Racial Differences in Adiponectin in Youth

Relationship to visceral fat and insulin sensitivity

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OBJECTIVE — The purpose of this study was to investigate *1*) whether adiponectin is associated with insulin sensitivity independent of visceral adipose tissue in African-American and Caucasian youth and *2*) whether adiponectin is associated with racial differences in insulin sensitivity.

RESEARCH DESIGN AND METHODS — Total body fat was measured by dual-energy X-ray absorptiometry and abdominal adipose tissue with computed tomography. Insulin sensitivity was measured by a 3-h hyperinsulinemic-euglycemic clamp.

RESULTS — Adiponectin was inversely associated ($P < 0.01$) with visceral adipose tissue, fasting insulin, and proinsulin and was positively related ($P < 0.01$) to insulin sensitivity after controlling for Tanner stage and sex independent of race. Stepwise multiple regression revealed that adiponectin was a strong independent predictor of insulin sensitivity, explaining 27% of the variance in insulin sensitivity. When subjects were categorized into tertiles of visceral adipose tissue and further low (≤50th) and high (>50th) adiponectin groups, insulin sensitivity was significantly different across the visceral adipose tissue groups (main effect, $P < 0.01$) in both races. However, within each visceral adipose tissue group, subjects with high adiponectin had higher insulin sensitivity (main effect, $P < 0.05$) than subjects with low adiponectin, independent of race. Racial differences in insulin sensitivity remained significant ($P < 0.01$) after controlling for leptin and visceral adipose tissue but not ($P > 0.05$) after additional adjustment for adiponectin.

CONCLUSIONS — Adiponectin is associated with insulin sensitivity independent of visceral adipose tissue in both African-American and Caucasian youth. Low adiponectin in African-American youth may be a biological marker that predisposes them to a greater risk of insulin resistance.

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It is well established that visceral adiposity is an independent predictor of cardiovascular disease risk factors (1,2), insulin resistance (3,4), and the metabolic syndrome (5). Visceral adipose tissue exhibits a high lipolytic activity and is drained by the portal circulation, resulting in increased lipoprotein and glucose production and reduced insulin clearance in the liver (6). Although this "portal theory" (6) has long been used to explain the link between abdominal adiposity and metabolic risk, adipose tissue is now recognized as a depot that secretes numerous active proteins, known as adipocytokines (7). Among these, adiponectin is one of the most abundant adipose tissue–specific cytokines that is closely linked to obesity (8). Unlike other adipocytokines, adiponectin concentration is reduced in obesity (8,9) and type 2 diabetes (9) and increases after weight loss (10). Further, it has been reported that adiponectin expression is significantly reduced in visceral adipose tissue of obese subjects with type 2 diabetes, while the decrease in adiponectin expression is less pronounced in abdominal subcutaneous adipose tissue (11).

A growing body of evidence suggests that adiponectin may play a role in the development of insulin resistance. It has been reported that circulating adiponectin level is positively associated with glucose tolerance (9,12) and insulin sensitivity (9,13) and inversely related to future development of type 2 diabetes (14,15). Administration of adiponectin to obese or diabetic rodents is associated with a reduction in endogenous glucose production (16) and an increase in insulin sensitivity (17). Recent findings suggest that the circulating adiponectin level predicts glucose tolerance and insulin sensitivity independent of visceral adiposity in adults (12). Whether this remains true for children and adolescents is currently unknown.

The prevalence of childhood obesity is already high and increasing rapidly in the U.S., particularly among African-American youth (18). African-American youth are hyperinsulinemic (19) and insulin resistant (19,20) by comparison to Caucasians of similar age and total adiposity. Recently, in a small number of prepubertal children, we have demonstrated that adiponectin level is lower in normal-weight African-Americans compared with Caucasian peers (21). This observation is consistent with those of Degawa-Yamauchi et al. (22) who reported that serum adiponectin level is 37% lower in African-American than Caucasian male subjects (aged 12–21 years). Whether this racial difference in adiponectin level explains the racial differences in insulin sensitivity in youth is currently unknown.

