Relationships Between IGF-1 and IGFBP-1 and Adiposity in Obese African-American and Latino Adolescents

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The purpose of this study was to examine interrelationships between insulin-like growth factor 1 (IGF-1), IGF binding proteins (IGFBPs), and adiposity in 49 African-American and 77 Latino obese adolescents (15.3 ± 0.1 and 15.4 ± 0.2 years; BMI: 33.0 ± 0.7 and 35.0 ± 1.0 kg/m^2, respectively). Immunoradiometric assays were used to measure IGF-1, IGFBP-1, and IGFBP-3. Total fat and soft lean tissue were measured by dual-energy X-ray absorptiometry and visceral adipose tissue (VAT), subcutaneous abdominal adipose tissue (SAAT), and hepatic fat fraction (HFF) were measured by magnetic resonance imaging. IGF-1 levels were 23.1% higher and IGFBP-1 were 40.4% higher in African Americans compared to Latinos after adjustment for total lean and total fat mass. IGF-1 and IGFBP-1 were inversely correlated with BMI, total fat mass, VAT, and HFF (r = –0.20 to –0.33, P < 0.05) while IGFBP-1 was inversely correlated with SAAT (r = –0.22, P < 0.05). These relationships did not differ by ethnicity, however, the relationship between IGF-1 and SAAT, as well as IGFBP-1 and HFF, differed by ethnicity. Predicted mean IGF-1 levels were 30.7% higher for African Americans at the 75th compared to 25th percentile of SAAT and only 11.7% higher for Latinos. Predicted mean IGFBP-1 levels were 158% higher for African Americans at the 25th compared to the 75th percentile of HFF while IGFBP-1 levels were 1.7% higher for Latinos at the 75th compared to the 25th percentile. These results demonstrate that the relationship between IGF-1 and SAAT as well as IGFBP-1 and HFF are different in African-American and Latino adolescents and may contribute to the higher IGF-1 levels in African-Americans.

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INTRODUCTION

The insulin-like growth factor (IGF) family of ligands and binding proteins make up an important growth factor system that is involved in the development and maintenance of normal cell function in the body. Circulating IGF-1 concentrations are regulated by growth hormone, present in systemic circulation and expressed in body tissues (1). The biologic activity of IGF-1 is determined by the circulating IGF-1 and IGF binding protein (IGFBPs) produced by the liver. Paracrine effects of IGFs, IGFBPs, and IGFBP proteases also influence the activity of IGF-1 (2). Numerous studies suggest that high levels of IGF-1 constitute as a risk factor for breast, prostate, colon, and lung cancer (3–8) through ligand involvement in growth and differentiation of normal and malignant cells (9). While obesity, age, and gender are known to correlate with serum IGF levels, some studies have shown that ethnicity may also be associated with IGF-1 and IGFBP-3 levels in children and adults, potentially explaining ethnic specific health disparities related to cancer (10–19).

Several studies have examined ethnic differences in IGF-1, IGFBP-1, and IGFBP-3 in children. It has been shown that Latino and Caucasian prepubertal females have lower IGF-1 levels compared to African-American females (16,20). Other studies have reported positive correlations between total body fat and IGF-1 concentrations in Caucasian children (21,22) and our laboratory demonstrated a positive relationship between IGF-1 and body fat in African-American and Caucasian children that was not explained by diet, physical activity, socioeconomic status, or adiposity, but was related to the degree of African admixture, suggesting a genetic basis for this difference (14). Additionally, our laboratory showed an inverse relationship between IGF-1 and IGFBP-3 with total fat mass and body fat compartments in overweight Latino children (15). These results demonstrate that African-American children have the highest levels of IGF-1 and exhibit a positive relationship between IGF-1 and adiposity, perhaps contributing to their increased risk of obesity-related cancers during adulthood (23).

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The IGF-axis differences seen among children persist in adulthood in most (12,24), but not all (13), of adult studies. One study showed lower levels of IGF-1 and IGFBP-3 in Latinos compared to Caucasians and African Americans (24). Another study demonstrated ethnic differences in which female Caucasians and Latinos had lower IGF-1 levels compared to African Americans but IGF-1 levels in males were similar among the ethnicities (13). Additionally, another study showed that plasma IGF-1 levels decline with increasing BMI in Latino adults and this decline is absent or "slightly reversed" in African Americans (12). Finally, after adjustment for age and BMI, adult African Americans have the highest molar ratio of IGF-1 to IGFBP-3, reflecting a larger bioavailability of IGF-1 compared to Caucasians and Latinos (13). Although ethnic differences in children are similar to that observed in adults, it is unknown how these relationship may differ among obese adolescents. In order to obtain a full picture of how IGF-1 and IGFBP levels are related to body composition/fat distribution, one must examine these relationships during adolescence.

