Visceral Fat, Insulin Sensitivity, and Lipids in Prepubertal Children

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In adults, visceral fat accumulation is associated with insulin resistance and dyslipidemia. The cause-and-effect nature of these relationships is not clear. The objective of the present study was to determine if similar relationships exist in prepubertal children. Specifically, we determined whether visceral fat was associated with fasting insulin, insulin sensitivity (S_i), serum triglyceride (TG) concentration, or serum HDL cholesterol (HDL-C) concentration; whether visceral fat or S_i was independently related to lipids; and whether ethnicity influenced the relationship between visceral fat and risk factors. Subjects were 61 prepubertal African-American and Caucasian children. Total body fat was determined by dual-energy X-ray absorptiometry, visceral fat by computed tomography, and insulin sensitivity by the tolbutamide-modified, frequently sampled intravenous glucose tolerance test with minimal modeling. In multiple linear regression analysis (adjusting for total fat, sex, and ethnicity), visceral fat was independently related to TG ($P < 0.05$) and fasting insulin ($P < 0.001$), but not S_i ($P = 0.425$). Total body fat was independently related to S_i ($P < 0.001$). S_i was independently related to fasting insulin ($P < 0.001$) but not to TG or HDL-C ($P = 0.941$ and 0.201, respectively). S_i in African-Americans was 42% lower than in Caucasians (0.50 ± 0.05 vs. $0.86 \pm 0.11 \times 10^{-5}$ $min^{-1} \cdot pmol^{-1} \cdot l$, mean ± SE after adjusting for total fat, $P < 0.001$). Nonetheless, ethnicity was not independently related to either TG or HDL-C ($P = 0.075$ and 0.619, respectively, after adjusting for total and visceral fat and sex). The slopes of the relationships of total and visceral fat with risk factors did not differ with ethnicity. In conclusion, visceral fat appears metabolically unique in children, being independently associated with elevated TG and insulin but not S_i. Obese children and African-American children were more insulin resistant, independent of visceral fat accumulation. Lower S_i was associated with higher, faster insulin, but not dyslipidemia. Thus, obesity, visceral fat accumulation, and ethnicity in children may confer negative, but independent, health risks.
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ANCOVA, analysis of covariance; CT, computed tomography; CV, coefficient of variation; DXA, dual-energy X-ray absorptiometry; GCRC, General Clinical Research Center; HDL-C, HDL cholesterol; SAAT, subcutaneous abdominal adipose tissue; S_i, insulin sensitivity; TG, triglyceride; UAB, University of Alabama at Birmingham.

In adults, visceral fat accumulation and insulin resistance often occur simultaneously and in concert with a suite of other metabolic disturbances ("syndrome X"), including hyperinsulinemia, glucose intolerance, low HDL cholesterol (HDL-C), elevated triglycerides (TGs), and hypertension (1,2). Presence of one or more of these metabolic abnormalities confers risk for coronary heart disease and type 2 diabetes (3).

Visceral fat accumulates with age and is greater in men and more obese individuals (4–6). It is metabolically unique when compared with subcutaneous adipose tissue, being more sensitive to lipolytic stimuli, such as norepinephrine (7). This characteristic, along with the proximity of visceral fat to the hepatic portal vasculature, is hypothesized to be responsible for the positive association between visceral fat, dyslipidemia, hyperinsulinemia, and glucose intolerance (8,9). By contributing free fatty acids to the liver, visceral fat leads to increased circulating TG, decreased HDL-C, increased hepatic glucose production, and decreased hepatic insulin extraction. Both predisposition to syndrome X and the distribution of body fat are influenced by ethnicity. Type 2 diabetes clusters more strongly with the components of syndrome X in Caucasians than in African-Americans (10), and 25–33% of African-Americans with type 2 diabetes are not insulin resistant (11). Compared with Caucasians, African-Americans have less visceral fat (12–15). The possible contribution of lower visceral fat among African-Americans to the reduced incidence and severity of syndrome X has not been thoroughly investigated.

Although well accepted as a common obesity-related disease in adults, syndrome X has not been extensively studied in children. Visceral fat accumulations of up to 114 cm^2 have been measured in prepubertal children (16), and lipid concentrations, insulin concentrations, and insulin resistance are associated with obesity in children (16–19). Few studies of children have included actual measures of both visceral fat and insulin sensitivity, however. An improved understanding of the importance of visceral fat to insulin and lipid metabolism in children may yield insight into the risks associated with child obesity and the early stages of the development of metabolic diseases in adults.

