body mass was accounted for. Since lean body mass, and not intrinsic racial factors, appears to explain the difference in cIMT found in this study, assessment of LBM should be included in future studies of the association of cardiovascular risk factors with cIMT in obese children.

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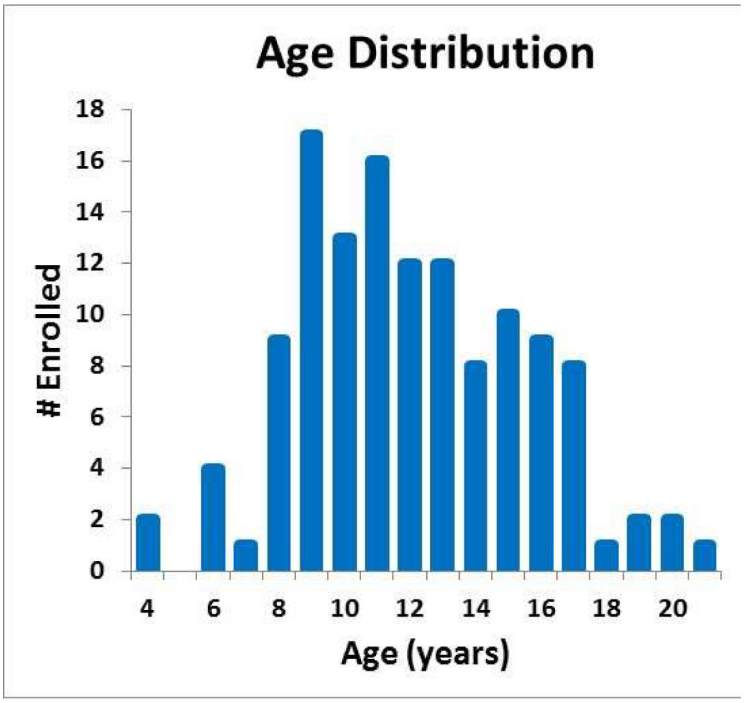

Figure 1. Age distribution of subjects

The figure demonstrates the age distribution of enrolled subjects.

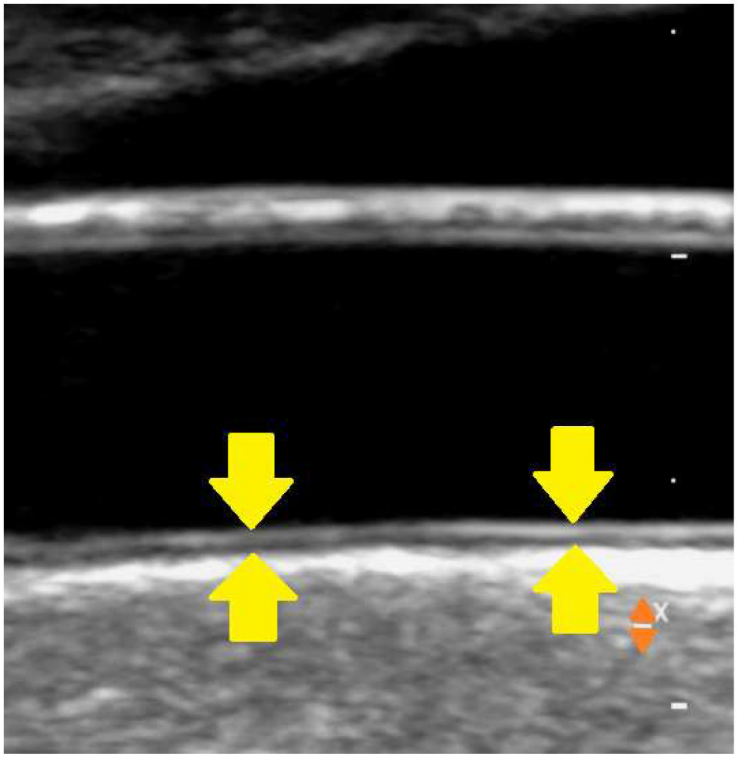

Figure 2. Common carotid artery ultrasound

Representative still frame at end-diastole from a right common carotid artery 1 cm below the carotid bifurcation with the ultrasound beam directed anterior to posteriorly. The yellow arrows bracket the intima-media of the far wall of the common carotid artery where measurements will be made. The distance between the depth markers (major and minor hash marks) to the right of the figure is 5mm. The two orange opposing triangles indicate the focal depth.