Studies in adolescents are advantageous as these relationships can be examined in a sexually mature group in the absence of confounding variables, such as aging, menopausal status, and hormone therapy. The aims of this study were to examine the relationships between IGF-1 levels, and its binding proteins, with body composition/fat distribution and to determine whether the observed relationships are different in overweight Latino and African-American adolescents. As similar relationships have been observed in Latino and African-American children and adults, we hypothesize that disparities in IGF-1 and IGFBP levels exist in Latino and African-American adolescents.

METHODS AND PROCEDURES

Participants

Participants were recruited for the SANO LA (Strength and Nutrition Outcomes for Latino Adolescents) and STAND (Strength Training and Nutrition Development for African American Youth) randomized control trials aimed at preventing type 2 diabetes. Data used for this analysis arise from baseline values from each study. Latino and African-American adolescents were recruited from Los Angeles County and met the following inclusion criteria: BMI ≥85th percentile, Latino or African-American ethnicity (i.e., parents and grandparents of Latino or African-American decent by parental self-report), and grades 9th through 12th (14–18 years of age). Participants were excluded from either study based on the following criteria: (i) were using medication or were diagnosed with any disease that could influence dietary intake, exercise ability, body composition, fat distribution, or insulin indexes, (ii) were previously diagnosed with any major illness, (iii) met any diagnostic criteria for diabetes, or (iv) participated in a structured exercise, nutrition, or weight loss program in the past 6 months. Prior to any testing procedure, informed written consent from parent and assent from the child was obtained. The institutional review board of the University of Southern California, Health Sciences Campus, approved this study. A brief description follows and a detailed study methodology has been reported previously (25).

Outpatient visit

Participants arrived at the General Clinical Research Center at 7:30 AM after an overnight fast. A licensed health care provider conducted a medical history exam and determined Tanner pubertal staging using established guidelines (26,27). Following the exam, a 3-h oral glucose tolerance test was performed. Fasting 2-h glucose levels were used to determine normal or impaired glucose tolerance as defined by the American Diabetes Association (26).

Anthropometry and body composition

Weight and height were measured to the nearest 0.1 kg and 0.1 cm using a beam medical scale and wall-mounted stadiometer. Whole body fat and soft lean tissue was measured by dual-energy X-ray absorptiometry using a Hologic QDR 4500W (Hologic, Bedford, MA). Central fat distribution was measured by magnetic resonance imaging, on a Siemens Magnetom 1.5-Tesla Symphony Maestro Class Syngo 2004A (Siemens, Erlangen, Germany) with a Numaris/4 software at the USC-HCCII imaging center. Slices were acquired using a 420 mm field of view and field of view phase of 75%. Three abdominal scans were performed consecutively and total acquisition time was 24 s per total abdominal scan. Each scan obtained 19 axial images of the abdomen with a thickness of 10 mm. After image acquisition, subcutaneous abdominal adipose tissue (SAAT) and visceral adipose tissue (VAT) were segmented using image analysis software (SliceOmatic Tomovision, Montreal, Canada) at Image Reading Center (New York City, New York). SAAT and VAT volumes were calculated from these images as previously described (28).

In-patient visit

Approximately 7–14 days following the outpatient visit, participants were admitted to the General Clinical Research Center and served a standardized dinner and evening snack. An insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed the following morning. At time zero, glucose (25% dextrose, 0.3 g/kg of body weight) was administered intravenously over a 1-min period. Blood samples were collected at −15, −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin (0.02 units/kg body weight, Humulin (R regular insulin for human injection); Eli Lilly, Indianapolis, IN) was injected intravenously at 20 min. Plasma collected during the frequently sampled intravenous glucose tolerance test was analyzed for glucose and insulin and values were entered into the MINMOD Millennium 2003 computer program (version 5.16, RN Bergman, USC) to determine insulin sensitivity (SI).

