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Insulin-like growth factor-I and insulin-like growth factor binding protein-1 are related to cardiovascular disease biomarkers in obese adolescents

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Abstract

Context—Insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-1 have been linked to cardiovascular disease (CVD) risk and pathophysiology in adults, but there are limited data in youth.

Objective—The aim of the study was to examine the relationship between IGF and IGFBP-1 with traditional and non-traditional CVD risk factors including inflammatory markers and body composition in an obese pediatric cohort.

Design—A cross-sectional study.

Setting—The study was carried out at a university children's hospital.

Subjects—Sixty-one obese non-diabetic adolescents.

Outcomes—Fasting IGF-I, IGFBP-1, lipoprotein profiles, high-sensitivity C-reactive protein (hsCRP), and total adiponectin as well as insulin sensitivity measures, blood pressure (BP), and anthropometrics.

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Conflict of interest

K. A. G., P. A., P. C. B., P. R. G., L. J. B., T. L., and D. K. have nothing to declare. L. L. K. consults for Janssen Pharmaceuticals and Takeda Pharmaceuticals.

Results—IGFBP-1 was negatively associated with insulin sensitivity measures, body mass index (BMI), and diastolic BP in males. IGF-I was negatively associated with hsCRP ($r = -0.479$, $p < 0.0005$), and IGFBP-1 was positively associated with adiponectin ($r = 0.545$, $p < 0.0005$). The IGF-I/CRP and IGFBP-1/adiponectin associations remained significant when controlling for both BMI and insulin sensitivity index (S_I). Both IGF-I and IGFBP-1 were negatively associated with waist circumference ($r = -0.327$ and $r = -0.275$, respectively) and sagittal abdominal diameter ($r = -0.333$ and $r = -0.371$, respectively), while IGFBP-1 was negatively associated with fat mass ($r = -0.347$, $p = 0.01$) as well as neck circumference and fat-free mass in males. Controlling for BMI z-score and S_I, IGFBP-1 remained negatively associated with diastolic blood pressure ($r = 0.706$, $p = 0.001$ and neck circumference ($r = -0.548$, $p = 0.15$) in males.

Conclusions—IGF-I and IGFBP-1 associate with CVD risk markers and may add to clinical assessments of cardiometabolic dysfunction in youth.

Keywords

adiponectin; CVD risk factors; IGF-I; IGFBP-1; neck circumference

The prevalence of cardiovascular disease (CVD) in children is expected to rise in parallel to increased pediatric obesity. As subclinical atherosclerosis begins in childhood, attempts at disease prevention must include early risk assessment. Derangements in insulin-like growth factor (IGF) axis components have been associated with CVD risk factors, including increased body mass index (BMI) in adults and youth and may represent novel biomarkers of cardiovascular risk (1, 2). IGF-I, synthesized predominantly in the liver in response to growth hormone (GH) stimulation, mediates the anabolic effects of GH in target tissues (3). Acute IGF-I bioavailability is regulated through direct binding of IGFBP-1, a small peptide whose synthesis is directly suppressed by insulin (4). Low serum IGF-I is associated with increased risk of ischemic heart disease in adults. One large prospective study reported that low IGF-I levels in adults predicted a relative risk of 1.94 (95% CI, 1.03–3.66) for ischemic heart disease during a 15-yr follow-up (5), while a population-based study from the Netherlands has reported a U-shaped association between IGF-I levels and CVD prevalence in older adults (1). In non-diabetic subjects, low IGFBP-1 levels have been linked with features of the metabolic syndrome in adults (6) and adolescents (2), whereas higher IGF-I levels seem to protect against endothelial dysfunction and early coronary artery disease in adults (7, 8). Such reports suggest IGF-axis perturbations relate to CVD risk and may thus aid in risk characterization.

