

# Adiponectin Is Lower Among African Americans and Is Independently Related to Insulin Sensitivity in Children and Adolescents

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Adiponectin is inversely related to adiposity and positively correlated with insulin sensitivity ( $S_i$ ). Sparse data exist on the contributions of ethnicity and body fat distribution to variance in serum adiponectin. Hypotheses tested were that adiponectin would be lower in African Americans compared with Caucasians; that adiponectin would be inversely related to central, not peripheral, fat; that adiponectin would be positively associated with  $S_i$ ; and that baseline adiponectin would predict change in  $S_i$  over 2 years in 150 African-American and Caucasian youth. Multiple linear regression modeling showed that adiponectin was lower in African-American versus Caucasian children (adjusted means  $10.8 \pm 0.5$  vs.  $12.3 \pm 0.5$   $\mu\text{g/ml}$ , respectively;  $P < 0.05$ ); inversely related to trunk fat ( $P < 0.05$ ); and positively related to limb fat ( $P < 0.01$ ). Addition of the acute insulin response to glucose to the model eliminated the significance of ethnicity.  $S_i$ , which was positively related to adiponectin ( $P < 0.05$ ), was lower in African Americans ( $P < 0.001$ ) and girls ( $P < 0.05$ ). Baseline adiponectin did not predict change in  $S_i$  over 2 years. In conclusion, adiponectin was positively correlated with  $S_i$ , inversely related to central fat, and positively related to peripheral fat. In addition, higher acute insulin response to glucose explained lower adiponectin among African-American children. *Diabetes* 54:2772–2778, 2005

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AIRg, acute insulin response to glucose; IAAT, intra-abdominal (visceral) adipose tissue; SAAT, subcutaneous abdominal adipose tissue; UAB, University of Alabama at Birmingham.

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Adiponectin, a hormone secreted exclusively by adipose tissue, has gained much attention secondary to its close association with insulin sensitivity ( $S_i$ ) and obesity (1). Discovered in the mid-1990s by four different groups of researchers, it is also referred to as Acrp30, AdipoQ, ApM1, and GBP28 (2–5). Adiponectin circulates at relatively high levels in the serum (2–30  $\mu\text{g/ml}$  range) as both a hexamer and a higher order complex (6). Research has indicated that adiponectin decreases serum glucose by inhibiting hepatic glucose production (7–9). Adiponectin has also been shown to increase skeletal muscle glucose uptake and fatty acid oxidation through phosphorylation and activation of 5'-AMP-activated protein kinase (10). In one study, adiponectin concentrations at one time predicted the change in  $S_i$  over the subsequent 2-year period (11).

Although a positive relationship between adiponectin and  $S_i$  has been well documented in adults (11–15), little research has been done in children. The potential role of adiponectin in determining  $S_i$  in children is of particular relevance with regard to ethnic differences in  $S_i$ . It has been shown that African-American children and adolescents have lower  $S_i$  than their Caucasian peers (16–18); however, the physiological basis for this difference is not known. The possibility that ethnic differences in adiponectin production or action play a role has not been investigated.

Little is known about ethnic differences in adiponectin. Recently, it was shown that adiponectin was lower among African-American versus Caucasian females, but only among nonobese subjects (19). Another study found that African-American males had the lowest adiponectin concentrations among a group of African-American and Caucasian males and females aged 12–21 years (20). In this study, no relationship was observed between adiponectin and estimated  $S_i$  (estimated using the homeostasis model), after controlling for BMI or BMI percentile (20). The relationship between adiponectin and  $S_i$  among African-American and Caucasian children has not been examined using robust measures of  $S_i$ .

In addition to generalized obesity, body fat distribution appears to affect both  $S_i$  and adiponectin concentrations. That central and visceral fat are inversely associated with  $S_i$  is well established (21–23). Considerably less is known about the relationship between fat distribution and adi-

ponectin. Studies have found both central and visceral adipose tissue to be inversely associated with adiponectin concentrations (24–26). Among healthy adults, visceral adipose tissue was independently related to adiponectin concentration after adjusting for measures of subcutaneous adipose tissue as well as other variables such as age, sex, fasting insulin, and glucose, homeostasis model assessment of insulin resistance, HDL cholesterol, and triglycerides (27,28). In contrast, among subjects with HIV, adiponectin was positively correlated with percent body fat, limb fat, and limb fat-to-total fat ratio (29). Little research exists on the relationship between peripheral fat and circulating adiponectin concentrations in healthy populations.

