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Insulin-like Growth Factor-I is Inversely Related to Adiposity in Overweight Latino Children

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Abstract

The purpose of this study was to examine interrelationships between IGF-I, IGF binding proteins (IGFBPs) and adiposity in 178 overweight Hispanic adolescents (11.2 ± 1.7 yr; body mass index: 28.2 ± 5.4 kg/m^2). Immunoradiometric assays were used to measure IGF-I, IGFBP-1 and IGFBP-3. Total fat and lean tissue mass were measured by DEXA and visceral and subcutaneous adipose tissue by MRI. IGF-I and IGFBP-3 remained inversely correlated with total body fat mass ($r = -0.52$, $p < 0.001$ and $r = -0.25$, $p < 0.01$, respectively) after controlling for covariates. IGFBP-1 was inversely correlated to total fat mass ($r = -0.55$, $p < 0.001$) in simple correlations; however, this relationship was eliminated after controlling for covariates ($r = 0.02$, $p = 0.85$). Correlations with visceral and subcutaneous adipose tissue yielded similar results. These results demonstrate that IGF-I, IGFBP-1 and IGFBP-3 are all inversely related to adiposity in Hispanic children.

Keywords

IGF; IGFBP-1; IGFBP-3; visceral fat; obesity; children

INTRODUCTION

Obesity has been associated with various abnormalities related to the growth hormone/insulin-like growth hormone factor (IGF) system. In adults, some studies[1,2], but not all[3–5], have documented increased IGF-I levels, and a decrease in IGF binding protein (IGFBP)-1 levels[6–8], with increasing adiposity. Growth hormone and insulin mediated mechanisms have been classically used to explain these results, but any meaningful conclusions regarding race or ethnicity have yet to be drawn. Few studies have examined the relationship between IGF and both total and regional body fat in pediatric populations, although specific ethnic differences in this relationship may exist. In the pediatric population, lower IGF-I levels in

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Latinos relative to African Americans have been noted in prepubertal females[9]. Our laboratory previously demonstrated a positive relationship between IGF-I and body fatness in African-American and Caucasian children[10]. The higher level of IGF-I in African-American compared to Caucasian children was not explained by environmental factors, such as diet, body composition, socio-economic status or birth weight, but was related to the degree of African admixture, suggesting a genetic basis for this difference[10]. Studies in children may be particularly useful as these complex relationships can be examined in the absence of potentially confounding variables, such as aging, menopausal status or other diseases. The aims of this study were to: 1) examine the relationships between IGF-I and its binding proteins with total, visceral and subcutaneous fat mass in overweight Latino children, and 2) determine whether the observed relationships remained after adjusting for potential covariates, including age, gender, total lean tissue mass, insulin sensitivity, and total fat mass (where appropriate).

CHILDREN AND METHODS

Participants (n = 178, 101 males and 77 females) were recruited from Los Angeles County through medical clinics, advertisements and local schools. The current analyses include participants from year 1 of the University of Southern California Study of Latino Adolescents at Risk for Diabetes (SOLAR), a longitudinal study exploring metabolic risk factors for type 2 diabetes mellitus (DM2). Study participants satisfied the following criteria for inclusion: age- and gender-specific body mass index (BMI) >85th percentile, 8–13 years of age, positive Latino ethnicity (i.e., parents and grandparents of Latino descent), positive family history for DM2, and absence of diabetes mellitus as assessed by oral glucose tolerance test (OGTT). Participants were excluded if they were using a medication or diagnosed with a condition known to influence body composition or insulin/glucose metabolism. Prior to any testing procedure, informed written consent from parents and assent from the children was obtained. This investigation was approved by the Institutional Review Board of the University of Southern California, Health Sciences Campus. Other analyses from this cohort have been previously reported[11–14].

Study protocol

Outpatient visit—Participants arrived at the USC General Clinical Research Center (GCRC) at 08.00 h after an overnight fast. A comprehensive medical history and physical examination was performed, including anthropometry by a licensed health care provider. Following the examination, an oral glucose tolerance test (OGTT) was performed to determine eligibility for the study. Participants ingested 1.75 g oral glucose solution/kg body weight (to a maximum 75 g). Blood was sampled and assayed for glucose and insulin at −5 min (‘fasting’) and 120 min (‘2-hour’).