The IGF axis may also associate with cardiometabolic risk through effects from systemic inflammation and adipocyte dysfunction – known CVD risk contributors. Among the most investigated biomarkers of systemic inflammation and adipocyte dysfunction are C-reactive protein (CRP) and adiponectin. CRP, an acute-phase reactant whose synthesis in hepatocytes is upregulated by the cytokines interleukin (IL)-6 (9) and tumor necrosis factor (TNF)-α, is a strong CVD risk predictor (10). CRP can also stimulate endothelial production of IL-6 (11). In turn, IGF-I levels are reduced by IL-1 and -6 and TNF-α, either by suppressing GH secretion (12) or by inducing GH resistance (13). Conversely, adiponectin is an insulin sensitizer that exhibits anti-inflammatory and anti-atherogenic properties (14) in part through the suppression of CRP (15). There is considerable crosstalk between CRP and

adiponectin-mediated processes. A cross-sectional study evaluating IGF-I/IGFBP-1 levels and inflammatory markers in non-diabetic adults demonstrated that low IGF-I and IGFBP-1 levels along with CRP levels in the highest tertile correlated with the development of metabolic syndrome and associated CVD (16). Few studies of IGF-I and IGFBP-1 in relation to CV risk markers in youth have been performed, and these are limited to a study of Chinese youth (17) and a European weight loss trial (2). There is also a dearth of studies of IGF-I/IGFBP-1 relationships with non-traditional CV risk markers such as hsCRP and adiponectin.

We have previously evaluated an obese adolescent cohort, examining the impact of obstructive sleep apnea syndrome (OSAS) and other sleep disturbances upon glucose homeostasis (18), suggested by evidence that OSAS may increase diabetes (19) and CVD risk (20). Growth factors may be implicated in the association between OSAS and cardiometabolic risk, as OSAS is associated with GH deficiency and low IGF-I levels (21). In this current analysis, we examined the relationships of IGF-I and IGFBP-1 with traditional CV risk factors measure in the study (lipids, blood pressure, and BMI), adiposity measures, and non-traditional CVD risk factors (CRP and adiponectin). Traditional markers are part of recommended guidelines, and the other markers may assist in risk identification by identifying estimates of visceral fat as well as inflammation. We hypothesized that IGF-I and IGFBP-1 would associate negatively with traditional CVD risk measures and measures of body fat, negatively with CRP, and positively with adiponectin, the primary protective biomarker.

Subjects and methods

Obese subjects were recruited from the Endocrine Assessment Clinic at the Children's Hospital of Philadelphia (CHOP) and admitted to the Clinical and Translational Research Center (CTRC) for a 2-d overnight assessment after consents/assents were obtained as part of a CHOP Institutional Review Board (IRB)-approved protocol. Medical history was obtained, and physical examination was performed, including Tanner staging based on breast development for girls and genitalia for boys (22, 23). After an overnight fast, subjects underwent an oral glucose tolerance test (OGTT), ingesting oral glucose solution (1.75 g/kg, maximum 75 g) with samples for glucose and insulin drawn at −10, 0, 10, 30, 60, 90, 12, 150, and 180 min. Two subjects of the original cohort of 63 were determined to have diabetes mellitus upon completion of the OGTT and were excluded from the current analysis, leaving 61 evaluated subjects.

Anthropometrics and blood pressure

Anthropometric measurements were assessed as follows: Weight was measured using a digital scale (Scaletronix, White Plains, NY, USA) and height using a wall-mounted stadiometer (Holtain Inc., Crymych, UK). BMI was calculated as weight in kilograms divided by squared height in meters. BMI percentiles and z-scores were assessed using age- and gender-specific reference data (24). Waist circumference (WC) was obtained with subject standing at end expiration (25), with tape measure in horizontal plane at narrowest part of torso as seen from anterior; hip circumference (HC) was measured around maximum

circumference of buttocks, and waist-hip ratio (WHR) was calculated. Abdominal height, also known as sagittal abdominal diameter, was measured with subject supine, knees at 45° angle, and feet flat on exam table. Abdominal caliper blades (Holtain Ltd, Crymych, UK) were placed above abdomen (just above iliac crest) and below back; distance between blades was measured at end expiration (26, 27). Neck circumference was measured immediately inferior to the laryngeal prominence and perpendicular to the neck's long axis (28). Procedures for each anthropometric measurement were completed in triplicate and then averaged to create a single data point. Body composition analysis was performed by DXA (Hologic QDR2000, Hologic, and Waltham, MA, USA); fat mass and fat-free mass were assessed. [Note: four subjects did not complete body composition analysis as their weight (>136 kg) exceeded the limit of the DXA table.] Blood pressure (BP) was also assessed in triplicate using a calibrated automated meter with an appropriately sized cuff (Dinamap V100, GE Healthcare, Little Chalfont, UK) and was then averaged.