The purpose of this study, in a population of healthy African American and Caucasian children and adolescents, was to test the hypotheses that adiponectin would be 1) lower in African Americans as compared with Caucasians; 2) inversely related to central, but not peripheral, body fat; and 3) positively associated with  $S_i$ . In addition, we determined whether baseline adiponectin would predict change in  $S_i$  over 2 years.

## RESEARCH DESIGN AND METHODS

This retrospective study contains both cross-sectional and longitudinal components. Subjects were obtained from an ongoing longitudinal study investigating intra-abdominal fat and risk of disease in adolescents conducted at the University of Alabama at Birmingham (UAB). The design of the parent study has been described elsewhere (30). Briefly, African-American and Caucasian boys and girls were recruited by newspaper advertisements, radio announcements, and word-of-mouth. All children were Tanner stage I (prepubertal) at enrollment. Tanner staging was determined by a pediatrician, using breast and pubic hair development in girls and genitalia in boys as markers for pubertal development (31,32). Hormone levels (estradiol and testosterone) were also measured to further evaluate developmental status and confirm Tanner staging. The children were followed annually through Tanner stage V. Age and ethnicity of the subjects were determined through self-report. Children were excluded from participation if they were taking medications (i.e., Ritalin or Prednisone) or if they had a disease (i.e., Down syndrome or diabetes) that was known to affect body composition. Children were also excluded if they had experienced any major illness since birth, including chronic conditions such as asthma, recurrent colds, and infections. Parents provided informed consent before any testing was performed, and the study was approved by UAB Institutional Review Board for human use (UAB Institutional Review Board protocol F020813002).

From the cohort of subjects followed in the parent study, a subset of subjects ( $n = 150$ ) was selected for this current study. They consisted of African-American and Caucasian boys (39%) and girls (61%) with ages ranging from 5 to 16 years. Fifty percent of the boys and 41% of the girls were African American. Subjects for this current study were included based on the availability of  $S_i$  and body composition data, as well as the availability of stored sera. Although not all measures were available on all subjects, for the cross-sectional component of the present study, there were at least 140 observations for any given variable, with a maximum of 150 observations for some variables, such as adiponectin, age, and BMI. For the longitudinal component of the present study, there were at least 88 observations for any given variable. Adiponectin concentrations were measured at the first visit only and were therefore not available at the 2-year follow-up visit. The Institutional Review Board at UAB approved this substudy.

Once enrolled, the children were scheduled for an overnight stay at the General Clinical Research Center. The children arrived during the late afternoon and were admitted, after which anthropometric measurements were obtained. At ~1700, a computed tomography scan was performed by the Department of Radiology at UAB. The children were served a standardized dinner meal and snack consisting of 55% carbohydrate, 15% protein, and 30% fat, which was to be consumed before 2000. The children fasted, receiving only water and noncaffeinated, noncaloric beverages, from 2000 until testing the next morning. Two weeks after the General Clinical Research Center testing, children returned for body composition analysis by dual-energy X-ray absorptiometry, which was performed at the Department of Nutrition Sciences at UAB.

**Tolbutamide-modified frequently sampled intravenous glucose tolerance test.** A frequently sampled intravenous glucose tolerance test was performed in the morning (~0700) after an overnight fast to determine  $S_i$  and the acute insulin response to glucose (AIRg) (16). Briefly, fasting blood samples were drawn for determination of glucose, insulin, lipid, and hormone concentrations. At time zero, glucose (25% dextrose; 11.4 g/m<sup>2</sup>) was given intravenously. Tolbutamide (125 mg/m<sup>2</sup>) was administered intravenously 20 min after glucose administration. A total of 18 additional blood samples were collected over a 3-h period. Values for glucose (Ektachem DT II System; Johnson & Johnson Clinical Diagnostics, Rochester, NY) and insulin (radioimmunoassay; Diagnostic Products, Los Angeles, CA) were obtained from the sera. These values were then entered into the MINMOD computer program (version 3.0; Richard N. Bergman, Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, CA) to derive  $S_i$  and AIRg.