The present study was conducted *1*) to examine the influence of visceral fat on fasting insulin, TG, HDL-C, and insulin sensitivity; *2*) to examine the relationship between insulin sensitivity and lipids (TG, HDL-C); and *3*) to determine in a biracial cohort if ethnic differences exist in the relationship between visceral fat and risk factors in children.

RESEARCH DESIGN AND METHODS

Subjects. Study subjects were part of an ongoing, longitudinal study on intra-abdominal fat and disease risk in children and adolescents. African-American and Caucasian children were originally recruited by newspaper and radio advertisements and word of mouth. The present study included only those subjects determined to be Tanner stage 1 (20,21) by physician evaluation of both breast development and pubic hair in females and genitalia in males. Children with evidence of either breast development or pubic hair growth were classified as stage 2. To further evaluate developmental status, serum levels of estradiol and testosterone were measured. All children classified as stage 1 had undetectable levels of estradiol (<15.42 pmol/l), and most had undetectable levels of testosterone (<0.41 nmol/l); when detectable (six cases), levels of testosterone ranged from 0.42 to 1.29 nmol/l, suggesting a minimal degree of maturation (below stage 2) (22). No child was taking medications known to affect body composition (such as Ritalin or growth hormone), diagnosed with syndromes or diseases known to affect body composition or fat distribution (such as Cushing's, Down's, or type 1 diabetes), or diagnosed with any major illness since birth. Ethnicity was determined by self-report. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham (UAB), and parents provided informed consent before testing commenced.

Protocol. Children were admitted to the General Clinical Research Center (GCRC) in the late afternoon for an overnight visit. Anthropometric measurements were obtained on arrival. A computed tomography (CT) scan was conducted in the Department of Radiology, UAB, at ~1700. The children were served dinner and an evening snack, with all food consumed before 2000. All children were fed a fixed meal of 55% carbohydrate, 15% protein, and 30% fat. Consumption of only water and noncaloric, noncaffeinated beverages was permitted between 2000 and testing the following morning. Two weeks after testing at the GCRC, children returned to the Department of Nutrition Sciences at UAB for body composition analysis by dual-energy X-ray absorptiometry (DXA).

Tolbutamide-modified frequently sampled intravenous glucose tolerance test. At 0600 on the morning after GCRC admission, a topical anesthetic (Emla cream) was applied to the antecubital space of both arms, and at ~0700, flexible intravenous catheters were placed. A blood sample was drawn for lipid analysis. Three additional blood samples (2.0 ml) were taken for determination of basal glucose and insulin. At time 0, glucose (25% dextrose; 11.4 g/m^2) was administered intravenously. Blood samples (2.0 ml) were then collected at the following times relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. Tolbutamide (125 mg/m^2) was injected intravenously at 20 min. Sera were analyzed for glucose and insulin, and values were entered into the MINMOD computer program (version 3.0) for determination of insulin sensitivity (23–25).

Assay of glucose and insulin. Glucose was measured in 10 µl serum using an Ektachem DT II System (Johnson and Johnson Clinical Diagnostics, Rochester, NY). In our laboratory, this analysis has a mean intra-assay coefficient of variation (CV) of 0.61% and a mean interassay CV of 1.45%. Insulin was assayed in duplicate 200-µl aliquots with Coat-A-Count kits (Diagnostic Products, Los Angeles, CA). According to the supplier, cross-reactivity of this assay with proinsulin is ~40% at midcurve; C-peptide is not detected. In our laboratory, this assay has a sensitivity of 11.4 pmol/l (1.9 µIU/ml), a mean intra-assay CV of 5%, and a mean interassay CV of 6%. Commercial-quality control sera of low, medium, and high insulin concentration (Lyphochek; Bio-Rad, Anaheim, CA) are included in every assay to monitor variation over time.

Determination of blood lipids. Total cholesterol, HDL-C, and TG were measured with the Ektachem DT II System. With this system, HDL-C is measured after precipitation of LDL and VLDL with Dextran sulfate and magnesium chloride. Control sera of low and high substrate concentration are analyzed with each group of samples, and values for these controls must fall within accepted ranges before samples are analyzed. The DT II is calibrated every 6 months with reagents supplied by the manufacturer. LDL cholesterol was estimated using the Friedewald formula (26). Due to their association with syndrome X and cardiovascular disease, TG and HDL-C were used as dependent variables in statistical analyses.