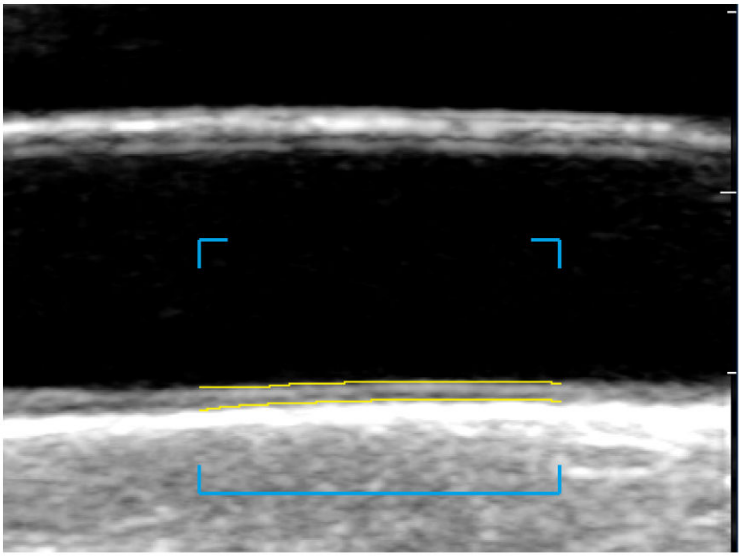

Figure 3. Measurement of carotid intima-media thickness

This figure shows the off-line software analysis of the common carotid ultrasound from Figure 2. The software requires the user to manually place a blue box of 1cm length over the far wall of the carotid artery. The software then automatically traces the intima-media borders (yellow lines). The reported carotid-intima media thickness in this patient was 0.51 mm. The distance between the depth markers (major and minor hash marks) to the right of the figure is 5mm.

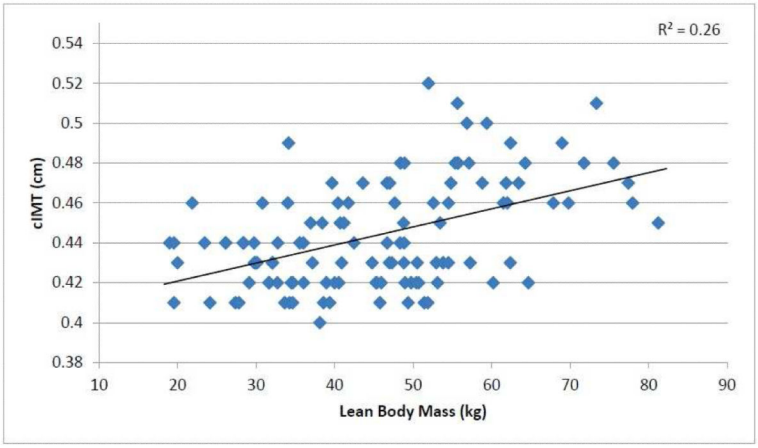

Figure 4. Lean Body Mass vs. cIMT

Linear regression plot demonstrating the association of lean body mass to cIMT. cIMT = carotid intima-media thickness.

