Subclinical Atherosclerosis in Latino Youth: Progression of Carotid Intima-Media Thickness and Its Relationship to Cardiometabolic Risk Factors

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Objective To assess carotid artery intima-media thickness (CIMT) change over 2 years in overweight Latino adolescents and examine its relationship to cardiometabolic risk.

Study design Seventy-two healthy overweight male and female Latino adolescents (mean age, 14.5 ± 1.7 years; mean body mass index, 31.5 ± 6.9 kg/m²) were evaluated at baseline and 2 years later for CIMT by high-resolution B-mode ultrasound, the metabolic syndrome and its features, body composition by dual-energy x-ray absorptiometry and magnetic resonance imaging, glucose/insulin measures by fasting blood, and oral and intravenous glucose tolerance tests.

Results Baseline CIMT did not differ from 2-year follow-up; however, 38 participants increased CIMT (0.017 ± 0.003 mm; +2.8%) and 34 decreased or remained the same (−0.019 ± 0.002 mm; −3.1%). ANCOVA analyses showed that participants with CIMT progression had higher baseline low-density lipoprotein (LDL)-cholesterol and total cholesterol (91.3 ± 3.4 and 150.3 ± 3.9 mg/dL) compared with those with CIMT non-progression (78.1 ± 3.6 and 135.6 ± 4.2 mg/dL, P < .05), independent of sex, baseline CIMT, age, and height. In multivariate regression, LDL-cholesterol was the sole predictor of CIMT progression, but the effect was small (odds of CIMT progression increased by 3% for each 1 mg/dL higher baseline LDL-cholesterol; 95% confidence interval, 1.004 to 1.006, P = .03).

Conclusions These results indicate a high variability in the magnitude of CIMT change in growing overweight Latino youth and support the use of LDL-cholesterol to assess subclinical atherosclerosis risk in this population. (J Pediatr 2011;■:■-■).

The increasing prevalence of pediatric childhood obesity1 warrants investigation into the link between obesity and atherosclerosis risk in youth. The Latino population in the United States is rapidly growing and has shown a variety of obesity related comorbidities, such as hypertension and diabetes, placing them at high risk for cardiovascular disorders. Latino children have a high prevalence of obesity,1 insulin resistance,2 metabolic syndrome,3 and impaired fasting glucose/pre-diabetes,4 all of which may contribute to the early development of atherosclerosis.

Carotid artery intima-media thickness (CIMT) is a noninvasive measure of subclinical atherosclerosis. The progression of CIMT in youth as related to the obesity has not been widely examined. Increased thickness of the carotid artery, and its associated cardiovascular disease events in adulthood, has various inter-related predictors such as obesity, male sex, metabolic dysfunction, dyslipidemias, and hypertension. Studies over the past decade have shown similar relationships of elevated CIMT and traditional cardiometabolic risk factors in children and young adults.5-14 We have previously shown that children with persistent metabolic syndrome over a 3-year period exhibited a higher CIMT than those who never had the metabolic syndrome.15 Of the metabolic syndrome components, high blood pressure and high waist circumference were the features most highly associated with higher CIMT.15

The first objective of this study was to assess the change of CIMT over a 2-year period. Next, we assessed the relationship of CIMT progression to potential CIMT predictors, including adiposity, the metabolic syndrome and its individual features, lipids, and insulin resistance. Finally, we examined any potential sex differences in these associations. We hypothesized that baseline systolic blood pressure, abdominal adiposity, and insulin resistance would predict CIMT progression.

Methods

Participants were enrolled in the Study of Latino Adolescents at Risk for Diabetes (SOLAR), a longitudinal study exploring metabolic risk factors for type 2 diabetes. Study participants satisfied the following criteria for inclusion at the initial
baseline visit: 8 to 13 years of age, Latino ethnicity (ie, parents and grandparents of Latino descent), age- and sex-specific body mass index (BMI) ≥85th percentile, positive family history for type 2 diabetes, and absence of diabetes as assessed by an oral glucose tolerance test. Participants were excluded if they were using a medication or diagnosed with a condition known to influence body composition or insulin/glucose metabolism. Before testing procedures, written informed consent from parents and assent from the children were obtained. This investigation was approved by the Institutional Review Board of the University of Southern California. To be included in this analysis, participants in the Study of Latino Adolescents at Risk for Diabetes study must have had a baseline CIMT in 2006 (n = 123) and a repeat CIMT measure in 2008 (n = 73) and all measures of cardiometabolic risk. One participant was diagnosed with diabetes and was excluded from this analysis (n = 72). The dropout rate was due to (1) losing contact with the participant and their families; (2) participants moving or leaving to attend college; and (3) disinterest in study after 6 to 8 years of annual participation. We conducted an analysis on this subgroup of excluded participants and observed no significant physical or metabolic differences between the excluded (n = 51) and included (n = 72) participants.