Following these procedures, subject underwent an overnight polysomnogram in the Sleep Laboratory. Overnight polysomnography was performed the night between the OGTT and the FSIGT. Sleep architecture (N1, N2, N3, and REM sleep stages) and respiratory disturbances respiratory parameters were scored using standard pediatric criteria (18).

The morning following the polysomnogram (PSG), subjects underwent an abbreviated frequently sampled intravenous glucose tolerance test (FSIGT), infusion of 0.25 g/kg of 25% dextrose IV over 30 s, an IV infusion of regular human insulin (0.015 units/kg) over 5 min at t = 20 min, and drawing of blood samples for glucose and insulin at t = −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min (29). The MINMOD Millenium software program (30) was employed to estimate indices of glucose and insulin dynamics. Both OGTT and FSIGT were performed because the latter was believed to be a better measure of insulin sensitivity and secretion as compared the gold standard hyperinsulinemic euglycemic clamp, while the former accounts for the incretin effect as well as enabling the diagnosis of prediabetes and type 2 DM.

Calculated insulin sensitivity and secretion parameters:

A. OGTT:

1. Homeostasis model assessment of insulin resistance (HOMA-IR) is a validated measure of insulin sensitivity (31), calculated as follows: HOMA-IR = [Fasting plasma insulin (FPI, in μIU/mol) × Fasting plasma glucose (FPG, in mmol/L)]/22.5.
2. Whole body insulin sensitivity index (WBISI) is an insulin sensitivity measure that has been validated in obese children and adolescents (32), calculated as follows:

$$\mathrm{WBISI}=\frac{10\,000}{\sqrt{(\text{fasting glucose}\times\text{fasting insulin})\times(\text{mean glucose}\times\text{mean insulin})}}$$

B. IVGTT: The FSIGT utilized in this study was the insulin-modified version, as published in the Insulin Resistance Atherosclerosis Study (IRAS). Researchers in

this study found that 11 samples (reduced from 18) were sufficient to produce effective results (29).

Sensitivity to insulin (S_I) is a parameter calculated from serial insulin and glucose values during the IVGTT (30).

Laboratory analysis

All blood samples were acquired following an overnight fast. Lipoprotein profiles were determined through standard clinical assays for total cholesterol, triglycerides (TG), and high-density lipoprotein (HDL)-cholesterol (VITROS 950 Chemistry Analyzer, Ortho-Clinical Diagnostics, Rochester, NY, USA). Low-density lipoprotein (LDL)-cholesterol was calculated by using the Friedwald equation.

The following were assayed using available enzyme-linked immunosorbent assay (ELISA) kits through the CHOP CTRC Biochemistry Core Laboratory:

- **i.** Total IGF-I, detection range 10–600 ng/mL (DSL Inc., Webster, TX, USA).
- **ii.** Total IGFBP-1, detection range 0.5–160 ng/mL, sensitivity 0.25 ng/mL (DSL Inc., Webster, TX, USA).
- **iii.** High-sensitivity-CRP (hsCRP) (ALPCO, Wind-ham, NH, USA) detection range 1.9–150 ng/mL, sensitivity 0.124 ng/mL.
- **iv.** Total adiponectin (ALPCO, Salem, NH, USA), detection range 0.375–12 ng/mL, sensitivity 0.234 ng/mL.

