

Lipolysis in African-American Children: Is It a Metabolic Risk Factor Predisposing to Obesity?*

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ABSTRACT

Rates of obesity and type 2 diabetes are higher in African-American (AA), compared with American white (AW), adults and children. It is not known whether biologic and/or environmental differences are responsible for this racial disparity. We and others have demonstrated that AA children are hyperinsulinemic, compared with their AW peers. This investigation tested the hypothesis that hyperinsulinemia in AA children is associated with lower rates of lipolysis, which could be a risk factor for future obesity. Forty prepubertal children (20 AA and 20 AW) with comparable body composition (assessed by dual-energy x-ray absorptiometry) and visceral adiposity (evaluated with computed tomography scan) were studied. Total body lipolysis was measured with [$^2\text{H}_5$]glycerol after overnight fasting.

Basal lipolysis was approximately 40% lower in AA vs. AW children, whether the data were expressed for total body (85.7 ± 8.9 vs. 130.3 ± 14.1 $\mu\text{mol}/\text{min}$, $P = 0.011$) or per-kilogram BW (2.4 ± 0.2 vs.

3.8 ± 0.4 $\mu\text{mol}/\text{min}\cdot\text{kg}$, $P = 0.002$) or per kilogram fat free mass (FFM) (3.3 ± 0.3 vs. 5.2 ± 0.5 $\mu\text{mol}/\text{min}\cdot\text{kg}$ FFM, $P = 0.004$), or per kg fat mass (FM) (13.7 ± 1.6 vs. 21.3 ± 3.3 $\mu\text{mol}/\text{min}\cdot\text{kg}$ FM, $P = 0.046$). Fasting insulin levels were higher in AA children (99.6 ± 7.8 vs. 77.4 ± 5.9 pmol/L, $P = 0.032$). Lipolysis correlated positively with fat mass, percent body fat, and abdominal fat mass. However, in multiple-regression analysis models after controlling for insulin and body composition, race remained a significant contributor to the variance in lipolysis.

In summary, the present study demonstrates that rates of lipolysis are significantly lower in AA children, compared with their white peers. This may constitute an early metabolic phenotype that may mediate fat trapping and susceptibility to obesity in a specific environmental context of energy excess conducive to fat accretion. (*J Clin Endocrinol Metab* 86: 3022–3026, 2001)

RATES OF OBESITY and type 2 diabetes are higher in African-Americans (AA), compared with American whites (AW) (1–4). The onset of racial differences in obesity relates temporally to puberty, with prevalence of obesity increasing in blacks, relative to their white peers, during pubertal maturation (5–9). The underlying reason(s) for this racial disparity in obesity and diabetes remains open for investigation. It is not known whether biologic differences or environmental differences in diet and activity, together or independently, explain the observed racial difference in obesity and type 2 diabetes. We and others (10–13) have demonstrated that AA children are hyperinsulinemic, compared with their AW peers. It is our hypothesis that this hyperinsulinemia inhibits lipolysis, leading, over time, to progressive fat accretion, in the presence of excess energy intake or diminished physical activity. Therefore, the aim of the current study was to investigate total body lipolysis in black vs. white prepubertal children to determine whether metabolic

differences are discernible early in life that could explain the increased risk of obesity in blacks. Nonobese children were the target of investigation, to avoid clouding of the metabolic phenotype consequent to obesity (14–17).

Subjects and Methods

Subjects

Twenty AA (10 males, 10 females) and 20 AW (10 males, 10 females) prepubertal children participated in the study. All studies were approved by the Human Rights Committee of Children's Hospital of Pittsburgh. Study participants were recruited by newspaper advertisements in the community. The clinical characteristics of the study participants are summarized in Table 1. All subjects were documented to be in good health by history, physical examination, and routine hematological and biochemical tests. None were receiving any medication that may affect glucose and lipid metabolism. Pubertal development was assessed by careful physical examination according to the criteria of Tanner (18) and confirmed to be Tanner stage I by measurements of plasma testosterone in males, estradiol in females, and dehydroepiandrosterone-sulfate in both.

Metabolic studies

All subjects were admitted to the General Clinical Research Center, on the previous afternoon, for testing on the morning after a 10–12 h overnight fast. Two iv catheters were inserted after the skin was anesthetized with Emla cream (Astra USA, Inc. Pharmaceutical Products, Westborough, MA). One was placed in a vein on the forearm for administration of [$^2\text{H}_5$]glycerol, and the second was placed in a vein on the dorsum of the contralateral heated hand for sampling of arterialized venous blood.