Assay of estradiol and testosterone. Estradiol was measured by double-antibody radioimmunoassay and testosterone by coated-tube radioimmunoassay (both from Diagnostic Products). In our laboratory, these assays can detect 15.42 pmol/l estradiol and 0.41 nmol/l testosterone. Intra- and interassay CV for estradiol are 3.6 and 5.2%, respectively, and for testosterone, 2.7 and 8.6%.

Measurement of body composition and fat distribution. Subcutaneous abdominal adipose tissue (SAAT) and visceral fat (intra-abdominal adipose tissue) were measured by CT scanning with a HiLight/Advantage Scanner (General Electric, Milwaukee, WI) as previously described (27). A single-slice scan (5 mm) of the abdomen was performed at the level of the umbilicus and analyzed for cross-sectional area of adipose tissue using the density contour program. CT data are presented as cross-sectional area of tissue (cm^2) with Hounsfield units for adipose tissue of –190 to –30. We have shown the test-retest reliability for visceral fat to be 1.7% (28). All scans were analyzed by the same investigator (T.R.N.). The total-body radiation dose to each subject was approximately 0.26 rad. This dose is less than that received from a standard chest X-ray.

Body composition (fat mass and fat-free mass) was measured by DXA using a Lunar DPX-L densitometer (LUNAR Radiation, Madison, WI). We have previously validated the use of DXA against carcass analysis in a pig model that encompassed the pediatric weight range (29). Subjects were scanned in light clothing while lying flat on their backs with arms at their sides. DXA scans were performed and analyzed with pediatric software version 1.5e.

Statistics. Body composition and biochemical measurements were log transformed before analyses to remove skewness in the distribution. Two-way analysis of variance was used to compare baseline physical and metabolic characteristics of the subjects by sex and ethnicity. Pearson correlation analysis was used to examine relationships within each ethnic group between insulin sensitivity (S_I), visceral fat, total fat, SAAT, and risk factors of interest.

TABLE 1
Descriptive statistics

	African-Americans		Caucasians		Two-way analysis of variance*
	Male	Female	Male	Female	
n	21	17	14	9	
Age (years)	8.6 ± 1.2 (7.0–10.9)	8.9 ± 1.4 (6.7–11.0)	9.0 ± 1.4 (6.6–11.0)	9.2 ± 1.0 (8.0–11.0)	NS
Body mass (kg)	38.9 ± 14.0 (24.6–72.5)	35.0 ± 12.6 (16.0–61.8)	40.0 ± 12.8 (22.1–63.9)	39.1 ± 17.0 (24.6–77.9)	NS
BMI (kg/m^2)	20.6 ± 5.0 (14.1–35.0)	18.8 ± 5.2 (13.1–30.5)	20.9 ± 4.5 (13.8–27.8)	20.5 ± 5.8 (15.5–30.7)	NS
Total fat mass (kg)	9.1 ± 7.5 (1.7–28.6)	10.5 ± 7.8 (1.9–27.9)	11.3 ± 8.2 (2.0–24.0)	12.1 ± 9.7 (4.7–33.8)	NS
Visceral fat (cm^2)	34.1 ± 24.1 (10.0–111.0)	26.6 ± 16.8 (9.4–57.8)	43.2 ± 23.8 (14.3–92.1)	48.4 ± 33.4 (15.2–104.3)	Ethnicity†
SAAT (cm^2)	74.2 ± 75.4 (9.9–270.0)	115.4 ± 120.3 (8.8–436.1)	143.4 ± 108.7 (19.5–297.0)	137.7 ± 127.7 (36.6–414.9)	Ethnicity‡
Fasting insulin (pmol/l)	83 ± 57 (24–216)	75 ± 32 (24–132)	72 ± 31 (24–120)	97 ± 72 (36–222)	NS
Fasting glucose (mmol/l)	5.2 ± 0.3 (4.7–5.7)	5.1 ± 0.4 (4.3–5.7)	5.2 ± 0.2 (4.9–5.5)	5.0 ± 0.2 (4.8–5.4)	Sex‡
S_I ($\times 10^{-5}$ min^{-1} · pmol^{-1} · l)	0.78 ± 0.47 (0.10–1.77)	0.52 ± 0.29 (0.13–1.19)	0.89 ± 0.58 (0.28–2.27)	1.41 ± 1.14 (0.11–3.85)	Ethnicity†
TG (mmol/l)	0.48 ± 0.18 (0.25–0.96)	0.56 ± 0.30 (0.25–1.43)	0.75 ± 0.35 (0.25–1.56)	0.80 ± 0.43 (0.32–1.66)	Ethnicity§
Total cholesterol (mmol/l)	4.52 ± 1.09 (3.26–7.37)	3.84 ± 0.82 (2.22–5.15)	4.05 ± 0.58 (3.15–5.28)	3.92 ± 0.42 (3.41–4.65)	Sex‡
HDL-C (mmol/l)	1.16 ± 0.30 (0.67–1.89)	1.06 ± 0.24 (0.67–1.40)	1.00 ± 0.19 (0.78–1.45)	0.88 ± 0.17 (0.62–1.06)	Ethnicity†; sex‡
LDL-cholesterol (mmol/l)	3.13 ± 1.21 (1.93–6.06)	2.52 ± 0.64 (1.36–3.56)	2.71 ± 0.57 (1.94–3.92)	2.68 ± 0.41 (2.14–3.27)	NS