The purpose of this study was twofold: *1*) to examine whether circulating adiponectin concentration is associated with insulin sensitivity independent of visceral adipose tissue and leptin in African-American and Caucasian youth and *2*) to investigate whether adiponectin is associated with racial differences in insulin sensitivity. To examine these questions, we evaluated abdominal adipose tissue and metabolic profiles in 161 African-American and Caucasian youth varying widely in adiposity.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— Subjects consisted of healthy African-American ($n = 83$) and Caucasian ($n = 78$) youth who participated in various body composition and metabolic studies, some of which have been previously reported (19,21,23). The subjects varied in age (8–17 years) and BMI (14–50 kg/m^2). Study participants were recruited via the general media. The investigation was approved by the institutional review board and performed in the General Clinical Research Center of Children's Hospital of Pittsburgh. Parental informed consent and child assent were obtained from all participants before participation in accordance with the ethical guidelines of Children's Hospital of Pittsburgh. All participants were in good health on the basis of clinical history, physical examination, and routine hematological and biochemical tests. None of the subjects were taking medications known to affect the primary outcome variables. Pubertal development was assessed by physical examination according to Tanner criteria and was confirmed by measurement of plasma testosterone in male subjects, estradiol in female subjects, and dehydroepiandrosterone sulfate in both.

Anthropometric measurements

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using standardized equipment.

Body composition

Total body fat was assessed by dual-energy X-ray absorptiometry. A single axial image (10-mm thickness) of the abdomen was obtained at the level of L4-L5 intervertebral disc space using a computed tomography to measure abdominal subcutaneous and visceral adipose tissue. Both dual-energy X-ray absorptiometry and computed tomography methods were previously described (19).

Insulin sensitivity

Each participant underwent a 3-h hyperinsulinemic-euglycemic clamp after 10–12 h of overnight fasting. Briefly, intravenous crystalline insulin (Humulin; Lilly, Indianapolis, IN) was infused at a constant rate of 40 mU $\cdot$ m^{-2} $\cdot$ min^{-1} in normal-weight and 80 mU $\cdot$ m^{-2} $\cdot$ min^{-1} in obese subjects, as we previously described (24,25), to suppress hepatic glucose production during the clamp. Plasma glucose was clamped at 5.6 mmol/l with a variable rate infusion of 20% dextrose based on arterialized plasma glucose determinations every 5 min. The insulin-stimulated glucose disposal rate was calculated using the average exogenous glucose infusion rate during the final 30 min of the clamp. Insulin sensitivity was calculated by dividing the insulin-stimulated glucose disposal rate by the steady-state insulin levels during the last 30 min of the clamp, as described previously (19).

Biochemical measurements

Adiponectin and leptin were measured using a commercially available radioimmunoassay kit (Linco Research, St. Louis, MO) (13). Plasma glucose was measured by the glucose oxidase method with a glucose analyzer (YSI, Yellow Springs, OH), and the insulin concentration was determined by radioimmunoassay (19). Proinsulin was measured at the Esoterix Endocrinology Laboratory (Calabasas Hills, CA) by immunochemiluminescent assays.

Statistical analyses

Statistical procedures were performed using SPSS (Version 13.0; SPSS, Chicago, IL). Independent *t* tests were used to compare racial differences in subject characteristics. Log transformations were employed to normalize the distribution for abdominal adipose tissue and metabolic variables. Pearson and partial correlation coefficients were used to determine the associations between abdominal adipose tissue and metabolic variables. A stepwise multiple regression was used to quantify the independent contribution of adiponectin, visceral adipose tissue, and leptin to insulin sensitivity. To further investigate the influence of visceral adipose tissue and adiponectin on insulin sensitivity, subjects were categorized as lowest ($<$14.2 cm^2), moderate (14.2–44.0 cm^2), or highest ($>$44.0 cm^2) tertiles of visceral adipose tissue and further classified as low ($\leq$9.7 μg/ml) and high ($>$9.7 μg/ml) adiponectin groups using the 50th percentile of adiponectin levels derived from all subjects. General linear models were used to determine the influence of adiponectin and visceral adipose tissue groups on insulin sensitivity. Insulin sensitivity was entered as a continuous variable, whereas visceral adipose tissue and adiponectin groups were entered as categorical variables. Racial differences in insulin sensitivity were examined using ANCOVA, with race as the fixed factor, adjusting for Tanner stage, sex, visceral and abdominal adipose tissue, leptin, and adiponectin.