Laboratory assays

Blood samples collected during the frequently sampled intravenous glucose tolerance test were centrifuged for 10 min at 2,500 rpm and 8–10 °C to obtain plasma, and aliquots were frozen at −70 °C until assayed. Insulin was assayed in duplicate using a specific human insulin enzyme-linked immunosorbent assay kit from Linco (St Charles, MO). IGF-1 (μg/ml), IGFBP-1 (μg/ml), and IGFBP-3 (μg/ml) concentrations were determined using the −15 min. sample and two-site coated tube immunoradiometric assay kits (Active, Diagnostic Systems Laboratories, Webster, TX) according to the manufacturer's instructions. Samples were assayed in duplicate. Minimal detection limits for IGF-1, IGFBP-1, and IGFBP-3 were 2.06, 0.33, and 0.05 μg/ml.

Hepatic fat fraction quantification

Hepatic fat fraction (HFF) was assessed by magnetic resonance imaging using a modification of the Dixon 3-point technique. Abdominal slices were acquired contiguously using a breath-hold dual-echo spoiled gradient-recalled echo sequence with repetition time of 156 ms and echo time of 2.3 ms for out of phase (OP) images and 4.78 ms for in-phase (IP) images. Images were acquired with flip angles of 70° and then 20° to provide T1-weighted and intermediate-weighted images. A third dual-echo gradient-echo breath-hold gradient-recalled echo sequence with two IP echoes (4.8 and 9.6 ms) was also performed to calculate T2. The HFF was estimated from the signal intensity index (SII) obtained from IP and OP images.

$$HFF = \frac{SIIP - SIOP}{2SIIP},$$

where SIIP and SOIP are the signal intensities of IP and OP images. Quantitative corrections for the influence of T2 decay on the fat fraction estimates are taken into account by the third dual-echo sequence, where T2 for the liver is estimated on a pixel-by-pixel basis. Since the HFF is estimated from low flip-angle images (20°), the effect of T1 relaxation on the quantification is minimized. Once the HFF images are calculated, three consecutive slices with maximum axial coverage of the liver are selected. Regions of interest are drawn on each slice, ranging from 1.8 cm^2 to 14.1 cm^2, while avoiding any major blood vessels, to report the average HFF value.

Statistical analysis

Data analysis included data summarization and multivariate regression modeling. Our total sample size included 126 participants. Of the 126 participants, 108 participants had SAAT and VAT data and 93 had HFF data. Those not included in the analysis were missing data for SI and/or total fat mass, SAAT, VAT, and HFF. Mean variable differences by ethnicity were analyzed by independent *t*-tests, χ^2 test, and ANOVA. All analyses were done in SAS, version 9.1 (SAS, Institute, Cary, NC).

Multivariate regression models were used to explore the relationship between the independent body composition/distribution variables (i.e., BMI, total fat mass, SAAT, VAT, and HFF) and the measures of IGF-1, IGFBP-1, and IGFBP-3. Regression models were also used to determine whether there were ethnic differences among these relationships by testing for an interaction between body composition variables and ethnicity. Partial correlations and parameter estimates were used to describe the relationship between body composition/fat distribution variables and IGF-1 and as well as body composition/distribution variables and IGFBPs after controlling for *a priori* covariates. If the interaction term was significant, the correlation and parameter estimate between the interaction term and dependent variable were examined. Due to our limited sample size, this method of analysis preserved statistical power that was lost by stratifying. *A priori* covariates included age, gender, Tanner stage, total fat mass (where appropriate), soft lean tissue, and SI. In Latino children, previous literature observed relationships between IGF-1 and IGFBPs with body composition/fat distribution variables that were diminished after controlling for these same covariates (15). Therefore, our regression models controlled for the same covariates. In addition to these variables, we controlled for ethnicity. *A priori* significance level was set at $P < 0.05$. All assumptions of multiple linear regression were satisfied and IGFBP-1 was log transformed in order to meet these assumptions. The IGF-1/IGFBP-3 molar ratio was calculated based on 1 μg/ml IGF-1 = 0.130 μmol IGF-1 and 1 μg/ml IGFBP-3 = 0.036 μmol IGFBP-3 (29). Independent variables were mean centered and we utilized dummy coding for ethnicity (Latinos = 0 and African Americans = 1).