Data are means ± SD (range). *Significant main effects. †$P < 0.05$; ‡$0.05 < P < 0.1$; §$P < 0.01$.

TABLE 2
Pearson correlation coefficients for S_i, adipose tissue, and risk factors

	S_i		Total fat		SAAT		Visceral fat	
	African-American	Caucasian	African-American	Caucasian	African-American	Caucasian	African-American	Caucasian
Fasting insulin	–0.72*	–0.81*	0.52*	0.85*	0.52*	0.85*	0.61*	0.87*
S_i	—	—	–0.70*	–0.78*	–0.69*	–0.79*	–0.50†	–0.75*
TG	–0.29	–0.34	0.45†	0.38	0.43†	0.43‡	0.48†	0.47‡
HDL-C	0.08	0.24	–0.36‡	–0.23	–0.30	–0.23	–0.33‡	–0.25

Data are Pearson correlation coefficients. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Multiple linear regression analysis was used to determine if ethnicity, visceral fat, and S_i were significantly related to risk factors after adjusting for confounding variables (total fat and sex, plus TG in the model for HDL-C). In the first analysis, total fat was entered into these models to adjust for greater visceral fat in more obese children. In the second analysis, SAAT was substituted for total fat to control for subcutaneous upper-body fat. In these analyses, a significant effect of visceral fat indicated a specific and unique relationship of visceral fat with the dependent variable, independent of either total fat mass or SAAT.

When risk factors were significantly and independently related to any of the independent variables used in multiple regression, analysis of covariance (ANCOVA) was used to generate adjusted means for each ethnic group. Adjusted means were generated for fasting insulin (covariate = visceral fat), insulin sensitivity (covariate = total fat), and TG (covariate = visceral fat). Interaction terms were included to determine if the relationship between fat (total or visceral) and risk factors differed with ethnicity. No adjusted mean was generated for HDL-C, because the only significant independent variable was another risk factor (TG). It was thought that a clearer view of ethnic differences in risk factors would be given by showing HDL-C without adjustment for TG. Likewise, fasting insulin was not adjusted for S_i. All analyses were performed with SAS version 6.12. Differences or effects were considered significant if $P < 0.05$.

RESULTS

Descriptive statistics. Caucasian and African-American children did not differ with respect to age, body mass, BMI, or total body fat mass (Table 1). On average, Caucasian children had more visceral fat and SAAT, as previously reported (15). On average, insulin sensitivity and TG were greater, and HDL-C lower, in the Caucasian group. Fasting concentrations of glucose, insulin, total cholesterol, and LDL cholesterol did not differ with ethnicity or sex, although glucose tended to be lower in girls. When ANCOVA was used to determine if an interaction existed between sex and ethnicity for any of the dependent variables of interest, no interaction terms were significant.