**Total body fat and abdominal fat.** Total body composition (fat mass and fat-free mass) was analyzed by dual-energy X-ray absorptiometry using the Lunar DPX-L densitometer (LUNAR Radiation, Madison, WI), which is described in detail elsewhere (33). As previously described (16), a computed tomography scan (HiLight/Advantage Scanner; General Electric, Milwaukee, WI) was used to measure visceral and subcutaneous abdominal fat. Briefly, a single slice (5-mm) scan taken at the level of the umbilicus was used for cross-sectional area analysis of intra-abdominal (visceral) adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT).

**Adiponectin assay.** After an overnight fast, three blood samples were collected during a 40-min period. The sera were separated, pooled, and stored at -85°C until needed for analysis. Adiponectin was measured using radioimmunoassay kits obtained from Linco Research (St. Charles, MO). The average intra-assay and interassay coefficients of variation at 50% bound were 9.23 and 13.3%, respectively. Manufacturer's directions were followed for each assay, and all samples were assayed in duplicate.

**Sample size considerations.** Preliminary power calculations, based on 100 children and adolescents, indicated that this study had adequate power to detect statistically significant correlations between measures of adiponectin,  $S_i$ , and body composition of 0.28 (or greater) with 80% power and of 0.32 (or greater) with 90% power. Additional preliminary power calculations on racial and sex subgroups indicated that 50 children and adolescents would be needed to detect statistically significant correlations of 0.39 with 80% power and 0.45 with 90% power and that for the race-by-sex subgroup, 25 children and adolescents would be needed to detect statistically significant correlations of 0.54 and 0.60 with 80 and 90% power, respectively. Each of these calculations assumed a significance level of 5% and a two-tailed statistical test.

**Statistical methods.** Descriptive statistics were computed for all variables of interest. Differences among the means for ethnic and sex subgroups were examined using a two-way ANOVA for endocrine, metabolic, anthropometric, and demographic variables. Adiponectin concentrations,  $S_i$ , AIRg, fasting insulin, and testosterone concentrations were log<sub>10</sub> transformed so that each of these variables followed an approximate normal distribution. Simple relationships between adiponectin and various metabolic and anthropometric variables were examined by using Pearson correlation analyses. Relationships among these variables were further quantified using multiple linear regression analyses. In particular, multiple linear regression models were developed for predicting serum adiponectin concentrations at baseline, for predicting  $S_i$  at baseline, and also for predicting the change in  $S_i$  over a 2-year period. Sex, race, and race-by-sex interaction were entered as covariates in the regression models for adiponectin,  $S_i$ , and change in  $S_i$  over a 2-year period. Testosterone and AIRg were tested as independent variables in individual models for baseline adiponectin because of their documented inhibitory effect on adiponectin expression and circulating concentrations (21,34,35). In addition, baseline measures of  $S_i$  and adiponectin were included as independent variables in the model for predicting change in  $S_i$  over a 2-year period, as were total fat mass, and Tanner stage at the 2-year follow-up visit. All statistical tests used a significance level of 5% and were two-tailed. Statistical analyses were performed using SAS (version 9.0; SAS Institute, Cary, NC).

## RESULTS

**Demographics and descriptive statistics.** Participants for this study were obtained from the parent study. Participants in the parent study came in for multiple, annual visits. Therefore, baseline measures for the present study are not necessarily baseline measures for the parent study but are instead the first time point (visit) for any one subject for which all measures (i.e., adiponectin,  $S_i$ , and body composition data) were available. Likewise, the 2-year