Table 1 Physical characteristics and metabolic parameters

	Latino (n = 77)	African Americans (n = 49)	P value
% Female	60.20%	68.60%	0.33
Age (years)[t]	15.3 ± 0.1	15.4 ± 0.2	0.56
Tanner stage			
1	1	0	0.14
2	1	2	
3	5	3	
4	25	7	
5	45	37	
IGF-1 (μg/ml)	519.9 ± 20.3	640.2 ± 26.0	<0.01
IGFBP-1 (μg/ml)[b]	5.8 ± 0.6	6.4 ± 0.8	0.97
IGFBP-3 (μg/ml)	4,675.1 ± 68.8	4,502.7 ± 108.5	0.16
IGF-1/IGFBP-3 molar ratio	0.40 ± 0.02	0.52 ± 0.02	<0.01
BMI (kg/m^2)[b]	33.0 ± 0.7	35.0 ± 1.0	0.08
Total fat (kg)[b]	33.1 ± 1.2	36.5 ± 1.8	0.14
Soft lean tissue (kg)	49.5 ± 1.2	54.7 ± 1.2	<0.01
SAAT (L)[b,c]	8.7 ± 0.5	15.4 ± 0.9	<0.01
VAT (L)[c]	1.4 ± 0.1	1.3 ± 0.1	0.39
HFF (%)[b,d]	9.4 ± 1.3	4.2 ± 0.3	<0.01
Fasting insulin (μU/ml)[b,e]	26.6 ± 1.5	22.5 ± 1.9	0.03
Fasting glucose (mg/dl)[f]	91.4 ± 0.8	89.6 ± 0.9	0.11
Insulin sensitivity ((×10–^{4}min–^{1})/(μU/ml))[a]	1.9 ± 0.2	1.2 ± 0.1	<0.01

HFF, hepatic fat fraction; IGF, insulin-like growth factor; IGFBP, IGF-binding proteins; SAAT, subcutaneous abdominal adipose tissue; VAT, visceral adipose tissue.
Data values are mean ± s.e. Independent *t*-tests were used to test for differences between ethnicities. Variables were not normally distributed so statistical tests were run with the [a]square-root or [b]log-transformed data. [t]Age remained non-normal with transformation and Wilcoxon two-sample test was used to obtain *P* value. [c]Latinos (Lat) n = 63 and African Americans (AA) n = 45. [d]Lat n = 51 and AA n = 42. [e]Lat n = 75 and AA n = 47. [f]Lat n = 77 and AA n = 49.

RESULTS

Physiological and metabolic parameters

Table 1 displays the mean physical characteristics and metabolic parameters of 77 Latino and 49 African-American male and female adolescents derived from the in-patient visit. Unadjusted mean levels of IGF-1 and IGF-1/IGFBP-3 were 23.1 and 30.0% higher in African-American compared to Latino adolescents ($P < 0.01$). Independent *t*-tests revealed a statistically significant higher soft lean tissue mass, and SAAT in African Americans compared to Latinos ($P < 0.05$). After controlling for age, gender, Tanner, soft lean tissue mass, total fat mass, and SI, African Americans maintained a higher adjusted mean level of IGF-1 (640.1 vs. 519.9 μg/ml, $P < 0.001$) and higher IGF-1/IGFBP-3 (0.52 vs. 0.40, $P < 0.001$) compared to Latinos. Lastly, African Americans showed a trend for higher levels of IGFBP-1 (7.3 vs. 5.2 μg/ml, $P = 0.07$) and lower levels of IGFBP-3 (4,461.9 vs. 4,701.1 μg/ml, $P = 0.07$). The partial correlations and parameter estimates between the dependent and independent variables are shown in Table 2.

Multivariate regression analysis for body composition and IGF proteins

Partial correlations between IGF-1 and binding proteins. In order to explore the relationship between plasma IGF-1 and its binding proteins we examined the partial correlations and parameter estimates between IGF-1 and IGFBP-1 and between IGF-1 and IGFBP-3. After accounting for age, gender, Tanner, soft lean tissue mass, total fat mass, SI, and ethnicity, we observed a positive parameter estimate and partial correlation between IGF-1 and IGFBP-3 ($\beta = 0.10$, $r = 0.36$, $P < 0.001$) and an inverse