Total body lipolysis was measured at baseline, for 2 h, by the use of

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TABLE 1. Clinical characteristics, body composition, hormonal profile and fasting lipid concentrations of study subjects

	Blacks (10 M ± 10 F)	Whites (10 M ± 10 F)	<i>P</i>
Age (yr)	10.0 ± 0.2 (8.5–11.9)	9.8 ± 0.3 (8.0–13.1)	ns
Weight (kg)	35.4 ± 1.8 (27.6–55.6)	34.1 ± 1.4 (25.3–53.0)	ns
Height (cm)	138.9 ± 1.4 (126.4–152.4)	138.9 ± 2.1 (125.3–160.8)	ns
BMI (kg/m ²)	18.2 ± 0.7 (14.7–27.0)	17.6 ± 0.3 (14.3–20.5)	ns
FFM (kg)	25.9 ± 0.7 (21.3–31.8)	25.4 ± 1.0 (19.1–36.0)	ns
FM (kg)	7.6 ± 1.2 (2.8–21.8)	6.8 ± 0.6 (3.1–14.4)	ns
% BF	20.0 ± 2.1 (9.4–40.2)	20.1 ± 1.3 (10.3–29.1)	ns
VAT (cm ²)	16.4 ± 3.1 (3.2–48.9)	15.1 ± 2.6 (5.2–48.7)	ns
DHEAS (μmol/L)	0.12 ± 0.01 (0.02–0.21)	0.13 ± 0.02 (0.01–0.25)	ns
Estradiol (pmol/L)	21 ± 2 (18–37)	18 ± 0 (18–18)	ns
Testosterone (nmol/L)	0.02 ± 0.004 (0.01–0.05)	0.03 ± 0.008 (0.01–0.09)	ns
Cholesterol (mmol/L)	4.39 ± 0.13 (3.6–5.7)	4.28 ± 0.20 (2.9–6.7)	ns
Triglycerides (mmol/L)	0.75 ± 0.05 (0.5–1.2)	1.2 ± 0.16 (0.4–3.0)	0.007
HDL (mmol/L)	1.42 ± 0.09 (0.8–2.5)	1.30 ± 0.07 (0.7–1.9)	ns
LDL (mmol/L)	2.64 ± 0.15 (1.4–4.3)	2.41 ± 0.18 (1.2–4.9)	ns
VLDL (mmol/L)	0.33 ± 0.02 (0.2–0.6)	0.55 ± 0.07 (0.2–1.3)	0.008

M, Male; F, female; DHEAS, dehydroepiandrosterone-sulfate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant; % BF, percent body fat; VAT, visceral adipose tissue. Data are mean ± SE (range). One black boy had a BMI >95th percentile with 40.2% body fat. Excluding his data did not change the outcome of the results; therefore, he is included.

a prime (1.2 μmol/kg) constant rate (0.08 μmol kg⁻¹ min⁻¹) infusion of [²H₅]glycerol (Isotec, Miamisburg, OH) described by us previously (19, 20). Blood was sampled at 0 min, at the start of the stable isotope infusion, and every 10 min, from 90–120 min, for determination of plasma glucose, insulin, FFA, glycerol, and isotopic enrichment of glycerol. Fasting blood was obtained for cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and very-low-density lipoprotein (VLDL) determination.

Continuous indirect calorimetry, by a ventilated hood system (Deltatrac metabolic monitor; SensorMedics, Anaheim, CA), was used to evaluate substrate oxidation, as described by us previously (11, 19, 20). Each evaluation was performed for a 30-min period at the end of the 2-h isotope infusion.

Body composition and abdominal adiposity

Body composition was assessed using dual-energy x-ray absorptiometry (21). Intraabdominal fat was measured by a 10-mm single axial computed tomography scan of the abdomen at the level of L₄₋₅ lumbar vertebrae, as described by us before (21).