TABLE 1  
Baseline demographic and descriptive characteristics for ethnic-sex groups

| Characteristic   | Caucasian       |                 | African American    |                   | Race<br><i>P</i> value* | Sex<br><i>P</i> value† |
|--|-----------------|-----------------|---------------------|-------------------|-------------------------|------------------------|
|  | Male            | Female          | Male                | Female            |                         |                        |
| <i>n</i>   | 29              | 54              | 29                  | 38                |                         |                        |
| Adiponectin (μg/ml)  | 12.51 ± 4.77    | 13.28 ± 6.38    | 11.66 ± 4.08        | 11.21 ± 3.51      | 0.038                   | 0.751                  |
| Age (years)  | 9.69 ± 1.56     | 10.79 ± 2.01    | 9.09 ± 1.75         | 9.44 ± 2.08       | 0.001                   | 0.021                  |
| AIRg (μIU/ml × 10 min)‡  | 619.39 ± 451.80 | 681.38 ± 430.86 | 2,085.70 ± 1,965.48 | 1,594.09 ± 644.07 | <0.001                  | 0.275                  |
| BMI (kg/m <sup>2</sup> )   | 19.30 ± 3.79    | 20.14 ± 4.04    | 21.02 ± 6.40        | 20.84 ± 4.96      | 0.165                   | 0.649                  |
| Fasting insulin (μIU/ml)‡  | 10.96 ± 4.18    | 13.18 ± 7.21    | 14.01 ± 7.49        | 15.62 ± 9.39      | 0.031                   | 0.203                  |
| IAAT (cm <sup>2</sup> )‡   | 38.10 ± 19.58   | 41.52 ± 23.85   | 37.63 ± 33.08       | 29.38 ± 15.42     | 0.065                   | 0.586                  |
| Limb fat (kg)‡   | 4.97 ± 3.56     | 6.59 ± 4.04     | 5.90 ± 5.56         | 7.01 ± 4.38       | 0.392                   | 0.061                  |
| SAAT (cm <sup>2</sup> )‡   | 122.95 ± 93.67  | 139.34 ± 106.50 | 107.74 ± 129.40     | 137.80 ± 109.74   | 0.710                   | 0.231                  |
| <i>S</i> <sub>i</sub> [×10 <sup>-4</sup> min <sup>-1</sup> /(μIU/ml)]‡ | 7.84 ± 4.09     | 5.82 ± 3.34     | 4.38 ± 2.63         | 3.56 ± 1.91       | <0.001                  | 0.029                  |
| Total fat (kg)‡  | 9.50 ± 7.24     | 12.59 ± 7.72    | 11.38 ± 11.18       | 13.33 ± 8.59      | 0.404                   | 0.081                  |
| Total LTM (kg)‡  | 26.14 ± 5.33    | 28.00 ± 6.92    | 27.42 ± 6.57        | 26.87 ± 7.56      | 0.875                   | 0.517                  |
| Testosterone (ng/dl)‡  | 41.09 ± 122.53  | 14.26 ± 6.02    | 16.32 ± 22.21       | 15.39 ± 7.97      | 0.578                   | 0.534                  |
| Trunk fat (kg)‡  | 3.67 ± 3.24     | 5.01 ± 3.51     | 4.56 ± 5.30         | 5.19 ± 3.94       | 0.480                   | 0.134                  |
| Weight (kg)  | 38.28 ± 12.03   | 42.90 ± 13.09   | 41.60 ± 19.17       | 42.13 ± 15.14     | 0.729                   | 0.277                  |

Data are means ± SD. \**P* values are for the effects of race by two-way ANOVA. †*P* values are for the effects of sex by two-way ANOVA. ‡Not all measures were available on all subjects. LTM, lean tissue mass.

follow-up visit is considered to be 2 years after the baseline used for the current study.

The number of subjects in each ethnic-sex subgroup is given in Table 1, along with baseline demographic and descriptive characteristics. Subjects ranged in age from 5 to 16 years, and the majority of subjects were Tanner stage I (*n* = 88; 59%). Results indicated that age and *S*<sub>i</sub> were significantly different between ethnic and sex groups, with African Americans being younger (*P* = 0.001) and having lower *S*<sub>i</sub> (*P* < 0.001) compared with Caucasians, and girls being older (*P* < 0.05) and having lower *S*<sub>i</sub> (*P* < 0.05) compared with boys. Additionally, measures of adiponectin were significantly lower in African Americans (*P* < 0.05), and measures of fasting insulin and AIRg were significantly higher in African Americans (*P* < 0.05 and *P* < 0.001, respectively). There was a trend toward significance for measures of IAAT among racial groups, with African Americans having less IAAT than Caucasians (0.05 < *P* < 0.10). A trend was observed for girls having more total fat and limb fat than boys (0.05 < *P* < 0.10 for both). The race-by-sex interaction term was not significant for any of the variables.