In-patient visit—Approximately 7–14 days following the outpatient visit, participants were admitted to the USC GCRC at ~13.00 h for an in-patient hospital visit. Body composition (total fat mass and total lean tissue mass) were determined by a whole-body dual-energy X-ray absorptiometry (DEXA) scan using a Hologic QDR 4500W (Bedford, MA). Central fat distribution was measured directly by magnetic resonance imaging (MRI)

at the LAC/USC Imaging Science Center using a General Electric 1.5 Signa LX-Echospeed device with a General Electric 1.5-Tesla magnet (Waukesha, WI). 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 adipose tissue and subcutaneous adipose tissue[15].

Frequently-sampled intravenous glucose tolerance test (FSIVGTT)—Following body composition measurements, participants were served dinner and a snack prior to 20.00 h, which marked the beginning of the overnight fast. Water was permitted during this period. At 06.30 h the following morning, intravenous catheters were placed in the antecubital area of both arms. To assess basal insulin and glucose concentrations, two fasting blood samples were taken at −15 and −5 min. At time 0, glucose was administered intravenously over a one-minute period. Subsequent blood samples were collected at 2, 4, 8, and 19 min. Insulin (0.02 U/kg body weight; Humulin®; Eli Lilly, Indianapolis, IN, USA) was administered intravenously at 20 min, followed by blood sample collection at 22, 30, 40, 50, 70, 100, and 180 min. Plasma was analyzed for glucose and insulin concentrations and results were then entered into MINMOD Millennium 2003 software (version 5.16; RN Bergman, Los Angeles, CA) for calculation of insulin sensitivity and acute insulin response (AIR) (a measure of insulin area under the curve above basal for the first 10 min of the FSIVGTT).

Laboratory assays

Blood samples taken during the OGTT were separated for plasma and immediately transported on ice to the Los Angeles County-USC Medical Center Core Laboratory where glucose was analyzed on a Dimension clinical chemistry system using an *in vitro* hexokinase method (Dade Behiring, Deerfield, IL). Blood samples collected during the FSIVGTT were centrifuged immediately for 10 min at 2,500 RPM and 8–10°C to obtain plasma aliquots, which were then frozen at −80°C until required for assay. Glucose was assayed using a Yellow Springs Instruments analyzer (YSI Inc., Yellow Springs, OH) that uses a membrane bound glucose oxidase technique. Insulin was assayed using a specific human insulin enzyme-linked immunosorbent assay kit from Linco (St. Charles, MO) (intra-assay coefficient of variation [CV] 4.7–7.0%, interassay CV 9.1–11.4%, and cross-reaction with human proinsulin 0%). IGF-I, IGFBP-1 and IGFBP-3 concentrations were determined using two-site coated tube immunoradiometric assay (IRMA) kits (Active, Diagnostic Systems Laboratories, Webster, TX), according to the manufacturer's instructions. Samples were all assayed in duplicate for IGF-I (intra-assay CV: 8.2%, interassay CV: 11.3%), IGFBP-1 (intra-assay CV: 6.8%, interassay CV: 11.4%), and IGFBP-3 (intra-assay CV: 7.0%, interassay CV: 3.6%). Minimal detection limits for IGF-I, IGFBP-1 and IGFBP-3 were 2.06, 0.33, and 0.50 ng/ml, respectively.