Statistical analysis

Statistical analyses were performed using SPSS v 16 and SPSS v17.0 (SPSS Inc., Chicago, IL). Histograms and Kolmogorov–Smirnov (K–S) one-sample tests examined normality of distribution. Descriptive statistics, including mean, and standard deviation (SD) for normally distributed variables and medians with minimum–maximum range for skewed variables (those with data sets that failed the K–S test) were generated. The natural log transformation was then applied to the data of skewed variables which were re-examined for normal distribution. Cohort gender and racial data were compared to chi-squared distribution. Measured outcomes were assessed for gender differences using Student's t-test, since log-transformation was able to normalize the distributions of all skewed variables.

Pearson correlations were used (on log transformed data when necessary) to examine the association between parameters of interest, e.g., IGF-I and IGFBP-1 levels with CVD risk factors and adiposity measures. We examined associations of IGF-I and IGFBP-1 with other potential covariates/confounders, including gender, race (AA vs. others), Tanner stage for breast and genitals, and BMI z-score. The sample size of 61 limited our ability to construct a model to evaluate all potential confounders. As such, we utilized partial correlations to examine the strength of significant relationships controlling for variables which were found to have significant association using correlation analysis. Simple linear regression analyses confirmed the form of significant correlations. The original aim of the study was powered to evaluate the relationships of sleep parameters with glucose homeostasis; this current analysis

of relationships between IGF-I and IGFBP-1 with CVD biomarkers is considered exploratory, with no adjustment for multiple testing. Statistical significance was conferred for type I error rates below 0.05 throughout the analysis.

Results

Table 1 summarizes this cohort. Most subjects were in late puberty (Tanner stages 4 or 5), African American and female. Mean characteristics revealed subjects to be between the 95th and 99th percentile for BMI, with lipid profiles within normal limits, and normotensive. Mean WC indicated the presence of central obesity, with measurements well above normative values listed for the IDF Consensus Statement on pediatric metabolic syndrome (33). Gender differences were seen for racial distribution, measurements of weight, systolic and diastolic blood pressure, neck circumference, and fat-free mass.

IGFBP-1 was strongly associated with all measures of insulin sensitivity examined, including fasting insulin ($r = -0.567$, $p < 0.0005$), homeostatic model assessment-insulin resistance (HOMA-IR) ($r = -0.560$, $p < 0.0005$), WBISI ($r = 0.571$, $p < 0.0005$), and insulin sensitivity index (S_I) ($r = 0.495$, $p = 0.001$) (Table 2A). Partial correlation analyses controlling for degree of obesity by BMI z-score revealed that the relationships with insulin sensitivity remained significant ($r = -0.5302$, -0.5320, 0.5921, respectively, $p < 0.0005$ and for S_I, $r = 0.372$, $p = 0.014$). The directions of these associations all point to a positive relationship between IGFBP-1 and insulin sensitivity. IGF-I was not significantly associated with any measure of insulin sensitivity (data not shown). We did not find significant associations of IGF-I and IGFBP-1 with race, gender, or Tanner stage for breasts and testes (data not shown).

Results of correlation analyses examining the relationships between IGF-I and IGFBP-1 with traditional markers of CVD risk markers are shown in Table 2B. CV outcomes that displayed gender differences in Table 1 were analyzed separately. The analyses revealed significant negative relationships between IGFBP-1 and, and multiple obesity measures. IGFBP-1 showed negative relationships with diastolic blood pressure in males. IGF-I was not significantly associated with any traditional CVD risk measure examined. Correlations between IGF-I and IGFBP-1 – with anthropometrics – are reported in Table 2C. Both IGF-I and IGFBP-1 were negatively associated with WC and sagittal abdominal diameter. IGFBP-1 was also negatively associated with fat mass across the entire cohort and neck circumference and fat-free mass in males. When partial correlation analysis was performed to control for BMI z-score and S_I (from the IVGTT), the relationships of WC and sagittal abdominal diameter with IGFBP-1 in Table 2B, C were no longer significant, indicating that the associations were due to insulin sensitivity. In males, the relationships of IGFBP-1 with diastolic blood pressure ($r = 0.706$, $p = 0.001$) and neck circumference ($r = -0.548$, $p = 0.015$) remained significant after controlling for BMI z-score and S_I.