RESULTS

— The subject characteristics are shown in Table 1.

Relation of adiponectin and leptin to body composition and metabolic profiles

In African-American and Caucasian youth, adiponectin was inversely associated with abdominal subcutaneous ($r = -0.43$, $r = -0.61$) and visceral ($r = -0.37$, $r = -0.61$) adipose tissue and fasting insulin ($r = -0.49$, $r = -0.59$) and proinsulin ($r = -0.51$, $r = -0.61$) and positively related to insulin sensitivity ($r = 0.51$, $r = 0.61$), respectively ($P <$ 0.01 for all correlations). By contrast, leptin was positively associated with abdominal subcutaneous ($r = 0.89$, $r = 0.90$) and visceral ($r = 0.76$, $r = 0.82$) adipose tissue and fasting insulin ($r = 0.66$, $r =$ 0.77) and proinsulin ($r = 0.57$, $r = 0.71$) and inversely related to insulin sensitivity ($r = -0.59$, $r = -0.74$), respectively ($P < 0.01$ for all correlations). These associations remained significant ($P <$ 0.01) after adjusting for Tanner stage and sex independent of race.

Stepwise multiple regression analysis to examine the independent association between adiponectin and insulin sensitivity

Stepwise multiple regression analysis revealed that Tanner stage, sex, and race explained a total of 21% of the variance in insulin sensitivity (Table 2). The addition of adiponetin in the regression model accounted for an additional 27% of the variance in insulin sensitivity, indicating that adiponectin is a strong independent predictor of insulin sensitivity (Table 2).

Influence of adiponectin and visceral adipose tissue on insulin sensitivity

Figure 1 describes the relationships between insulin sensitivity, adiponectin, and visceral adipose tissue. Insulin sensitivity was significantly different across the visceral adipose tissue groups (main effect, $P < 0.01$) in both African-American and Caucasian youth. However, within each visceral adipose tissue group, subjects with high adiponectin had higher insulin sensitivity than subjects with low adiponectin (main effect, $P < 0.05$) independent of race. No significant ($P > 0.1$) visceral adipose tissue $\times$ adiponectin

Table 1—*Subject characteristics*

	African Americans	Caucasians
n (male/female)	41/42	41/37
Age (years)	12.2 ± 2.0 (8.5–16.8)	12.3 ± 2.1 (8.0–17.2)
Tanner stage		
I	22	20
II–V	61	58
Weight (kg)	60.5 ± 25.9 (27.6–128.8)	61.5 ± 30.1 (25.3–139.1)
BMI (kg/m^2)	24.8 ± 8.2 (14.7–49.6)	24.6 ± 8.5 (13.9–47.1)
Fat mass (kg)*	18.3 ± 14.5 (2.7–51.0)	17.5 ± 14.3 (3.1–50.6)
Total fat (%)*	27.7 ± 13.3 (6.1–51.1)	27.7 ± 12.4 (9.2–51.1)
Viseral adipose tissue (cm^2)	32.2 ± 26.5 (3.2–108.1)†	43.3 ± 39.5 (5.2–161.4)
Abdominal subcutaneous adipose tissue (cm^2)	231.1 ± 222.2 (7.0–890.1)	247.6 ± 228.5 (20.8–822.6)
Leptin (ng/ml)	18.3 ± 14.6 (1.5–61.6)	16.3 ± 14.0 (1.9–65.2)
Adiponectin (μg/ml)	10.2 ± 5.5 (2.7–28.4)†	12.1 ± 6.0 (1.6–30.4)
Fasting glucose (mg/dl)	95.0 ± 5.4 (83.0–108.0)	96.5 ± 6.4 (84.3–117.7)
Fasting insulin (μU/ml)	24.5 ± 16.0 (8.1–91.1)	24.6 ± 16.0 (6.8–95.5)
Proinsulin (pmol/l)	19.7 ± 20.5 (3.2–112.0)	23.1 ± 21.2 (3.2–108.0)
Insulin sensitivity (mg · kg FFM^{-1} · min^{-1})*	11.0 ± 5.9 (1.1–24.2)‡	13.2 ± 8.0 (1.9–40.1)
Total cholesterol§	157.0 ± 28.8 (76.0–232.0)‡	166.3 ± 31.6 (84.0–258.0)
Triglycerides§	76.8 ± 33.3 (32.0–164.0)†	112.6 ± 65.7 (36.0–395.0)
HDL§	48.0 ± 11.7 (27.0–97.8)	46.6 ± 10.3 (28.8–78.7)
LDL§	93.7 ± 26.6 (22.0–167.0)	97.0 ± 27.6 (35.0–189.0)