Statistical analysis

The total sample size of 178 participants was used for descriptive analysis. Mean variable differences by Tanner stage were analyzed by a general linear model (GLM). Simple correlations assessed the relationship of IGF-I, IGFBP-1, and IGFBP-3 to total body fat mass, and visceral and subcutaneous adipose tissues. Adjusted partial correlation analysis was used to re-examine these relationships while controlling for age, gender, total lean tissue mass, total fat mass, and insulin sensitivity. Tanner stages were divided into groups as

follows: Tanner 1, Tanner 2, and Tanner 3–5. Tanner 3, 4 and 5 were combined into one group due to smaller sample sizes in these groups and no differences in insulin sensitivity between Tanner stage 3, 4 or 5. In instances in which age was used as a covariate, Tanner stage was also used and no significant differences were noted; hence, age rather than Tanner stage was reported as a covariate in all subsequent regression analyses. Multivariate regression models were used to test whether the independent variables (total body fat mass, visceral and subcutaneous adipose tissue) were significant contributors to the variance in the measures of IGF-I, IGFBP-1, and IGFBP-3, independent of covariates. Data were analyzed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL), with an *a piori* significance level set at $p < 0.05$. Data reported are means ± SD.

RESULTS

Physiological and metabolic parameters

Table 1 displays the mean physical characteristics and blood parameters of the 178 Latino male and female children derived from the inpatient visit. Unadjusted GLM analyses revealed statistically significant differences by Tanner stage. Statistically significant increasing trends (all at least <0.05) were observed in all parameters except total percent fat, visceral fat, fasting insulin, fasting glucose, and AIR.

Simple and partial correlations between IGF proteins and regional adiposity

Simple and partial correlations between IGF-I, IGFBP-1, and IGFBP-3 to total body fat mass are shown in Table 2. Total body fat mass was positively correlated with IGFBP-3 ($r = 0.17$, $p < 0.05$), but not with IGF-I ($r = 0.09$, $p = 0.24$). However, after adjusting for covariates (age, gender, total lean tissue mass, and insulin sensitivity) IGF-I was inversely correlated with total fat mass ($r = -0.52$, $p < 0.001$) (Fig. 1 A) as was IGFBP-3 ($r = -0.25$, $p < 0.01$). IGFBP-1 was inversely correlated to total fat ($r = -0.55$, $p < 0.001$); however, this relationship was eliminated after controlling for covariates, including insulin sensitivity ($r = 0.02$, $p > 0.05$).

IGF-I was negatively correlated with visceral adipose tissue ($r = -0.22$, $p < 0.01$) (Table 2), which was strengthened once adjusted for covariates ($r = -0.37$, $p < 0.001$) (Fig. 1B). Adjusted partial correlations also revealed a negative relationship of IGF-1 with subcutaneous adipose tissue ($r = -0.17$, $p < 0.05$). Similarly, IGFBP-3 was inversely related with both visceral adipose tissue (VAT) ($r = -0.17$, $p < 0.05$) and subcutaneous adipose tissue (SAT) ($r = -0.15$, $p < 0.05$) when adjusted for covariates. The negative relationship between IGFBP-1 to both VAT ($r = -0.43$, $p < 0.001$) and SAT ($r = -0.51$, $p < 0.001$) was diminished after the addition of covariates (VAT: $r = -0.14$, $p = 0.06$; SAT: $r = 0.02$, $p > 0.05$).

Multivariate regression analysis for body composition and IGF proteins

Multivariate regression analysis was used to assess the relationship of the independent variables of total body fat mass, VAT and SAT with the dependent variables of IGF-I, IGFBP-3, and IGFBP-1 (Table 3). With each progressive model, these analyses revealed an increasingly negative association between IGF-I and total fat mass, with the final cumulative model showing the strongest negative relationship ($\beta = -0.65$, $p < 0.001$). The predominate

binding protein, IGFBP-3. followed the same pattern with each cumulative covariate (model 3, β = −0.35, p <0.01). IGFBP-1 was also inversely related to total fat mass in models 1 and 2, yet this association was eliminated after controlling for insulin sensitivity (model 3). No significant changes in the relationships were noted when adjusting for fasting insulin or AIR instead of insulin sensitivity (data not shown). The inverse relationship with VAT remained the same after addition of all five covariates in model 4 (β = −0.33, p <0.001). As with total fat, the inverse relationship of IGF-I with SAT was strengthened as covariates were added to the model (β = −0.29, p <0.05). Analyses of IGFBP-3 with VAT revealed a significant inverse relationship only after adjustment for all covariates (β = −0.19, p <0.05). IGFBP-1 was significantly inversely related to both VAT and SAT; however, with the addition of insulin sensitivity (and then with total fat mass) IGFBP-1 was no longer inversely associated with regional adiposity (β = −0.16, p <0.05 and β − 0.04, p >0.05, respectively). All of these associations remained when adjustment was made for fasting insulin or AIR instead of insulin sensitivity (data not shown).