Details of the longitudinal study protocol and design have been previously described. In brief, participants attended two annual visits to at the University of Southern California General Clinical Research Center. On the first visit, participants received a comprehensive medical history and physical examination by a licensed health care provider. Clinical staff then collected vital signs, blood pressure in triplicate, and performed a 2-hour oral glucose tolerance test. Approximately 7 to 14 days after the outpatient visit, participants were admitted for an inpatient visit at the University of Southern California General Clinical Research Center for their second visit. They were examined once more by a licensed health care provider and were given dinner. After a supervised, overnight fast, a 3-hour, modified, frequently sampled intravenous glucose tolerance test (with 13 time points) was performed by certified nursing and phlebotomy staff. Detailed information on glucose, insulin measures, and lipid assays can be referenced from a similar previous study. We defined the metabolic syndrome with criteria similar to the Adult Treatment Panel that we adapted for pediatric populations.

Body composition measures and CIMT measure were performed at either visit based on availability of the participant and staff. Total body composition was completed by dual-energy x-ray absorptiometry, and magnetic resonance imaging was used to assess abdominal adiposity. Using a GE 1.5 Sigma LX-Ecospeed with 1.5-T magnet (GE Healthcare, Piscataway, New Jersey), a single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus was analyzed for cross-sectional area of visceral and subcutaneous abdominal adipose tissue.

CIMT was determined at the University of Southern California Atherosclerosis Research Unit Core Imaging and Reading Center as previously described. High-resolution B-mode ultrasound images were obtained using a Siemens Acuson CV70 (13-MHz linear array; Siemens Medical Solutions Inc, Mountain View, California) imager. CIMT was measured from computer-processed images of the right distal common carotid artery approximately 1 to 2 cm from the bifurcation into external and internal carotids. The same sonographer and reader performed all baseline and follow-up CIMT measures, and she was blinded to all participant information. The intraclass correlation coefficient for CIMT measures was 0.96 (95% CI, 0.93 to 0.97).

Statistical Analysis
To assess the change of the dependent variable (CIMT), each participant’s CIMT change was calculated by taking the difference of the 2-year follow-up CIMT from the baseline CIMT. In preliminary analyses, CIMT change was used as a continuous variable while in ANCOVA analyses, and participants were placed in one of three groups: nonprogression (CIMT change ≤0.000 mm), normal progression (CIMT change >0.000 mm and <0.01 mm), or advanced progression (CIMT ≥0.01 mm). Advanced CIMT progression was based on a conservative cutoff using normal rates of CIMT progression in healthy adults (approximately 0.005 mm/y; hence, ≥0.01 mm over 2 years was deemed advanced progression). For logistic regression, CIMT progression was defined to include any CIMT progression (CIMT ≥0.01 mm) or advanced CIMT progression only (CIMT ≥0.01 mm). The independent variables (adiposity measures, metabolic syndrome, blood pressure, lipids, and measures of glucose/insulin metabolism) were measured at baseline and follow-up CIMT assessments. The Shapiro-Wilkes W test was used to test the gaussian distribution of residual values of all continuous variables, none of which deviated from normality (P > .05).

For descriptive analysis, independent t test tests were performed to assess mean physical and metabolic characteristics by sex and then at baseline and 2-year follow-up. This followed by a preliminary analysis of simple and partial correlations of CIMT change with each independent variable at baseline. This analysis was repeated to examine the relationship between CIMT change and changes in adiposity (BMI, BMI z-score, total fat mass, and visceral and subcutaneous adiposity), blood pressure, lipids (triglycerides, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, and total cholesterol), and glucose and insulin indices (fasting and 2-hour glucose and insulin, insulin sensitivity, acute insulin response, disposition index, glucose and insulin AUC). ANCOVA was used to compare differences of each cardiometabolic risk factor at baseline (as well as 2-year change) by CIMT progression groups. A priori covariates included sex, baseline age, and height due to their documented effects on CIMT progression. Baseline measures were used to adjust for any analysis of 2-year change in the variables of interest.