Biochemical measurements

Plasma glucose, insulin, FFA, and urinary nitrogen were measured according to our previously reported methods (10, 11, 19, 20). Serum glycerol was measured with a triglyceride kit (Sigma, St. Louis, MO). Plasma lipid levels were measured using the standards of the Centers for Disease Control and Prevention (22). Deuterium enrichment of glycerol in plasma was determined according to a modification of our previously described method (20). Plasma samples were deproteinized with methanol. The supernatant was dried in a vacuum centrifuge. The aldonitrile pentacetate derivatives were formed by adding 40 μL pyridine:acetic anhydride (1:1 vol) and incubating for 30 min at 70 C. The sample was cooled, briefly centrifuged, and dried in a vacuum centrifuge to remove all of the pyridine. Before analysis, 50 μL ethyl acetate was added. All analyses were carried out on a 5971 mass spectrometer (Hewlett-Packard Co., Palo Alto, CA), in the electron impact mode, coupled to a Hewlett-Packard Co. 5890 Series II gas chromatograph. The data acquisition was in the selective ion monitoring mode for masses *m/z* 145 and 148 for unlabeled and labeled glycerol. Standard curves of known enrichments were performed with each assay.

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Calculations

Total-body lipolysis was calculated from the rate of appearance of glycerol (Ra) in plasma according to steady-state tracer dilution equations (19, 20). Substrate oxidation rates were calculated from indirect calorimetric measurements according to the formulas of Frayn as described before (19, 20).

Statistical analysis

For continuous outcomes, between-group analyses (*i.e.* race or gender comparisons) were performed using ANOVA, in an attempt to control the experiment-wide α -rate. Data are presented as mean ± SE. $P \leq 0.05$ was considered statistically significant. Multiple-regression analysis was applied to evaluate multivariate relationships.

Results

AA and AW children were comparable, in regards to age, puberty (Tanner stage I), body mass index (BMI), body composition, and visceral adiposity (Table 1). BMI percentiles, based on race and gender specific data (23), ranged from 15–90th percentile in whites and 10–90th percentile in blacks except for one boy, who was above the 95th percentile. Excluding the latter subject from analysis did not change the outcome of the results; therefore, his data were kept in the analysis. Fasting lipid concentrations were similar except for triglycerides and VLDL, which were significantly lower in black children (Table 1).

Metabolic data

There were no differences between AA and AW children in fasting glucose (5.1 ± 0.07 *vs.* 5.2 ± 0.06 mmol/L), FFA (277 ± 34 *vs.* 235 ± 23 μmol/L), and glycerol levels (74 ± 5 *vs.* 67 ± 4 μmol/L). Fasting insulin concentrations were higher in AA children (99.6 ± 7.8 *vs.* 77.4 ± 5.9 pmol/L, $P = 0.032$). Figure 1 depicts that steady-state plasma isotopic enrichment was achieved during the last 30 min of [²H₅]glycerol infusion. Rates of lipolysis after overnight fasting were lower in AA children, compared with AW children, whether the data were expressed for total body (85.7 ± 8.9 *vs.* 130.3 ± 14.1 μmol/min, $P = 0.011$) or per kg body weight (2.4 ± 0.2 *vs.* 3.8 ± 0.4 μmol/min·kg, $P = 0.002$) or per kg FFM (3.3 ± 0.3 *vs.* 5.2 ± 0.5 μmol/min·kg FFM, $P = 0.004$), or per kg fat mass (13.7 ± 1.6 *vs.* 21.3 ± 3.3 μmol/min·kg FM, $P = 0.046$) (Fig. 2). Rates of fat oxidation (2.9 ± 0.3 *vs.* 2.8 ± 0.3 μmol/kg·min) and glucose oxidation (21.0 ± 1.4 *vs.* 22.8 ± 1.8 μmol/kg·min) were similar between the two groups. When the results were analyzed separately for each gender, data remained consistent with the total group. Basal rates of lipolysis were lower in AA girls *vs.* AW girls (2.8 ± 0.2 *vs.*

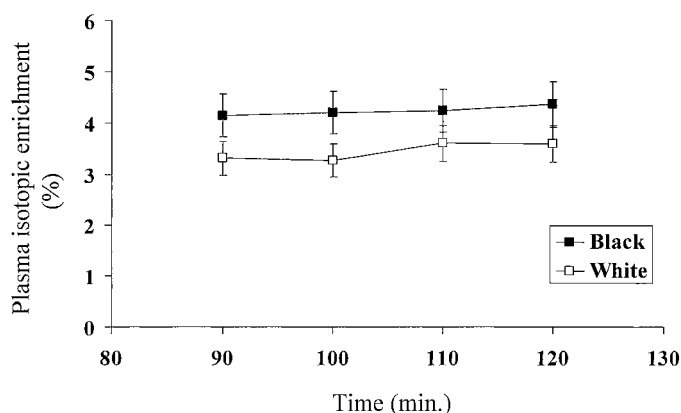


FIG. 1. Steady-state plasma isotopic enrichment of $[^2\text{H}_5]$ glycerol during the last 30 min of the 2-h isotope infusion.