DISCUSSION

The aims of the present study were to examine the relationships between IGF-I and its binding proteins with total, visceral and subcutaneous fat mass in overweight Latino children, and to determine whether the observed relationships remained after adjusting for related covariates. IGF-I and IGFBP-3 were inversely related to total fat mass in overweight Hispanic youth, and this relationship remained significant after controlling for age, gender, total lean tissue mass, and insulin sensitivity. Our findings may be explained, in part, by ethnic-related genetic differences[16,17], insulin-mediated mechanisms[18], and/or growth hormone-mediated mechanisms[18–20].

Our findings appear to support ethnic differences in the IGF/adiposity axis in the pediatric population. Several prior studies have reported, contrary to the current results, positive correlations between total body fat and IGF-I concentrations in Caucasian children[21,22]. Our laboratory previously reported a positive relationship between IGF-I and total body fat mass (r = 0.35) in African-American and Caucasian children. Furthermore, IGF-I concentrations were significantly higher in African-American compared to Caucasian prepubertal children[10]. This observed ethnic difference in IGF-I was not related to psychosocial behaviors, obesity, or social status, but instead was explained by genetic admixture[10]. Additionally, unpublished observations (P.B. Higgins *el al.*) demonstrated that IGFBP-1 and IGFBP-3 were lower and IGF-I was higher in African-American children than their European-American counterparts. The results suggest that ethnic differences exist in IGF-I/adiposity relationships.

Support for ethnic differences in adult studies include a multi-ethnic study which demonstrated IGF-I levels were lower in Latina women compared to African-American women[23]. In addition, a more recent study reported a negative relationship between IGF-I and BMI in Latinos and a positive association in African-Americans[24]. This support, in conjunction with the pediatric findings, could lead us to believe that genetic variants may be contributing to the ethnic differences observed. Studies describing the IGF-I CA 19/19 allele repeat have found this genotype to be related to lower levels of circulating IGF-I[16], and the

IGF-I $(CT)_n$ repeat polymorphism influences changes in lean mass with aerobic exercise training[17]. Most recently, a multi-ethnic study discovered that circulating IGFBP-3 was associated with inherited variation of IGFBP-3[25]. It is plausible that if genetic polymorphisms such as these were found with higher frequency in the Latino population, they may authenticate our findings. However, no studies have confirmed this link between ethnic-related IGF genetic mechanisms with adiposity.

Insulin-mediated mechanisms may also contribute to the current findings, specifically the relationship between IGFBP-1 and adiposity. Insulin sensitivity is inversely related to IGFBP-1, thus the low IGFBP-1 in Latinos may be a reflection of their low insulin sensitivity, and may explain the inverse relationship between adiposity and IGFBP-1. However, decreased hepatic IGFBP-1 is associated with elevated free IGF-I[1,7,26]. Despite these mechanisms providing possible insight into the pathophysiology of our findings, we still do not understand why the Latino children in this study, who are overweight and profoundly insulin resistant, exhibit low IGF-I.

Regional adiposity was also analyzed in addition to total fat mass, and parallel findings were observed between IGF-I and IGFBP-3 with SAT and VAT masses. Free of obesity-related complications of the adult population, our results demonstrate that VAT has a more robust inverse relationship with IGF-I than does SAT, a novel finding in youth. Marin *et al.*[27] observed lower concentrations of IGF-I with increasing visceral adiposity, as did a study of Japanese overweight males[28]. Metabolic differences have been found between VAT and SAT, suggesting that any metabolic relationships of the IGF axis and abdominal adiposity in adults may already exist in children.