Significant associations were further examined using multivariate linear regression and by 2-way ANCOVA for the
metabolic syndrome. Interaction terms were used to test whether sex significantly modified the relationship between each of the cardiovascular risk factors and change in CIMT while adjusting for baseline CIMT, age and height.

Multiple logistic regression analysis was used to determine the relative contribution of the baseline predictors (independent continuous variables in model 1: fasting insulin, glucose effectiveness, and LDL-cholesterol) to the CIMT progression (CIMT was coded as a binary dependent variable, CIMT nonprogression, and CIMT progression), while considering the confounding effects of sex, baseline age, and height. The second model included the same independent variables but used CIMT coded as a binary variable with CIMT nonprogression and advanced CIMT progression. Data were analyzed using SPSS for Mac version 16.0 (SPSS Inc, Chicago, Illinois), with an a priori significance level of $P < .05$.

### Results

The distribution of each participant’s change in CIMT showed that of the 72 participants, 38 showed an increase in CIMT (mean increase: $0.017 \pm 0.002$ mm, $-3.1\%$).

Descriptive statistics of physical and metabolic characteristics of 72 Latino adolescents are shown in Table I. Body composition or cardiometabolic risk characteristics did not significantly differ between baseline and 2-year follow-up, with the exception of fasting glucose that was higher at the baseline measure ($P < .05$). Males were significantly taller and had higher total lean tissue mass than females ($P < .001$). Systolic and diastolic blood pressures were higher in males than females ($P < .05$). HDL-cholesterol was significantly lower in males than in females ($P < .05$). Females had a lower disposition index than males ($P < .05$). CIMT did not differ by sex but females had a lower maximum carotid diameter than males ($P < .05$).

Simple and partial correlations between baseline cardiovascular risk factors and CIMT change revealed that LDL-cholesterol, fasting insulin, and insulin AUC were positively correlated to change in CIMT ($r = 0.21$ to $0.24$, $P < .05$), with glucose effectiveness the only factor negatively correlated with change in CIMT ($r = -0.30$, $P = .01$). The only inverse relationship between glucose effectiveness and CIMT change remained significant after adjustment for sex, age, height, and baseline CIMT ($r = -0.30$, $P = .01$). Correlations between baseline body composition (including abdominal adiposity), insulin sensitivity and blood pressure with CIMT change were not significant (range: $-0.03$ to $0.13$, $P > .05$). All correlations between change in any given cardiometabolic risk factor and CIMT change were also not significant, and there were no significant sex interactions independent of baseline CIMT (range: $-0.12$ to $0.09$, $P > .05$).

Participants with the metabolic syndrome at baseline showed an increase in CIMT change compared with those who did not have the metabolic syndrome, but this difference did not reach significance (ANOVA, $0.007 \pm 0.005$ versus $-0.003 \pm 0.003$ mm, $P = .16$). Sex did not modify the effect of CIMT change between participants with or without the metabolic syndrome (2-way ANOVA interaction, $P > .05$).

Descriptive statistics of physical and metabolic characteristics at baseline and 2-year follow-up ($n = 72$) are shown in Table II. With the exception of LDL and total cholesterol, there were no significant associations between cardiometabolic risk factors with the 3 CIMT progression groups. After adjustment with covariates, the baseline LDL-cholesterol and total cholesterol were significantly higher in the advanced CIMT progression group (adjusted means shown in Figure 4, $92.6 \pm 4.4$ and $152.9 \pm 5.1$ mg/dL) versus those in the CIMT nonprogression group ($77.7 \pm 3.7$ and $135.5 \pm 4.2$ mg/dL, $P < .05$), independent of sex, baseline CIMT, age, height, and HDL-cholesterol.