Table 2 Results of the multiple regression analysis

Outcome	Parameters	$\beta_{(Parameter)}$	$r_{(Parameter)}$	*P* value	$B_{(AA)}$	$r_{(AA)}$	*P* value
IGF-1	BMI[a] (kg/m^2)	−11.11	−0.31	<0.001	119.07	0.31	<0.001
	Total fat mass (kg)	−0.01	−0.28	0.002	120.24	0.31	<0.001
	SAAT (L)	−2.53	−0.02	0.818	156.73	0.22	0.030
	VAT (L)	−66.69	−0.20	0.048	127.15	0.32	<0.001
	HFF (%)	−8.76	−0.33	0.002	92.80	0.24	0.027
Log IGFBP-1	BMI[a] (kg/m^2)	−0.05	−0.32	<0.001	0.30	0.17	0.065
	Total fat mass (kg)	−0.00003	−0.32	<0.001	0.30	0.17	0.066
	SAAT (L)	−0.11	−0.22	0.028	0.88	0.24	0.016
	VAT (L)	−0.36	−0.22	0.025	0.10	0.05	0.585
	HFF (%)	−0.002	−0.17	0.873	0.19	0.10	0.366

$n = 126$.
Each model includes African Americans and Latinos. Controlled for sex, age, Tanner, soft lean tissue, total fat mass, SI, and ethnicity. All parameter estimates (β) are shown in μg/ml. The use of dummy coding (Latinos = 0 and AA = 1) yielded parameter estimates for African Americans (AA) compared to Latinos. [a]Model does not control for total fat mass in addition to other covariates.

relationship between IGF-1 and IGFBP-1 ($\beta = -9.26$, $r = -0.25$, $P < 0.01$). Interaction terms between the binding proteins and ethnicity were nonsignificant.

Partial correlations between IGF-1 and body composition/fat distribution. In our combined sample, we observed a negative parameter estimate and partial correlation between adiposity and IGF-1. IGF-1 was inversely correlated with BMI ($\beta = -11.11$, $r = -0.31$, $P < 0.001$), total fat mass ($\beta = -0.01$, $r = -0.28$, $P < 0.01$), VAT ($\beta = -66.69$, $r = -0.20$, $P < 0.05$) and HFF ($\beta = -8.76$, $r = -0.33$, $P < 0.01$) after controlling for age, gender, Tanner, soft lean tissue mass, total fat mass (where appropriate), SI, and ethnicity. In order to explore the bioavailability of IGF-1, we performed the same regression analysis on IGF-1/IGFBP-3 and found the partial correlations to reflect the same relationships seen between total IGF-1 and adiposity (data not shown).

Partial correlations between IGFBPs and body composition/fat distribution. In our combined sample of adolescents, there were negative parameter estimates and partial correlations between our measures of adiposity and log IGFBP-1. The log of IGFBP-1 was inversely correlated with BMI ($\beta = -0.05$, $r = -0.32$, $P < 0.001$), total fat mass ($\beta = -0.00003$, $r = -0.32$, $P < 0.001$), SAAT ($\beta = -0.11$, $r = -0.22$, $P < 0.05$), and VAT ($\beta = -0.36$, $r = -0.22$, $P < 0.05$) after controlling for age, gender, Tanner, soft lean tissue mass, total fat mass (where appropriate), SI, and ethnicity. There were no significant relationships between body composition/distribution variables (i.e., BMI, total fat mass, SAAT, VAT, and HFF) and IGFBP-3 (data not shown).

Partial correlations between ethnicity and IGF-1, IGF-1/IGFBP-3, or IGFBP-1. In a majority of our models, ethnicity was associated with IGF-1 and log IGFBP-1. The parameter estimates and partial correlations between ethnicity and our dependent variables revealed African Americans, compared to Latinos, had a higher predicted mean level of IGF-1 when IGF-1 was regressed on BMI ($\beta = 119.07$, $r = 0.31$, $P < 0.001$), total fat mass ($\beta = 120.24$, $r = 0.31$, $P < 0.001$), SAAT ($\beta = 156.73$, $r = 0.22$, $P < 0.05$), VAT ($\beta = 127.15$, $r = 0.32$, $P < 0.001$), and HFF ($\beta = 92.80$, $r = 0.24$, $P < 0.05$). Similar results were seen when examining the relationship between the IGF-1/IGFBP-3 ratio in place of total IGF-1.