Obesity is associated with reduced levels of growth hormone, a key regulator of circulating IGF-I and IGFBP-3[29]. The observed inverse relationships between IGF-I and IGFBP-3 with adiposity may be explained by higher IGF-I produced through negative pituitary feedback on growth hormone secretion[19,20]. Obese individuals exhibit increased hepatic growth hormone sensitivity, secondary to increased growth hormone binding protein[30], which may affect the levels of free IGF-I. As the reliability of determining free IGF-I has been questioned[31], we chose not to directly evaluate the relationship between free IGF-I and adiposity, and instead used a surrogate of free IGF-I, the IGFBP-3 to IGF-I ratio (data not shown). This revealed the same relationships as observed with total IGF-I. However, our results regarding IGFBP-3 do appear reasonable, as the majority of circulating IGF-I is bound to IGFBP-3, explaining any concomitant results of IGF-I and IGFBP-3.

Several limitations of our study arc acknowledged. We did not directly analyze growth hormone levels, which, given its pulsatile secretion pattern, requires assessment over 24 hours. We enrolled only overweight Latinos and did not include different ethnic groups or normal weight children. Given the discordance in findings from prior studies in the pediatric population[9], additional studies including lean Latino children and other ethnicities are needed. Since the study was cross-sectional, a longitudinal analysis is needed to investigate whether the progression of obesity affects IGF-I levels over time. Despite these limitations, our study is strengthened by the use of accurate measures of total and regional body

composition, direct measures of insulin sensitivity, and a large homogeneous sample of understudied minority youth.

In summary, we identified strong inverse relationships between IGF-I and IGFBP-3 with total fat and visceral adipose tissue, independent of age, gender, total lean tissue mass, or insulin sensitivity, in overweight Latino children. This potentially important ethnic difference may contribute to differences in future IGF axis-related disease risk. Additional studies exploring the significance and clinical implications of ethnic differences in the IGF-I/adiposity relationship are warranted.

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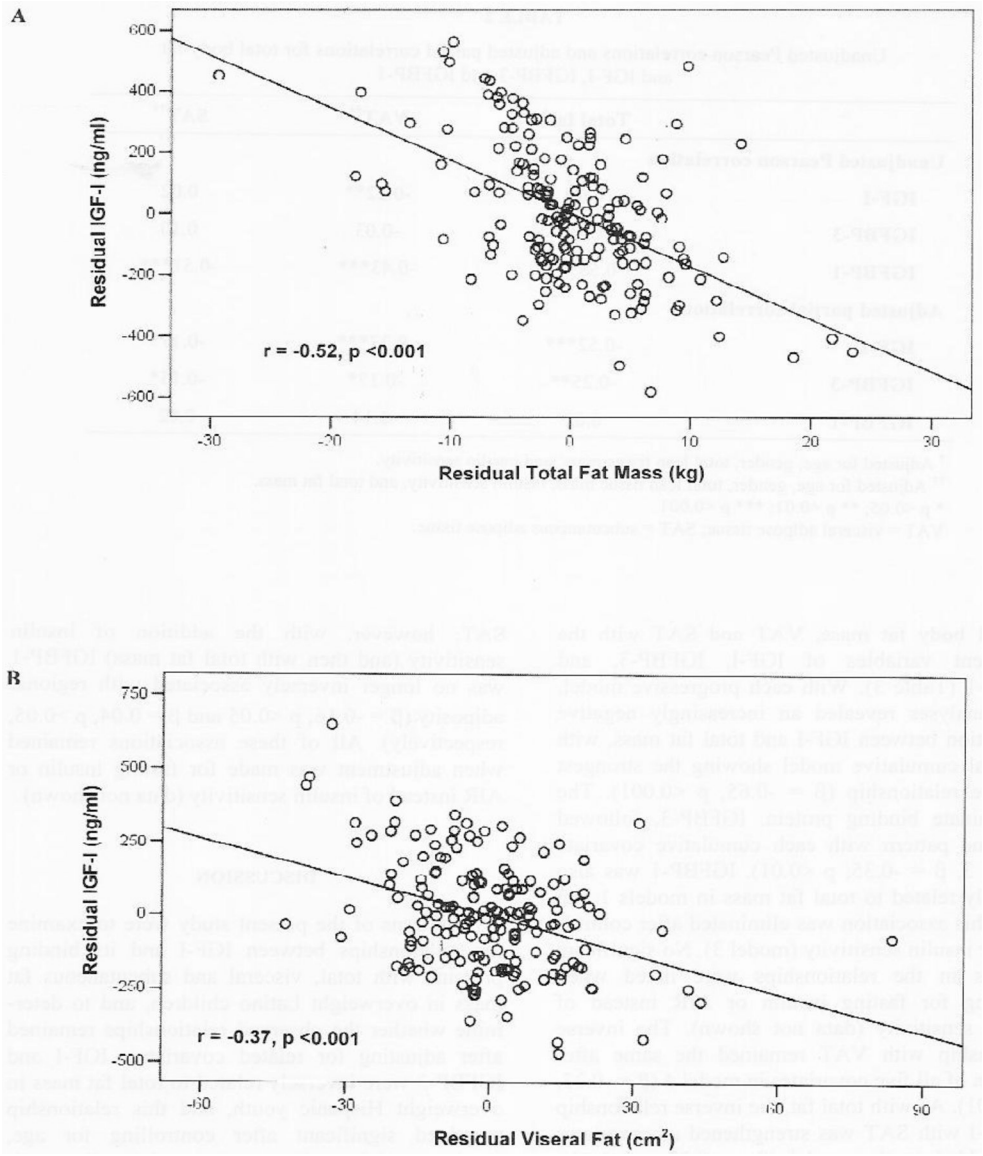