**Pearson correlation analysis for adiponectin and insulin sensitivity.** Adiponectin was positively correlated with *S*<sub>i</sub> (Table 2). Strong inverse correlations were ob-

TABLE 2  
Correlation coefficients for the relationships of adiponectin and baseline *S*<sub>i</sub> with body fat variables and fasting insulin at baseline

| Variables   | Adiponectin* | <i>S</i> <sub>i</sub> * |
|---|--------------|-------------------------|
| Adiponectin (μg/ml)   | —            | —                       |
| Total fat (kg)  | -0.36        | -0.59                   |
| IAAT (cm <sup>2</sup> )   | -0.33        | -0.45                   |
| SAAT (cm <sup>2</sup> )   | -0.38        | -0.54                   |
| Trunk fat (kg)  | -0.39        | -0.57                   |
| Limb fat (kg)   | -0.34        | -0.58                   |
| <i>S</i> <sub>i</sub> [×10 <sup>-4</sup> min <sup>-1</sup> /(μIU/ml)] | 0.38         | —                       |
| Fasting insulin (μIU/ml)  | -0.45        | -0.76                   |

Adiponectin, *S*<sub>i</sub>, and fasting insulin were log transformed for statistical analysis. \**P* < 0.001 for all.

served between all measures of body fat and both serum adiponectin and *S*<sub>i</sub>. Fasting insulin was also inversely correlated with both serum adiponectin and *S*<sub>i</sub>.

**Multiple linear regression models for dependent variable adiponectin.** Multiple linear regression models for the dependent variable adiponectin are presented in Tables 3 and 4. In the first model (Table 3), a significant inverse relationship was observed between race and adiponectin (*P* < 0.05). Peripheral fat (i.e., limb fat) was positively related to adiponectin (*P* < 0.01), whereas trunk fat was inversely related (*P* < 0.05). This model explained ~21% of the variance in adiponectin.

The second model for adiponectin (Table 4) included AIRg as an independent variable and eliminated testosterone, which was not significant in the previous model. In this model, AIRg was inversely associated with adiponectin (*P* < 0.05). Additionally, the inclusion of AIRg in the model eliminated the significant relationship between race and adiponectin. This model explained ~24% of the variance in adiponectin. In preliminary analyses, other variables included in the models were the race-by-sex interaction, total lean tissue mass, fasting insulin, and IAAT. None of these variables was found to be a significant

TABLE 3  
Multiple linear regression model for the dependent variable log adiponectin (*R*<sup>2</sup> = 0.21)

| Variables                  | Parameter estimate ± SEE | <i>P</i> |
|----------------------------|--------------------------|----------|
| Intercept                  | 1.264 ± 0.111            | <0.0001  |
| Age                        | -0.005 ± 0.008           | 0.5144   |
| Race*                      | -0.058 ± 0.029           | 0.0469   |
| Sex†                       | 0.008 ± 0.027            | 0.7788   |
| SAAT (cm <sup>2</sup> )    | -0.0006 ± 0.0004         | 0.1417   |
| Trunk fat (kg)             | -0.031 ± 0.015           | 0.0420   |
| Limb fat (kg)              | 0.033 ± 0.012            | 0.0077   |
| Total testosterone (ng/dl) | -0.044 ± 0.062           | 0.4798   |

All variables are baseline measures. \*Race coded such that Caucasians = 1 and African Americans = 2. †Sex coded such that males = 1 and females = 2. SEE, SE of estimate.