The growth factors were highly associated with the serum markers of CVD risk examined (e.g., increased hsCRP and decreased adiponectin): specifically, IGF-I was strongly, negatively associated with hsCRP ($r = -0.479$, $p < 0.0005$), and IGFBP-1 was strongly, positively associated with adiponectin ($r = 0.545$, $p < 0.0005$) (Fig. 1). Partial linear

correlation analyses between IGFBP-1 and adiponectin, controlling for BMI z-score, revealed that IGFBP-1 remained significantly, positively associated with adiponectin ($r = 0.562$, $p < 0.0005$). As adiponectin expression is lower in insulin resistance, we subsequently performed a further partial correlation analysis controlling for the influence of S_I; the relationship between IGFBP-1 and adiponectin remained significant ($r = 0.495$, $p = 0.001$). The relationship of IGF-I to hsCRP was also controlled for both BMI z-score and S_I and remained significant ($r= -0.421$, $p = 0.013$).

Discussion

In this study, we have demonstrated relationships between IGF-I and IGFBP-1 with WC and other anthropometric and serum-based non-traditional measures of CVD risk in obese adolescents, suggesting that higher IGF-I and IGFBP-1 are associated with overall lower CVD risk. The most notable findings are the inverse association between IGF-I and hsCRP and the positive association of IGFBP-1 with adiponectin. The previous limited reports correlating IGFBP-1 with adiponectin (34, 35) have not, to our knowledge, included investigation in obese adolescents and have not controlled for confounding factors such as BMI and insulin sensitivity.

While IGFBP-1 was inversely related to DBP and BMI in our study, the relationships between IGF-I and IGBP-1 with traditional CVD risk factors were less predictable. This is not entirely unexpected as there is a divergence of data with respect to growth factors and CVD risk measures as seen in Chinese, Caucasian, and African American adolescents (2, 17, 36). Data from one cohort of obese European Caucasian adolescents did report negative associations between IGFBP-1 and SBP, DBP, and TG, but only the last correlation held up longitudinally (2). Additional lipid analysis showed no significant correlation between IGF-I with TG, HDL, or LDL. Results from adult studies examining the relationships of IGF-I and lipids are conflicting, providing no further clarification on these relationships.

Further elucidation of CVD risk has also focused on the characterization of adipose tissue distribution revealing independent effects for various deposits [i.e., visceral, upper-body subcutaneous (SC), and lower-body fat] (37). Neck circumference and sagittal abdominal diameter are surrogates for upper-body SC fat and visceral adiposity, respectively. Neck circumference has been shown to correlate with traditional CVD risk factors as well as OSAS in adult and pediatric cohorts (27, 38, 39), while sagittal abdominal diameter has been found to outperform waist circumference, BMI, and body fat percentage in identifying metabolic risk in obese boys (40). The significant correlation of IGF-I and IGFBP-1 with sagittal abdominal diameter as well as the correlation of IGFBP-1 with neck circumference appear to be the first reports of IGF-axis constituents associating with novel adiposity measures.

While neither race nor sex associated with the growth factors in our study, both of these variables impact CVD risk profiles. Our patient population was mostly African American, and studies suggest that central obesity, low HDL, insulin resistance, and elevated BP are the strongest markers of metabolic syndrome in this racial group (41). Published differences in the general population suggest that metabolic risk may need to be ethnicity specific, as

African American adults and youth are known to not exhibit the typical CVD risk profile of high triglycerides (42). In light of these published racial differences, the association here between growth factors and other risk markers in our study, such as WC and CRP, may reveal CVD risk in this population beyond that typically derived from a lipid panel. Gender may also impact atherogenic risk (43). As shown in Table 1, our male subjects had higher weight, fat-free mass, systolic and diastolic blood pressure, as well as neck circumference. Indeed, males have been shown to have larger neck circumference than females (44, 45). Associations of IGFBP-1 with DBP, fat-free mass, and neck circumference were only seen in males in our study, potentially illustrating early divergence of CVD risk by gender.

Adult and pediatric data have shown strong associations between CRP and traditional CVD risk factors (11). Laboratory and epidemiologic data link inflammation and hsCRP to insulin resistance (46). Such findings have spurred the investigation of CRP's relationship to non-traditional risk factors. This report broadens the negative IGF-I-CRP association to obese adolescents of several ethnicities, beyond the previous reports for selective adults (47) and the limited, albeit epidemiological, report in Chinese adolescents (17).