Fig. 1:

A. Partial regression plot of relationship between IGF-I and total fat mass of total sample, controlling for age, gender, total lean tissue mass and insulin sensitivity ($r = -0.50$, $p < 0.001$). **B.** Partial regression plot of relationship between IGF-I and VAT of total sample, controlling for age, gender, total lean tissue mass, total fat mass and insulin sensitivity ($r = -0.37$, $p < 0.001$).

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TABLE 1

Physical characteristics and metabolic parameters

	Total Sample (n = 78)	Tanner 1 (n = 68)	Tanner 2 (n = 57)	Tanner 3–5 (n = 53)
Age (years)	11.2 ± 1.7	9.9 ± 1.4††	11.3 ± 1.5	12.6 ± 0.9
Weight (kg)	63.9 ± 19.3	54.2 ± 14.4††	63.0 ± 19.8	77.1 ± 16.9
Height (cm)	148.9 ± 11.3	141.1 ± 8.9††	148.5 ± 9.7	158.8 ± 7.8
Body mass index (kg/m^2)	28.2 ± 5.4	26.6 ± 4.7†	28.0 ± 5.9	30.4 ±5.1
Total fat mass (kg)	24.8 ± 10.2	21.4 ± 8.2††	24.9 ± 11.0	29.1 ±10.2
Total lean tissue mass (kg)	36.6 ± 10.1	30.8 ± 6.5††	35.7 ± 9.1	45.2 ±9.1
Total fat (%)	38.6 ± 6.6	39.1 ± 5.4	39.0 ± 6.7	37.5 ± 7.7
Total trunk Fat (kg)	12.2 ± 5.3	10.3 ± 3.9††	12.1 ± 5.6	14.6 ±5.6
Subcutaneous fat (cm^2)	336.0 ± 148.1	301.2 ± 139.2†	331.9 ± 147.7	385.0 ± 149.0
Visceral fat (cm^2)	47.5 ± 20.9	46.2 ± 19.4	48.0 ± 21.5	48.8 ± 22.4
Fasting insulin (μU/ml)	19.3 ± 9.7	16.1 ± 7.9	19.3 ± 9.6	23.5 ± 10.5
Fasting glucose (mg/1)	93.3 ± 6.3	92.8 ± 5.8	94.7 ± 5.3	92.5 ±7.4
Insulin sensitivity [(×10^{-4}/min^{-1})/(μU/ml)]	2.1 ± 1.4	2.6 ± 1.6††	2.1 ± 1.2	1.5 ± 1.1
Disposition index (×10^{-4}/min^{-1})	2,611.5 ± 1,185.0	3,027.1 ± 1,217.7††	2,531.9 ± 1,270.3	2,164.0 ±833.4
Acute insulin response (μU/ml)	1,710.8 ± 1,165.5	1,624.9 ± 1,171.9	1,598.5 ± 1,113.9	1,941.8 ± 1,200.0
IGF-I (ng/ml)	477.0 ± 271.4	286.6 ± 125.4††	444.1 ± 248.4	756.8 ± 189.0
IGFBP-1 (ng/ml)	16.1 ± 14.5	22.4 ± 16.7††	15.3 ± 11.1	8.8 ± 11.0
IGFBP-3 (ng/ml)	3,987.3 ± 801.9	3,625.0 ±715.2††	3,920.1 ± 759.4	4,524.4 ± 662.1