Data are means ± SD (range). *Obtained from $n = 80$ and $n = 72$ in African Americans and Caucasians, respectively. †$P < 0.05$; ‡$P = 0.05$; §$n = 82$ in African Americans. FFM, fat free mass.

group interactions for insulin sensitivity was observed within each racial group.

Racial differences in adiponectin and insulin sensitivity

Adiponectin and insulin sensitivity did not differ ($P > 0.1$) between male and female subjects within each race (data not shown). Despite having similar age, BMI, and total adiposity, African-American youth had lower ($P < 0.05$) adiponectin and insulin sensitivity compared with Caucasians (Table 1). Racial differences in adiponectin remained significant ($P < 0.01$) after controlling for Tanner stage, sex, abdominal subcutaneous and visceral adipose tissue, and leptin. Differences in insulin sensitivity between the two racial groups remained significant ($P < 0.01$) after controlling for Tanner stage, sex, abdominal subcutaneous and visceral adipose tissue, and leptin but not ($P > 0.05$) after additional adjustment for adiponectin concentration (Fig. 2).

CONCLUSIONS — The primary findings of this study are that *1*) adiponectin is a predictor of insulin sensitivity independent of visceral adipose tissue, leptin, and race and 2) racial differences in insulin sensitivity do not remain significant after adjustment for adiponectin. These findings suggest that adiponectin level is a strong marker of insulin sensitivity and that the lower adiponectin level in African-American youth may predispose them to a greater risk of insulin resistance despite lower visceral fat.

Our observation of lower visceral adipose tissue in African-American youth is consistent with other pediatric (26) and adult (27) studies. It is interesting to note that despite lower visceral adipose tissue in African-American youth, adiponectin levels as well as insulin sensitivity are lower compared with Caucasians. Whether this unfavorable metabolic profile in African Americans can be attributable to other fat depots (e.g., skeletal muscle lipid) is unknown and warrants further investigation.

The current data demonstrate that adiponectin explains 27% of the variance in insulin sensitivity independent of race, visceral adipose tissue, and leptin. Our findings in children are consistent with recent findings in adults (9,12). Weyer et al. (9) have shown that a low adiponectin level is a determinant of hyperinsulinemia and insulin resistance independent of total adiposity in both Caucasian and Pima Indians. Further, Cote et al. (12) demon-

Table 2—*Stepwise multiple regression to quantify the independent contribution of adiponectin, viseral adipose tissue, and leptin to insulin sensitivity*

Dependent variable	Step	Independent variable	*P*	R^2
Insulin sensitivity	1	Tanner stage	<0.001	
		Sex	0.320	
		Race	0.233	0.21
	2	Tanner stage	<0.001	
		Sex	0.045	
		Race	0.744	
		Adiponectin	<0.001	0.48
	3	Tanner stage	<0.001	
		Sex	0.037	
		Race	0.255	
		Adiponectin	<0.001	
		VAT	<0.001	0.60
	4	Tanner stage	<0.001	
		Sex	0.896	
		Race	0.686	
		Adiponectin	<0.001	
		VAT	0.125	
		Leptin	<0.001	0.64

Insulin sensitivity, adiponectin, viseral adipose tissue, and leptin were log transformed to normalize their distribution. VAT, viseral adipose tissue.