The insulin-independent positive association that we uncovered between IGFBP-1 and adiponectin supports investigational findings that intimate at a feedback mechanism between the two biomarkers through the actions of peroxisome proliferator-activated receptor (PPAR)-γ signaling. PPAR-γ signaling is directly stimulated by adiponectin (48); PPAR-γ has in turn been found to increase IGFBP-1 gene transcription (49). These inter-relationships are undoubtedly more convoluted than presented here, as the converse relationship has also been shown *in vivo*, whereby non-adiponectin ligand PPAR-γ activation stimulates adiponectin release (50). Nevertheless, the *a priori* assertion that the positive association between IGFBP-1 and adiponectin is the result of sequential mediation through insulin appears insufficient, especially in light of our findings.

The insulin-independent associations with hsCRP and adiponectin are in keeping with the literature demonstrating regulation of IGFBP-1 by inflammatory cytokines (51). We found that the relationship of IGF-I/IGFBP-1 with traditional CV risk factors and adiposity measures was related in part to insulin resistance. The insulin-mediated decrease in IGFBP-1 serves to decreases IGF-1 bioactivity. Newgard et al. have postulated a mechanism of insulin resistance in which the relative IGF-1 deficiency caused by overnutrition in obese subjects diverts branched chain amino acids away from protein synthesis and into catabolic pathways (52). In addition, reduced IGFBP-1 levels directly (53) and through possible modulation of the insulin/IGF-I axis may result in an unfavorable effect on vascular function (54, 55).

This study has limitations. Without true CVD outcomes in youth, the definition of CVD risk factors is difficult. The design of the original study did not include a lean control group. Our population was mostly African American, and metabolic risk profiles may vary between racial and ethnic groups. The cross-sectional design in an obese study group precludes insight on causation among the significant correlations, indicating the need for future longitudinal studies of multiethnic youth of varied weight. On the continuum of obese adolescents, future studies of the IGF-I and IGFBP-1 related to cardiovascular risk could be

performed in diabetic youth (56–58). A larger sample size will allow for specific IGF-I levels to be interpreted in the context of standard deviation score for age, gender, and Tanner stage. More specific to the methods, total adiponectin was measured as opposed to high molecular weight (HMW) adiponectin, which has been shown to be the most significant isoform, though this awaits consensus.

In summary, we report a significant inverse correlation between IGF-I and CRP as well as a direct correlation between IGFBP-1 and adiponectin in multiethnic obese adolescents. These correlations were independent of BMI and insulin sensitivity, as were the associations between IGFBP-1 and diastolic blood pressure and neck circumference in males. In addition, we demonstrate associations of IGF-I/IGFBP-1 with traditional markers of CV risk and body fat distribution that are related to insulin sensitivity. Thus, IGF-I and IGFBP-1 trend with biomarkers of CVD and may add to clinical assessments of cardiometabolic dysfunction in youth. IGF-I and IGFBP-1 may play a role in CVD risk characterization that is both insulin-dependent as well as insulin-independent. The growth factors are not as well characterized with regard to atherogenic risk as waist circumference, blood pressure, and lipid panels, which are less expensive, more widely available, and predict cardiovascular outcomes in adults. Future longitudinal studies in large population-based samples of youth with a range of BMI will shed further light on the impact of IGF-I/IGFBP-1 on CVD risk.