Table 1

Differences by Race in Clinically Derived Anthropometrics and Laboratory Data

Measure	White	Black	t-test or Mann Whitney U (p-value)
Age (years)	12.5 ± 3.6	11.8 ± 3.3	0.30
Height (cm)	158 ± 12.8	155 ± 13.7	0.30
Weight (kg)	79.5 ± 25.7	88.1 ± 32.3	0.13
Body surface area (m^2)	1.8 ± 0.3	1.9 ± 0.4	0.43
Systolic blood pressure (mmHg)	113 ± 13	112 ± 17	0.63
Diastolic blood pressure (mmHg)	63 ± 8	61 ± 9	0.15
Insulin (μIU/mL)	22 (7-119)	28 (11-116)	0.03
Glucose (mg/dL)	91 ± 7.6	92 ± 8.2	0.53
QUICKI	0.30 ± 0.03	0.29 ± 0.02	0.02
Low density lipoprotein (mg/dL)	103 ± 24	104 ± 24	0.73
High density lipoprotein (mg/dL)	41 ± 11	42 ± 9.2	0.49
Triglycerides (mg/dL)	95 (32-297)	65 (29-175)	<0.01
hsCRP (mg/dL)	0.25 (0.02-2.41)	0.38 (0.01-1.98)	0.11

Results are reported in means ± standard deviation for normally distributed data and in median (range) for non-normally distributed data. QUICKI = quantitative insulin sensitivity check index, hsCRP = high sensitivity c-reactive protein.

Table 2

Differences by Race in Body Composition and cIMT

Measure	White	Black	t-test (p-value)
BMI (kg/m^2)	31.2 ± 7.4	35.3 ± 8.9	0.01
Lean body mass index (kg/m^2)	17.3 ± 3.2	19.3 ± 3.4	0.02
Fat mass index (kg/m^2)	13.0 ± 4.3	14.3 ± 4.6	0.13
% Body fat	41 ± 4.8	41 ± 5.5	0.60
Mean cIMT (cm)	0.43 ± 0.02	0.45 ± 0.03	<0.01

Results are reported in means ± standard deviation. BMI = body mass index, cIMT = carotid intima-media thickness.

Table 3

Results of Simple and Multivariable Linear Regression Analysis

Simple Linear Regression									
Model	**Variable**	**B**	**SE**	**β**	**t**	**p**	**F**	**R**	**R^2**
LBM						<0.01	38.70	0.51	0.26
	Constant	0.397	0.008		51.88	<0.01			
	LBM	0.001	<0.001	0.51	6.221	<0.01			
Race						<0.01	30.21	0.46	0.21
	Constant	0.326	0.021		15.33	<0.01			
	Race	0.001	<0.001	0.46	5.50	<0.01			
SBP						<0.01	34.51	0.52	0.27
	Constant	0.391	0.010		39.36	<0.01			
	SBP	0.035	0.006	0.52	5.87	<0.01			
Multiple Variable Linear Regression									
Model	Variable	B	SE	β	t	p	F	R	R^2
1						<0.01	6.23	0.55	0.30
	Constant	0.379	0.049		7.74	< 0.01			
	LBM	0.001	<0.001	0.48	3.06	<0.01		0.51	
	Race	0.008	0.004	0.17	1.95	0.05		0.19	
	SBP	<0.001	<0.001	0.08	0.80	0.43		0.31	
	Age	<0.001	0.001	−0.4	−0.27	0.78		0.32	
	LDL	<0.001	<0.001	−0.10	−1.19	0.24		−0.19	
	QUICKI	0.017	0.116	0.0	0.15	0.88		−0.23	
	hsCRP	−0.002	0.006	−0.03	−0.37	0.72		0.08	
2						<0.01	14.71	0.54	0.29
	Constant	0.363	0.021		17.54	<0.01			
	LBM	<0.001	<0.001	0.44	4.81	<0.01		0.51	
	Race	0.007	0.004	0.15	1.90	0.06		0.18	
	SBP	<0.001	<0.001	0.12	1.30	0.20		0.32	
3						<0.01	21.32	0.53	0.28
	Constant	0.286	0.010		40.18	<0.01			
	LBM	0.001	<0.001	0.50	6.15	<0.01		0.51	
	Race	0.007	0.004	0.15	1.78	0.08		0.18	

Results of simple and multiple variable linear regression analysis above. A p value of < 0.05 was considered significant. hsCRP = high sensitivity c-reactive protein, LBM = lean body mass, LDL = low density lipoprotein, QUICKI = quantitative insulin sensitivity check index, SBP = systolic blood pressure.