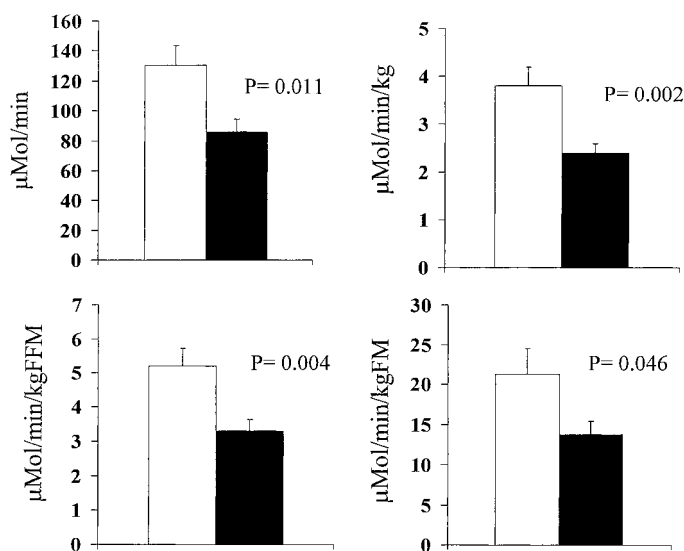


FIG. 2. Basal lipolysis (glycerol, Ra) in black (■) and white children (□).

$4.1 \pm 0.5 \mu\text{mol}/\text{kg}\cdot\text{min}$, $P = 0.029$) and in AA boys vs. AW boys (2.0 ± 0.3 vs. $3.6 \pm 0.6 \mu\text{mol}/\text{kg}\cdot\text{min}$, $P = 0.028$).

In all the subjects, lipolysis correlated with fat mass ($r = 0.42$, $P = 0.007$), percent body fat ($r = 0.38$, $P = 0.014$), visceral fat ($r = 0.39$, $P = 0.015$), and sc abdominal fat ($r = 0.42$, $P = 0.008$). These correlations were stronger in blacks (fat mass: $r = 0.743$, $P = 0.005$; percent body fat: $r = 0.737$, $P = 0.005$; visceral fat: $r = 0.643$, $P = 0.002$; and sc abdominal fat: $r = 0.635$, $P = 0.003$) than in whites (fat mass: $r = 0.41$, $P = 0.077$; percent body fat: $r = 0.19$, $P = 0.4$; visceral fat: $r = 0.35$, $P = 0.15$; sc abdominal fat: $r = 0.45$, $P = 0.06$). Fasting insulin

concentrations were weakly correlated with rates of lipolysis ($r = -0.295$, $P = 0.065$). Multiple-regression models were done to investigate the differential race effects on the measures of lipolysis after controlling for measures of body composition and insulin. These models were generated for each of the measures of lipolysis separately (Table 2). Race was the significant variable contributing to the variance in rates of lipolysis.

Discussion

The aim of the present study was to investigate whether it is possible to detect, early in childhood, biologic/metabolic markers that could potentially predispose black children to increased risk of obesity and type 2 diabetes. Our results demonstrate that AA children have approximately 40% lower rates of whole-body lipolysis, compared with their AW peers.

AA children are generally taller and heavier than Caucasian children of similar age (6, 8, 24–26), with a clear divergence in weight gain originating in late adolescence or early adulthood (6–8). Moreover, the disturbing increase in pediatric obesity and obesity-related type 2 diabetes in the United States is more pronounced in black children (4, 9, 27, 28). Differences in body fatness are believed to be the outcome of complex interactions among genetics, hormonal, and environmental influences that favor the net deposition of calories as fat (29). Based on previous observations of hyperinsulinemia in AA children (10–13), we hypothesized that hyperinsulinemia, through inhibiting lipolysis, promotes fat accretion and thus may play a pathophysiological role in the excess risk of development of obesity in blacks. Our results show that whole-body lipolysis is significantly lower in prepubertal AA children, compared with AW children, but independent of hyperinsulinemia. This black/white contrast is unlikely to be attributable to differences in body composition, body fat topography, and fat cell size (14, 30, 31), because blacks and whites had comparable body composition parameters (Table 1). Also, in multiple-regression analysis, after controlling for these variables, race remained a significant contributor to the variance in lipolysis. Data are almost nonexistent, with respect to black/white differences in fat metabolism. Obese middle-age black women were reported to have increased glycerol release from sc adipose tissue, compared with white women (32); however, the black women were insulinopenic. *In vitro* adipocyte studies from black men showed higher epinephrine-stimulated lipolytic values, compared with white men (33). Comparison between the results of these studies and ours is not appropriate be-