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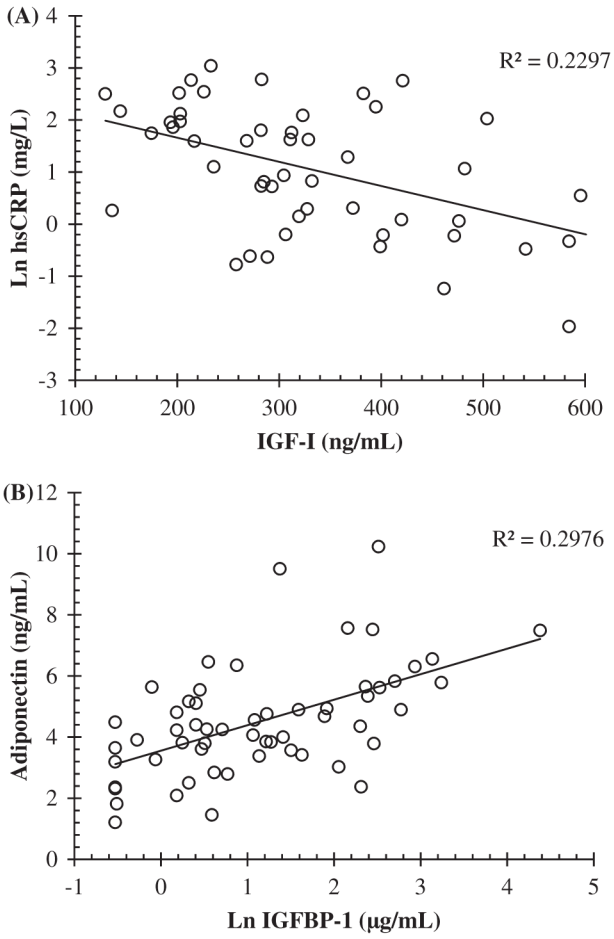

Fig. 1.

The linear relationships between adipocytokines and growth factors: (A) CRP and IGF-I and (B) adiponectin with the natural log values of IGFBP-1 serum levels.

Table 1

Subject characteristics

Demographics	Cohort	Male	Female	p
Age (yr)	14.4 ± 2.1	14.6 ± 1.9	14.2 ± 2.1	0.447
Sex	–	27 (44.3%)	34 (55.7%)	
Race				
Caucasian	23 (37.7%)	5 (8.2%)	18 (29.5%)	**0.038***
African American	34 (54.1%)	19 (31.1%)	14 (23.0%)	
Asian American	1 (1.6%)	1 (1.6%)	0 (0%)	
>1 race or other	4 (6.5%)	2 (3.3%)	2 (3.3%)	
Ethnicity				
Hispanic	8 (13.1%)	2 (3.3%)	6 (9.8%)	0.442*
Non-Hispanic	50 (82%)	24 (39.3%)	26 (42.6%)	
Unknown	3 (4.9%)	1 (1.9%)	2 (3.3%)	
Tanner stage				
II	5 (8.3%)	3 (5.0%)	2 (3.3%)	0.171*
III	12 (20%)	8 (13.3%)	4 (6.7%)	
IV	14 (23%)	6 (10%)	8 (13%)	
V	29 (43%)	9 (15%)	20 (33%)	
Serum measures				
Total cholesterol (mg/dL)	161 ± 31.1	156 ± 32.5	165 ± 29.9	0.270
HDL (mg/dL)	41 ± 8.9	41 ± 9.5	41 ± 8.8	0.979
LDL (mg/dL)	98 ± 29	93 ± 31	102 ± 37	0.209
Triglycerides (mg/dL)†	86 (31, 438)	82 (41, 438)	92 (31, 242)	0.937
Fasting insulin (μIU/mL)†	20.2 (6.6, 66)	18.0 (6.0, 64.2)	24.0 (6.9, 66.0)	0.340
HOMA-IR†	4.4 (1.4, 17.6)	4.13 (1.43, 14.8)	5.07 (1.40, 17.6)	0.541
WBISI	2.55 ± 1.58	2.57 ± 1.45	2.53 ± 1.69	0.908
S_I	2.1 ± 1.4	1.8 ± 1.2	2.3 ± 1.6	0.222
IGF-I (ng/mL)	321 ± 119	305 ± 105	333 ± 128	0.361
IGFBP-1 (ng/mL)†	2.65 (0.59, 79.9)	3.39 (0.59, 23.0)	2.22 (0.59, 79.9)	0.957
hsCRP (mg/L)†	2.96 (0.14, 20.9)	3.26 (0.29, 20.9)	2.92 (0.14, 16.1)	0.510
Adiponectin (μg/mL)	4.5 ± 1.8	4.4 ± 1.9	4.7 ± 1.7	0.611
Anthropometrics				
BMI (kg/m^2)	36.4 ± 6.39	36.8 ± 6.61	36.0 ± 6.29	0.609
BMI z-score	2.37 ± 0.38	2.47 ± 0.40	2.23 ± 0.35	0.068
Weight (kg)	100 ± 20.94	107 ± 23.9	94.3 ± 16.3	**0.019**‡
Fat mass (kg)	36.7 ± 8.86	35.1 ± 9.19	38.0 ± 8.55	0.224
Fat-free mass (kg)	61 ± 11.4	65.9 ± 12.8	57.4 ± 8.81	**0.008**‡
Waist circumference (cm)	108 ± 14.21	112 ± 15.23	106 ± 13.65	0.151
Waist to hip ratio	0.93 ± 0.07	0.94 ± 0.07	0.92 ± 0.06	0.195