TABLE 4  
Multiple linear regression model for the dependent variable log adiponectin with the independent variable AIRg ( $R^2 = 0.24$ )

| Variables                           | Parameter estimate $\pm$ SEE | <i>P</i> |
|-------------------------------------|------------------------------|----------|
| Intercept                           | 1.231 $\pm$ 0.090            | <0.0001  |
| Age                                 | -0.010 $\pm$ 0.007           | 0.1705   |
| Race*                               | -0.032 $\pm$ 0.030           | 0.2860   |
| Sex†                                | 0.010 $\pm$ 0.026            | 0.7022   |
| SAAT (cm <sup>2</sup> )             | -0.00083 $\pm$ 0.00043       | 0.0574   |
| Trunk fat (kg)                      | -0.025 $\pm$ 0.014           | 0.0822   |
| Limb fat (kg)                       | 0.035 $\pm$ 0.012            | 0.0049   |
| AIRg ( $\mu$ IU/ml $\times$ 10 min) | -0.000035 $\pm$ 0.000014     | 0.0109   |

All variables are baseline measures. \*Race coded such that Caucasians = 1 and African Americans = 2. †Sex coded such that males = 1 and females = 2. SEE, SE of estimate.

independent predictor of adiponectin, and including them in the model did not alter the results to any substantial degree. Therefore, these variables were not included in the final model.

**Multiple linear regression model for dependent variable insulin sensitivity.** In multiple linear regression modeling, adiponectin was positively related to  $S_i$  ( $P < 0.05$ ; Table 5). Race, sex, and total fat were inversely related to  $S_i$  ( $P < 0.001$ ,  $P < 0.05$ , and  $P < 0.001$ , respectively). The model presented in Table 5 explained ~50% of the variance in  $S_i$ . In preliminary analysis, the race-by-sex interaction and total lean tissue mass were included in the model but were not significant predictors of  $S_i$  and therefore were not included in the final model. Although fat distribution measures were tested in the model, they were not significant predictors of  $S_i$  and did not alter the significance of other variables in the model. In addition, the model with fat distribution variables explained less of the variance ( $R^2 = 0.49$ ) than the model with total fat ( $R^2 = 0.50$ ). Therefore, the final model included only total fat.

**Multiple linear regression model for dependent variable insulin sensitivity at 2-year follow-up.** Eighty-eight of the initial 150 subjects were used in the longitudinal analysis of adiponectin and  $S_i$  over a 2-year period. Results from the multiple linear regression model for  $S_i$  at 2-year follow-up ( $S_{i2}$ ) are presented in Table 6. This model explained 66% of the variance in  $S_{i2}$ , with baseline  $S_i$  being significantly and positively related to  $S_{i2}$  ( $P < 0.01$ ) and with race and total fat being significantly

TABLE 5  
Multiple linear regression model for the dependent variable log  $S_i$  ( $R^2 = 0.50$ )

| Variable                  | Parameter estimate $\pm$ SEE | <i>P</i> |
|---------------------------|------------------------------|----------|
| Intercept                 | 1.070 $\pm$ 0.229            | <0.0001  |
| Age                       | -0.015 $\pm$ 0.015           | 0.3004   |
| Race*                     | -0.220 $\pm$ 0.043           | <0.0001  |
| Sex†                      | -0.108 $\pm$ 0.042           | 0.0107   |
| Total fat (kg)            | -0.019 $\pm$ 0.003           | <0.0001  |
| Tanner                    | 0.054 $\pm$ 0.030            | 0.0729   |
| Adiponectin ( $\mu$ g/ml) | 0.318 $\pm$ 0.136            | 0.0206   |

All variables are baseline measures. \*Race coded such that Caucasians = 1 and African Americans = 2. †Sex coded such that males = 1 and females = 2. SEE, SE of estimate.

TABLE 6  
Multiple linear regression model for the dependent variable log  $S_{i2}$  ( $R^2 = 0.66$ )

| Variable   | Parameter estimate $\pm$ SEE | <i>P</i> |
|--|------------------------------|----------|
| Intercept  | 0.922 $\pm$ 0.317            | 0.005    |
| Age  | 0.008 $\pm$ 0.023            | 0.721    |
| Race*  | -0.216 $\pm$ 0.054           | <0.001   |
| Sex†   | -0.052 $\pm$ 0.049           | 0.298    |
| $S_i$ [ $\times 10^{-4}$ min <sup>-1</sup> /( $\mu$ IU/ml)]‡ | 0.315 $\pm$ 0.106            | 0.004    |
| Adiponectin ( $\mu$ g/ml)                                    | 0.063 $\pm$ 0.180            | 0.729    |
| Tanner 2   | -0.009 $\pm$ 0.036           | 0.805    |
| Total fat 2 (kg)   | -0.015 $\pm$ 0.003           | <0.001   |