TABLE 2. Multiple regression models

Outcome variable	Model 1			Model 2			Model 3			Model 4		
	r^2	P	Race P	r^2	P	Race P	r^2	P	Race P	r^2	P	Race P
Glycerol Ra												
$\mu\text{mol}/\text{min}\cdot\text{kg}$.26	.014	.002	.276	.011	.001	.258	.014	.007	.282	.009	.001
$\mu\text{mol}/\text{min}\cdot\text{kg FFM}$.309	.004	.002	.303	.006	.001	.283	.008	.009	.330	.003	.001
$\mu\text{mol}/\text{min}\cdot\text{kg FM}$.20	.052	.078	.179	.079	.074	.139	.148	.196	.188	.070	.070
$\mu\text{mol}/\text{min}$.383	.001	.002	.375	.001	.002	.336	.002	.009	.392	.001	.002

Models independent variables are as follows: model 1 fasting insulin + race + FM; model 2 fasting insulin + race + visceral fat; model 3 fasting insulin + race + % BF; model 4 fasting insulin + race + sc abdominal fat.

cause of major differences in age, presence or absence of obesity, and local *vs. in vitro vs.* total body lipolysis. The lower rates of lipolysis could explain the significantly lower triglyceride and VLDL levels in black children in our study and in others (24, 34, 35). Despite lower rates of lipolysis in black children, rates of fat oxidation were similar to those of whites. Thus, it seems that black children burn fat more efficiently than whites. Whether or not this is a physiologic compensatory mechanism to protect against weight gain remains to be determined.

Lipolysis is exquisitely sensitive to the antilipolytic effect of insulin (14, 15, 17). In the present study, fasting insulin level was approximately 20% higher in black, compared with white, children. This is in agreement with other investigators' findings of approximately 25% higher fasting insulin in black children (13). Contrary to our hypothesis, however, this hyperinsulinemia does not seem to explain the lower rates of lipolysis in blacks. It is possible though that blacks have increased fat cell sensitivity to the antilipolytic effect of insulin. This issue should be pursued further by performing stepwise insulin clamp experiments to generate insulin dose-response curves for suppression of lipolysis in blacks *vs.* whites. In this regard, it is interesting to note that a recent publication demonstrated that obese AA women, despite being resistant to insulin as a glucoregulatory hormone, were sensitive to insulin's antilipolytic action (36). It remains to be investigated whether, in black children, there is differential sensitivity to the action of insulin on glucose *vs.* fat metabolism starting early in life.

Debate continues in the literature as to whether or not hyperinsulinemia is a result or a cause of obesity (37, 38). In 1962, the so-called thrifty genotype hypothesis was proposed by Neel (39). Fundamental to this theory is the hypothesis that hyperinsulinemia precedes obesity, with a differential in the insulin action on glucose *vs.* fat metabolism (40). The sum total of the antilipolytic effect of insulin would be increased, and mobilization of stored fat would be inhibited, *i.e.* lipid trapping. In 5- to 9-yr-old Pima Indian children who were followed longitudinally for approximately 10 yr, higher baseline fasting insulin concentration was associated with higher rates of weight gain and excess fat deposition in favor of the thrifty genotype (41). Furthermore, decreased rates of lipolysis *in vitro* were predictive of weight gain in nondiabetic Pima Indians (42). In agreement with the thrifty genotype theory, our results in AA children, a high-risk population for obesity and type 2 diabetes, demonstrate lower rates of lipolysis and higher levels of insulinemia. To our knowledge, the present study represents the first attempt to investigate black/white differences in rates of lipolysis early in childhood.

In summary, the present results suggest that nature may contribute to the increased risk of obesity in black children. Reduced rates of lipolysis in black normal children may constitute an early metabolic phenotype that may mediate fat trapping and susceptibility to obesity in a specific environmental context of energy surplus and hyperinsulinemia. It is intuitive that biologic risk markers be investigated at an early stage, before obesity sets in, because obesity-associated metabolic adaptations will overshadow the primary events ultimately leading to obesity. Longitudinal follow-up, how-

ever, is of utmost importance to investigate the future outcome of these biologic/metabolic markers and their relationship to weight gain.

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