Demographics	Cohort	Male	Female	p
Abdominal height (cm)	25.5 ± 3.12	25.4 ± 3.02	25.6 ± 3.50	0.848
Neck circumference (cm)	39.3 ± 3.80	41.0 ± 3.70	37.9 ± 3.32	**0.001**
Blood pressure				
Systolic blood (mmHg)	118 ± 12	125 ± 10	112 ± 10	**<0.0005**
Diastolic blood (mmHg)	63 ± 6.6	65 ± 5	60 ± 7	**0.004**

BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; WBISI, whole body insulin sensitivity index.

Continuous variables listed as mean ± standard deviation (SD); discrete variables listed as N (percent); percentages may not total to 100 due to rounding.

The bold values indicate statistically significant results.

*Pearon's chi-squared test p-valve.

†Skewed variable, results reported as median (minimum, maximum), natural log transformed data analyzed.

‡Unequal variance between gender groups assumed.

Table 2

Pearson coefficients for IGF-I and IGFBP-1 with CVD risk factors

Risk measure	IGF-1		IGFBP-1*	
	r	*p*	*r*	*p*
(A) Insulin measures				
Fasting insulin*	0.117	(0.307)	**−0.567**	**(<0.0005)**
HOMA-IR*	0.053	(0.683)	**−0.560**	**(<0.0005)**
WBISI	−0.159	(0.221)	**0.571**	**(<0.0005)**
S_I	0.277 x	(0.221)	**0.495**	**(0.001)**
(B) Traditional risk factors				
Systolic blood pressure				
Males	0.199	(0.320)	−0.130	(0.545)
Females	−0.003	(0.988)	−0.254	(0.147)
Diastolic blood pressure				
Males	0.208	(0.299)	**−0.664**	**(<0.0005)**
Females	0.016	(0.928)	−0.133	(0.453)
Total cholesterol	0.006	(0.965)	−0.108	(0.421)
HDL	−0.116	(0.373)	0.19	(0.154)
LDL	0.136	(0.296)	−0.12	(0.369)
Triglycerides*	−0.18	(0.164)	−0.133	(0.320)
BMI	−0.25	(0.052)	**−0.368**	**(0.004)**
BMI *z*-score	−0.185	(0.154)	**−0.374**	**(0.004)**
(C) Body composition				
Waist circumference	**−0.327**	**(0.011)**	**−0.333**	**(0.011)**
Abdominal height	**−0.275**	**(0.040)**	**−0.371**	**(0.006)**
Neck circumference				
Males	−0.039	(0.846)	**−0.716**	**(<0.0005)**
Females	−0.036	(0.840)	−0.253	(0.156)
Fat mass	−0.196	(0.144)	**−0.347**	**(0.010)**
Fat-free mass				
Males	0.143	(0.505)	**−0.591**	**(0.005)**
Females	−0.236	(0.186)	−0.054	(0.767)

BMI, body mass index; CVD, cardiovascular disease; IGF-I, insulin-like growth factor-I; IGFBP-1, IGF binding protein-1; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.

The bold values indicate statistically significant results.

*Skewed variable (natural log transformed data used).