\*Race coded such that Caucasians = 1 and African Americans = 2. †Sex coded such that males = 1 and females = 2. ‡ $S_i$  at baseline. SEE, SE of the estimate;  $S_{i2}$ , insulin sensitivity at 2-year follow-up; Tanner 2, Tanner stage at 2-year follow-up; total fat 2, total fat at 2-year follow-up.

inversely related to  $S_{i2}$  ( $P < 0.001$  and  $P < 0.001$ , respectively). Total fat in this model refers to measures of total fat at the 2-year visit. Baseline adiponectin was not significantly related to  $S_{i2}$ . Substituting change in fat mass from baseline to year 2 for total fat mass in the model did not substantially alter the results.

## DISCUSSION

Although African-American children and adolescents have lower  $S_i$  compared with Caucasians (16,36), few studies have addressed the potential contribution of serum adiponectin to this difference. We found that among children and adolescents, adiponectin was lower among African Americans compared with Caucasians. Furthermore, within the group as a whole, adiponectin was a significant independent determinant of  $S_i$ . Further research is needed to determine whether lower adiponectin is mechanistically related to lower  $S_i$  among African Americans.

In the present study, lower adiponectin among African Americans was apparent after adjusting for potential confounding factors (age, sex, body fat distribution, and total testosterone). Because African Americans enter puberty at an earlier age and because previous studies have found a relationship between increased testosterone and decreased adiponectin concentrations (37,38), we reasoned that higher testosterone among African-American males may account for the lower adiponectin previously reported in this sex-ethnic subgroup (20). However, we did not observe a significant relationship between adiponectin and either Tanner stage or testosterone concentration. It is possible that the early pubertal status of our subjects resulted in concentrations of testosterone that were too low to affect adiponectin secretion.

Because African Americans have less IAAT but more subcutaneous fat and limb fat than Caucasians (21,22), we reasoned that ethnic differences in body fat distribution may account for ethnic differences in adiponectin. The relationship between body fat distribution and adiponectin has not been widely investigated. We found that trunk fat was inversely related to adiponectin after adjusting for limb fat, and that limb fat was positively related to adiponectin after controlling for central fat (both trunk fat and SAAT). To the best of our knowledge, this positive relationship between adiponectin and peripheral fat is a

novel observation in a healthy population. However, such a positive relationship between adiponectin and peripheral fat has been observed in the HIV population (29).

Most of the literature indicates that increased adiposity, as assessed by either BMI or dual-energy X-ray absorptiometry, is inversely correlated with adiponectin. Of studies that examined fat distribution in adolescents, Bacha et al. (39) reported that a group of obese adolescents not only had lower adiponectin concentrations than their normal weight peers, but that the obese adolescents with high IAAT had significantly lower adiponectin concentrations than obese adolescents with low IAAT, suggesting that IAAT accumulation may result in lower adiponectin concentrations. In our study, we did not find IAAT to be independently related to adiponectin, as has been reported in adults (27,28); this may have been due to the younger age and developmental status of this group as well as lower IAAT among this population. IAAT also was not associated with  $S_i$  in this cohort (16).

In the present study, the ethnic difference in adiponectin disappeared when the data were statistically adjusted for AIRg. This observation suggests that the higher AIRg typically observed in African Americans (16,36,40) may explain the lower adiponectin concentrations. Studies have shown that African-American children have higher AIRg compared with Caucasian children, independent of differences in  $S_i$ , due to both increased insulin secretion as well as decreased hepatic insulin clearance (36,41). Thus, although both Caucasian and African-American subject populations exhibit characteristic "compensatory hyperinsulinemia" as demonstrated by an inverse relationship between  $S_i$  and AIRg (42), at any given level of  $S_i$ , African Americans have higher AIRg (41). Data have indicated that insulin suppresses adiponectin both in vitro and in vivo (34,35). Thus, higher AIRg among African Americans may lead to lower adiponectin secretion, which in turn may lead to lower  $S_i$ .