Those of African-American ethnicity had higher levels of predicted log IGFBP-1 when log IGFBP-1 was regressed on SAAT ($\beta = 0.88$, $r = 0.24$, $P < 0.05$). Finally, African Americans showed higher mean predicted levels of IGF-1 when IGF-1 was regressed on IGFBP-1 ($\beta = 139.49$, $r = 0.35$, $P < 0.001$) and IGFBP-3 ($\beta = 143.03$, $r = 0.38$, $P < 0.001$).

In each of these models, African Americans compared to Latinos had a higher predicted mean level of IGF-1, IGF-1/IGFBP-3 molar ratio, and log IGFBP-1 in relation to adiposity after adjustment for age, gender, Tanner, soft lean tissue mass (where appropriate), total fat mass, and SI. Due to the strong associations between ethnicity and IGF measures in each model, we tested interaction terms between ethnicity and body composition/distribution variables. Tests of heterogeneity were significant in two of our models.

Ethnic difference in relationship between IGF-1 and SAAT. In the multivariate regression of IGF-1 on SAAT we found that ethnicity significantly modified the effect of SAAT on IGF-1. There was a significant interaction between SAAT × ethnicity ($\beta = 19.86$, $r = 0.20$, $P < 0.05$) after controlling for age, gender, Tanner, total lean tissue mass, total fat mass, SI, and ethnicity. Stratifying our sample by ethnicity revealed nonsignificant parameter estimates and partial correlations between SAAT and IGF-1 in Latinos ($\beta = 24.12$, $r = 0.14$, $P = 0.32$) and African Americans ($\beta = -6.91$, $r = -0.06$, $P = 0.71$). Therefore, we simplified our model containing the interaction term to yield separate regression equations for each ethnicity. Including covariates, the model for Latinos contained an intercept of 412.31 μg/ml and a parameter estimated of 7.13 μg/ml for every 1-liter increase in SAAT volume while the model for African Americans revealed an intercept of 471.40 μg/ml and a parameter estimate of 27.00 μg/ml for every 1-liter increase in SAAT volume. From these results, and all

covariates being equal, predicted mean IGF-1 levels were 30.7% higher for African Americans at the 75th compared to 25th percentile of SAAT and only 11.7% higher for Latinos at the 75th compared to the 25th percentile of SAAT.

Ethnic difference in relationship between IGFBP-1 and HFF. In the multivariate regression of log IGFBP-1 on HFF we found a significant interaction between HFF × ethnicity ($\beta = 0.19$, $r = 0.32$, $P < 0.01$) after controlling for age, gender, Tanner, total lean tissue mass, total fat mass, SI, and ethnicity. From these results, and all covariates being equal, predicted mean IGFBP-1 levels were 1.7% higher for Latinos with a HFF at the 75th percentile compared to the 25th percentile. Additionally, predicted mean IGFBP-1 levels were 158% higher for African Americans at the 25th compared to the 75th percentile of HFF. Stratifying our sample by ethnicity revealed nonsignificant parameter estimates and partial correlations between HFF and log IGFBP-1 in Latinos ($\beta = -0.0004$, $r = -0.005$, $P = 0.98$) and African Americans ($\beta = -0.13$, $r = -0.29$, $P = 0.09$).

DISCUSSION

The aims of the present study were to examine and compare the relationships between IGF-1 and its binding proteins with total fat mass, SAAT, VAT, and HFF in overweight Latino and African-American adolescents after adjusting for related covariates. We hypothesized that overweight Latino adolescents would show an inverse relationship between IGF-1, IGFBP-1, and IGFBP-3 with our dependent variables, similar to what we saw in overweight Latino children (15). Although we saw similar results for the relationship between IGF-1 and our dependent variables, we saw different results for IGFBP-1 and IGFBP-3. These results indicate that by adolescence, Latinos no longer have a significant inverse relationship between IGFBP-3 and BMI, total fat mass, SAAT, VAT, and HFF. By adolescence Latinos and African Americans showed a large and significant inverse relationship between plasma IGFBP-1 levels and these variables. We also hypothesized that overweight African-American adolescents would show results that were similar to those seen in adult studies (14). Despite this, we found that those with higher total fat mass had lower plasma IGF-1 levels, as did those with a higher BMI.