Data values are means ± SD.

† p <0.05;

†† p <0.01;

††† p <0.001 - general linear model (GLM) for Tanner stage.

TABLE 2

Unadjusted Pearson correlations and adjusted partial correlations for total body fat and IGF-I, IGFBP-3 and IGFBP-1

	Total fat†	VAT††	SAT††
Unadjusted Pearson correlation			
1GF-I	0.09	−0.22**	0.02
IGFBP-3	0.17*	−0.03	0.10
IGFBP-1	−0.55***	−0.43***	−0.51***
Adjusted partial correlation			
IGF-I	−0.52***	−0.37***	−0.17*
IGFBP-3	−0.25**	0.17*	−0.15*
IGFBP-1	0.02	−0.14	0.02

† Adjusted for age, gender, total lean tissue mass, and insulin sensitivity.

†† Adjusted for age, gender total lean tissue mass, insulin sensitivity, and total fat mass.

* p <0.05;

** p <0.01;

*** p <0.001.

VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue.

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TABLE 3

Multivariate linear regression of IGF-I, IGFBP-3, and IGFBP-1 with total fat mass, visceral adipose tissue (VA T) and subcutaneous adipose tissue (SAT)

	Total fat mass			VAT			SAT		
	Cumulative R^2	Beta	SE	Cumulative R^2	Beta	SE	Cumulative R^2	Beta	SE
IGF-I									
Model 1	0.33	−0.22**	0.002	0.39	−0.32***	0.781	0.33	−0.22**	0.123
Model 2	0.52	−0.61***	0.002	0.53	−0.47***	0.740	0.52	−0.56***	0.129
Model 3	0.52	−0.65***	0.002	0.53	−0.49***	0.775	0.52	−0.58***	0.136
Model 4	–	–	–	0.59	−0.33***	0.837	0.54	−0.29*	0.241
IGFBP-3									
Model 1	0.11	0.02	0.006	0.11	−0.09	2.780	0.11	−0.03	0419
Model 2	0.21	−0.27**	0.008	0.21	−0.21**	2.830	0.22	−0.29**	0.486
Model 3	0.22	−0.35**	0.008	0.24	−0.28***	2.919	0.25	−0.37***	0.501
Model 4				0.26	−0.19*	3.336	0.25	−0.33*	0.907
IGFBP-1									
Model 1	0.35	−0.43***	0.000	0.33	0.36***	0.044	0.34	−0.39***	0.007
Model 2	0.41	−0.21*	0.000	0.44	−0.23***	0.043	0.41	−0.18*	0.008
Model 3	0.51	−0.07	0.000	0.63	−0.08	0.037	0.63	0.02	0.006
Model 4	–	–	–	0.63	−0.16	0.043	0.63	0.04	0.012

Independent variables are adjusted sequentially for age, gender, total lean tissue mass, and insulin sensitivity.

* p <0.05;

** p <0.01;

*** p <0.001.

Model 1: Adjusted for age and gender as covariates.

Model 2: Adjusted for age, gender, and total lean tissue mass as covariates.

Model 3: Adjusted tor age, gender, total lean tissue mass, and insulin sensitivity as covariates.

Model 4: Adjusted for age, gender, total lean tissue mass, insulin sensitivity, and total fat mass as covariates.