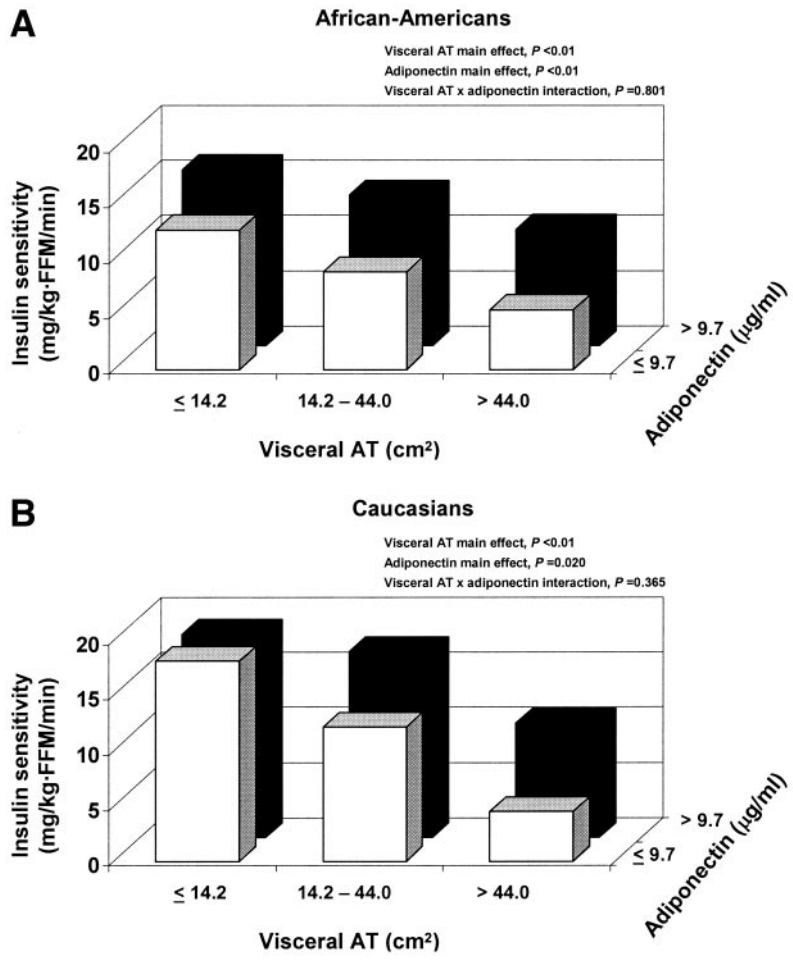

Figure 1— *Influence of adiponectin and visceral adipose tissue (AT) on insulin sensitivity in African-American* (A) *and Caucasian* (B) *youth. FFM, fat-free mass.*

strated that adiponectin is an independent predictor of HDL cholesterol and glucose tolerance after controlling for visceral adipose tissue in middle-aged men. Together, these observations suggest that hypoadiponectinemia is a strong predictor of insulin resistance independent of total and abdominal obesity in both adults and children.

The underlying mechanism by which adiponectin has a beneficial effect on glucose metabolism has yet to be firmly established. Evidence suggests that adiponectin inhibits the production and action of tumor necrosis factor-α (28), a cytokine known to interfere with the insulin signaling cascade (29). Others also have shown that adiponectin activates 5′–AMP-activated protein kinase, an insulin-independent mechanism that stimulates glucose transport in skeletal muscle (30). Administration of adiponectin was shown to increase the expression of proteins involved in fatty acid transport and β-oxidation in rodent skeletal muscle, resulting in decreased skeletal muscle lipid (17). Weiss et al. (31) reported a strong inverse relationship between adiponectin and intramyocellular lipid content ($r = -0.73$) independent of total and abdominal fat in a limited number of lean and obese adolescents. In that study, a positive association between adiponectin and insulin sensitivity was completely abolished after controlling for intramyocellular lipids. Together, these observations suggest that adiponectin may in part modulate insulin sensitivity by regulating skeletal muscle lipid content, a well-known marker of insulin resistance (32).