Two logistic regression models (Table III) were used to determine the independent predictors of CIMT progression, which was evident in 53% of the sample. In model 1, LDL-
This study examined CIMT progression during childhood growth and development and its cardiometabolic predictors in healthy, overweight Latino youth. Our results indicate that change in CIMT was highly variable. Moreover, 36% of participants showed progression beyond that of the physiological norm (advanced CIMT progression group with CIMT ≥0.01 mm over 2 years). Participants in the advanced CIMT progression group had significantly higher baseline LDL and total cholesterol than those in the CIMT nonprogression group. Another predictor of CIMT change was baseline glucose effectiveness, which had a negative relationship with CIMT change independent of sex and baseline CIMT, age, and height. Finally, the odds of CIMT progression increased 1.03 times (or 3%) for each 1 mg/dL increase of baseline LDL-cholesterol, independent of glucose effectiveness and other covariates. These results highlight the baseline effects of LDL-cholesterol in youth that results in advanced CIMT progression.

Contrary to our hypothesis, baseline systolic blood pressure, abdominal adiposity, or insulin sensitivity were not associated with change in CIMT over a 2-year period. We have previously shown that Latino children with persistent high cholesterol was the sole predictor of any type of CIMT progression (CIMT >0.000 mm), where the odds for CIMT progression over a 2-year period was 1.03 for each 1 mg/dL higher baseline LDL-cholesterol (95% confidence interval, 1.004 to 1.006, \( P = .03 \)). Model 2 shows that LDL-cholesterol was a marginally significant predictor of advanced CIMT progression.

**Discussion**

blood pressure and high waist circumference, along with children with persistent metabolic syndrome, had a higher CIMT than those children without these risk factors. The cumulative effects of the metabolic syndrome, high blood pressure, and waist circumference resulted in elevated CIMT. Our present report shows that these same risk factors were not associated with the rate of CIMT progression. Instead, LDL-cholesterol was the defining cardiometabolic risk factor that translated into more CIMT progression. Together, these two studies suggest that multiple risk factors are involved in elevated CIMT and its progression and that all of these risk factors are important in determining atherosclerosis risk in overweight Latino youth.

The relationship between LDL-cholesterol and CIMT has been well documented in adults but is still ambiguous in studies of healthy children; two studies have observed this relationship,22,23 whereas two others have not.24,25 We have got results that are consistent with our findings.
shown a statistically significant relationship with LDL-cholesterol and CIMT progression after only 2 years in overweight Latino youth with a family history of type 2 diabetes. Our data showed that small changes in LDL-cholesterol at baseline were still sufficient to observe differences between CIMT progressors and nonprogressors. It is important to note that only five participants (all male) had a clinically abnormal level of LDL-cholesterol level (above the 90th percentile for sex and age), and three of these five participants had families histories of hypercholesterolemia. Studies have shown that children with a familial hypercholesterolemia consistently had increased CIMT compared with healthy control subjects. Based on these studies, we repeated our analyses excluding the five participants with abnormal high LDL-cholesterol. We found that baseline LDL-cholesterol and CIMT progression after only 2 years in overweight Latino youth was still higher in the advanced CIMT progression group compared with healthy control subjects.

Several limitations must also be discussed. First, the moderate sample size and a short time frame of this longitudinal study may have impeded any other predictors of CIMT progression, particularly when one considers the large number of predictors analyzed. This limitation was addressed to some extent by building the multivariate statistical models with only a chosen number of predictors. Another limitation related to this small and highly specific group of overweight Latino youth was the narrow range of BMI change that these children incurred during the 2-year time frame. Most studies of subclinical atherosclerosis in overweight children have shown a relationship between adiposity and CIMT. In contrast, our study has been limited to a small BMI change, and we were unable to show this relationship. Broadening the BMI range by adding lean participants would be beneficial to further examine the effects of BMI and adiposity. Last, we were unable to statistically control for other important covariates such as physical activity data or for C-reactive protein and other cardiovascular biomarkers because we did not collect these data or assay blood for these proteins.

These findings extend our previous findings in which persistent metabolic syndrome, high blood pressure, and high waist circumference were related to CIMT and suggest that LDL-cholesterol contributes to CIMT progression in overweight Latino youth.

We thank the staff of the University of Southern California/Los Angeles County General Clinical Research Center and the SOLAR staff. Our gratitude is especially extended to the loyal participants and their families for their continued participation.
References