Our findings illustrate similar relationships between IGF-1 and IGFBP-1 with adiposity in Latino and African-American adolescents. Both ethnic groups showed significant inverse relationships between IGF-1 and IGFBP-1 with BMI, total fat mass, VAT, and HFF. Our results demonstrate that VAT has an inverse relationship with IGF-1 in Latinos and African Americans while SAAT has an effect on IGF-1 that is modified by ethnicity. Unique to this study, we show that IGF-1 and IGFBP-1 levels have a large inverse relationship with HFF in Latinos and African Americans and that the relationship between IGFBP-1 and HFF is modified by ethnicity.

The observed negative correlation between HFF and IGF-1, as well as IGFBP-1, suggests an association between the amount of liver fat and serum IGF-1 and IGFBP-1 levels. Since serum IGF-1 and IGFBP-1 are mainly produced in the liver (30), a higher fat content may be affecting the process in which the liver synthesizes IGF-1 and IGFBP-1. This is consistent with a previous study that was able to show an association between hepatic steatosis and IGF-1, as well as IGFBP-3, serum levels. Their results suggest a relationship between elevated liver fat and low serum IGF-1 levels and high IGFBP-3 levels (31). In addition to these correlations, we determined that ethnicity significantly decreased mean predicted levels of IGF-1 in our model containing HFF, and significantly modified the effect of HFF on predicted mean levels of IGFBP-1. These finding illustrate that, possibly as a result of higher liver fat, Latinos have lower predicted mean IGF-1 levels and higher predicted mean levels of IGFBP-1.

Alternatively, our findings appear to support ethnic differences in fat depot accumulation. Other studies have shown that Latinos have a higher HFF compared to African Americans (32). It is hypothesized that differences in fat depot accumulation stems from genetic differences in lipid storage pathways. African Americans may be able to expand SAAT stores, through proliferation and differentiation of new adipocytes, to sequester dietary lipids away from ectopic organs. The increased spillover of lipids into ectopic depots in Latinos may be explained by an impaired ability to expand their SAAT stores. Since IGF-1 appears to control the expansion of adipocytes (33), these results, in conjunction with higher total IGF-1 levels in African-American adolescents, suggest a possible mechanism in which adipocyte differentiation is impaired in Latinos.

One limitation of our study is that we did not directly analyze growth hormone levels, which, given its pulsatile secretion pattern, requires assessment over 24 h. We enrolled only overweight Latino and African-American adolescents and did not include normal weight participants. There were significant differences in fasting insulin and SI between African-American and Latino adolescents (**Table 1**) and SI was significantly correlated with IGFBP-1 ($r = 0.27$, $P < 0.05$). When controlling for HFF, SI was not significantly correlated with IGF-1 ($r = -0.04$, $P = 0.69$) but was significantly correlated with IGFBP-1 levels ($r = 0.24$, $P < 0.05$). When adjusting for our *a priori* covariates and HFF, IGF-1 and IGFBP-1 were not significantly correlated with SI ($r = -0.03$, $P = 0.77$; $r = 0.11$, $P = 0.30$). Despite the inclusion of SI as a covariate in each model, we cannot rule out the possibility that insulin insensitivity, in addition to liver fat, may be affecting the process in which the liver synthesizes IGF-1 and IGFBP-1. Since this analysis was cross-sectional, a longitudinal analysis is needed to determine if the progression of obesity and its distribution pattern affect plasma IGF-1 levels over time. Despite these limitations, our study is unique in that we utilized accurate measurements of total and regional body fat composition, direct measures of SI, and were able to compare two homogeneous samples of understudied minority adolescents.

In summary, we identified strong inverse relationships between IGF-1 and IGFBP-1 with BMI, total fat mass, VAT, and HFF in Latinos and African Americans. Additionally, we identified a modifying effect of ethnicity on the relationship

between IGF-1 and SAAT as well as IGFBP-1 and HFF. These potentially important ethnic differences were independent of age, gender, Tanner stage, total lean tissue mass, total fat mass, and SI. Our results demonstrate a larger predicted increase in African-American plasma IGF-1 levels in response to increasing SAAT compared to Latinos. In addition to this, we demonstrated that African Americans with a HFF at the 75th percentile have lower levels of IGFBP-1 while Latinos at the 75th percentile show higher IGFBP-1 levels. These findings illustrate that SAAT and HFF contribute to the higher plasma IGF-1 levels, relative to obesity, seen in African-American compared to Latino adolescents.

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DISCLOSURE

The authors declared no conflict of interest.

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