Consistent with the metabolic studies, epidemiological findings suggest that adiponectin has a protective effect on the development of type 2 diabetes in Pima Indians (14), Japanese (33), Caucasian (34), and African-American (34) men and women. Recently, Duncan et al. (34) reported that higher adiponectin levels were associated with a lower incidence of type 2 diabetes after controlling for other confounding variables (e.g., BMI, waist-to-hip ratio, and fasting insulin and glucose) in a large representative sample of U.S. African-American and Caucasian adults. In that study (34), individuals in the highest quartile of adiponectin had ~40% lower risk of developing type 2 diabetes than those in the lowest quartile over 9 years of follow-up, a finding that remained true for both men and women independent of race.

The lower adiponectin level in African-American youth compared with their Caucasian peers is consistent with our previous observations in a limited number of prepubertal children (21), others in adolescents (22), and adults (35). Our findings that the racial difference in insulin sensitivity did not remain significant after adjusting for adiponectin level suggest that lower adiponectin level in African-American youth may in part explain the lower insulin sensitivity despite lower visceral adipose tissue. It has been proposed that the association between variants in the adiponectin gene and metabolic profiles may differ between ethnic groups. A recent publication of the HERITAGE (Health, Risk Factors, Exercise Training, and Genetics) Family Study (36) found racial differences between blacks and whites in body composition and lipids according to adiponectin gene sequence variations. In blacks but not in whites, *IVS2+G62T* polymorphism was associated with adiposity, while in whites *Tyr111His* polymorphism was associated with insulin sensitivity and secretion (36). Such findings suggest that differences in adiponectin gene polymorphism could underlie the observed racial differences in adiponectin and its association with physical and metabolic parameters between African-American and Caucasian children.

In conclusion, our findings suggest that adiponectin is associated with insulin sensitivity independent of visceral adipose tissue and leptin in both African-American and Caucasian youth. Furthermore, racial differences in insulin sensitivity disappear after adjusting for differences in adiponectin concentration. These findings suggest that adiponectin is a strong independent marker of insulin sensitivity and that a lower adiponectin level in African-American youth may predispose them to a greater risk of insulin resistance and type 2 diabetes. The mechanism(s) responsible for the lower adiponectin levels in African-American youth remain to be determined.

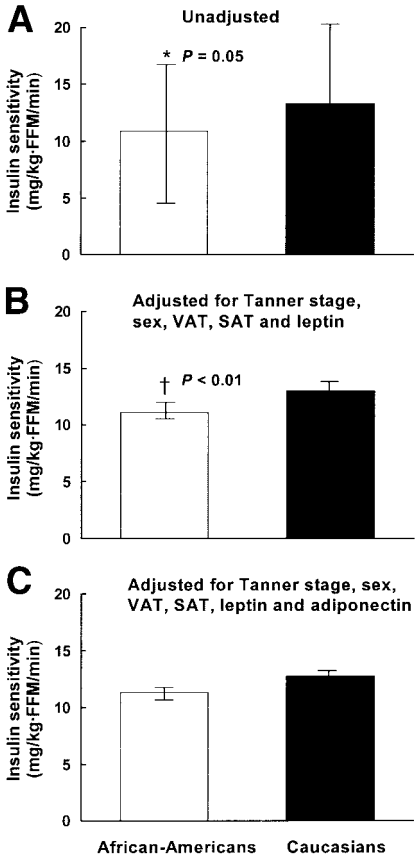

Figure 2— *Racial differences in insulin sensitivity before and after adjusting for Tanner stage, sex, visceral and abdominal subcutaneous adipose tissue (VAT and SAT, respectively), leptin, and adiponectin. FFM, fat-free mass.*

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