The second aim of this study was to determine whether adiponectin would be an independent determinant of  $S_i$  among children and adolescents after adjusting for confounding factors. We found that adiponectin was independently and positively related to  $S_i$ . Several studies have shown similar findings in both children and adults (12–14,43). The relationship between adiponectin and  $S_i$  was independent of total body fat, sex, and race, all of which were independently related to  $S_i$ . In this population, girls had lower  $S_i$  than boys, independent of pubertal status and adiposity. The reason for lower  $S_i$  among girls is not clear. As has previously been shown (16), total fat, rather than IAAT and/or SAAT, was the best predictor of  $S_i$  among relatively young, healthy children.

Although African Americans had both lower  $S_i$  and lower adiponectin, the lower adiponectin did not account for the ethnic difference in  $S_i$ . Rather, both ethnicity and adiponectin made significant independent contributions to  $S_i$ . The design of this study did not enable us to determine whether any of the variance in  $S_i$  attributed to ethnicity was explained by lower adiponectin among African Americans. However, the significant association observed among adiponectin and  $S_i$  is impetus for future research on the potential contribution of lower adiponectin among African Americans to impairment in glucose tolerance and risk for

type 2 diabetes. This is especially true in light of recent findings suggesting that circulating adiponectin levels predict insulin resistance in certain adolescent populations (44,45). For example, Mexican children and adolescents with higher levels of adiponectin had decreased prevalence of type 2 diabetes (45).

The third aim of our study was to determine the relationship between baseline adiponectin and change in  $S_i$  over a 2-year period. Yamamoto et al. (11) reported that baseline adiponectin was negatively related to changes in insulin and insulin resistance as measured by homeostasis model assessment in 590 Japanese men ages 30–65 years. We were interested in determining whether similar findings would be observed in healthy children and adolescents. In a multiple linear regression model for  $S_i$  at year 2, we adjusted for baseline  $S_i$ , Tanner stage at follow-up visit, total fat at follow-up visit, sex, race, and age. We did not find that baseline adiponectin predicted change in  $S_i$  over a 2-year period. Results did not differ if change in total fat was substituted for fat mass in the model.

Between-study differences may have been due to differences in methodology or to differences in the study population. Yamamoto et al. (11) used a surrogate measure of  $S_i$  derived from fasting glucose and insulin, rather than a direct measure, such as the intravenous glucose tolerance test and minimal modeling used in the present study. Additionally, our population was comprised of both boys and girls and was, on average, younger than the population of Yamamoto et al. (11). The peripubertal status of our population may have influenced our results.  $S_i$  decreases during the middle stages of puberty but recovers by the end of puberty (30). Perhaps the innate pubertal fluctuations in  $S_i$ , along with the changes in other hormones related to growth and maturation, overshadowed any potential effect of adiponectin on  $S_i$ . However, results did not differ if analyses were conducted separately for pre-/early pubertal subjects (Tanner stages I and II) and for mid-to-late pubertal subjects (Tanner stages III–V).

Strengths of the study include the relatively large population size; robust measures of body composition, fat distribution, and  $S_i$ ; and statistical control for pubertal development via both Tanner stage and testosterone concentration. Limitations include the use of frozen, and in some cases previously thawed, sera, and missing measures on some subjects. Additionally, evidence suggests that the concentration or relative amount of the high versus low molecular weight form of adiponectin is more closely associated with insulin sensitivity than is the concentration of total adiponectin (46). We did not have measures of the high or low molecular weight forms of adiponectin; such measures are likely to provide greater insight into both ethnic differences in adiponectin and  $S_i$ , and the longitudinal relationship between adiponectin and  $S_i$ .

In conclusion, the major findings of this study are that adiponectin was lower among African-American versus Caucasian children and was positively related to  $S_i$ . The lower adiponectin among African Americans was statistically explained by their higher AIRg. Among children, peripheral fat was significantly and positively related to adiponectin, whereas central fat was inversely related, suggesting that fat distribution should be considered when examining associations between measures of body com-

position and adiponectin. Future research is warranted on the potential contribution of lower adiponectin among African Americans to impairment in glucose tolerance and risk for type 2 diabetes.

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