TABLE 3
Multiple linear regression models for risk factors, including total fat as an independent variable to test for unique contributions of visceral fat

Variables	Parameter estimate ± SE	P
Dependent variable: log fasting insulin (model $R^2 = 0.68$)		
Independent variables		
Log total fat	–0.10 ± 0.10	0.325
Log visceral fat	0.427 ± 0.113	<0.001
Log S_i	–0.391 ± 0.074	<0.001
Sex (M = 1, F = 2)	0.029 ± 0.038	0.447
Ethnicity (Caucasian = 1, African-American = 2)	–0.010 ± 0.044	0.813
Dependent variable: log TG (model $R^2 = 0.35$)		
Independent variables		
Log visceral fat	0.308 ± 0.140	0.032
Log total fat	0.041 ± 0.120	0.734
Log S_i	0.007 ± 0.092	0.941
Sex (M = 1, F = 2)	0.050 ± 0.047	0.295
Ethnicity (Caucasian = 1, African-American = 2)	–0.099 ± 0.054	0.075
Dependent variable: log HDL-C (model $R^2 = 0.31$)		
Independent variables		
Log visceral fat	–0.060 ± 0.078	0.445
Log total fat	–0.062 ± 0.065	0.339
Log S_i	–0.064 ± 0.050	0.201
Log TG	–0.146 ± 0.072	0.049
Sex (M = 1, F = 2)	–0.042 ± 0.026	0.111
Ethnicity (Caucasian = 1, African-American = 2)	0.015 ± 0.030	0.619
Dependent variable: log S_i (model $R^2 = 0.54$)		
Independent variables		
Log total fat	–0.602 ± 0.154	<0.001
Log visceral fat	–0.162 ± 0.201	0.425
Sex (M = 1, F = 2)	–0.017 ± 0.068	0.802
Ethnicity (Caucasian = 1, African-American = 2)	–0.254 ± 0.071	<0.001

$P < 0.05$ is considered significant.

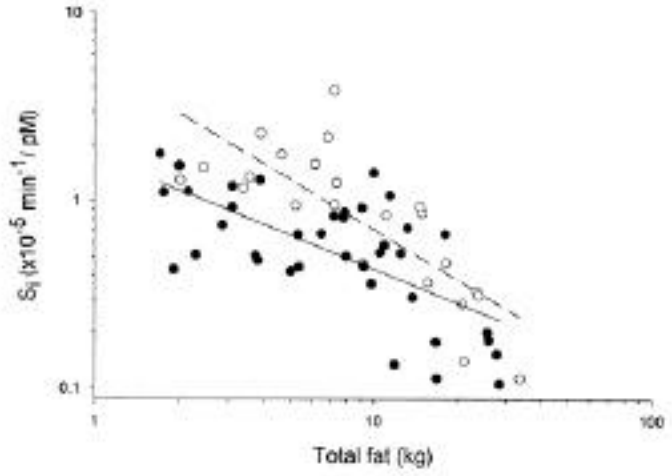

FIG. 1. Insulin sensitivity versus total fat in African-American (●) and Caucasian (○) children. Slopes of the two lines do not differ (–0.60 [$\times 10^{-5}$ min^{-1} · pmol^{-1} · l]/kg total fat for African-Americans and –0.88 [$\times 10^{-5}$ min^{-1} · pmol^{-1} · l]/kg total fat for Caucasians; P = 0.138).

Pearson correlation coefficients. Correlation analysis indicated that all adipose depots were positively correlated with fasting insulin and TG (with the exception of total fat and TG in Caucasians) and inversely correlated with insulin sensitivity in both groups of children (Table 2). Visceral and total fat were correlated (inversely) with HDL-C only among African-American children. Insulin sensitivity was inversely correlated with fasting insulin in both ethnic groups but was not associated with TG or HDL-C in either group.

Regression models. Multiple linear regression analysis indicated that both visceral fat and S_i were independently related to fasting insulin, after adjusting for total fat, sex, and ethnicity (Table 3). For the dependent variable TG, only visceral fat was independently related. The model for HDL-C indicated that only TG was independently and inversely related. For the dependent variable S_i, both total fat and ethnicity were independently and inversely related, with more obese children and African-American children having lower S_i (Fig. 1). Substitution of SAAT for total fat resulted in essentially identical results, with SAAT replacing total fat as having a significant independent contribution to S_i (Table 4).

ANCOVA. After adjusting for adiposity (total or visceral, as indicated in multiple regression) via ANCOVA, fasting insulin was 25% higher and insulin sensitivity was 42% lower in African-Americans; TG was 26% greater in Caucasians. None of the interaction terms (log visceral or total fat × ethnicity) were significant.

Figure 2 illustrates schematically the relationships between body fat and risk factors found in the present study. Obesity (total body fat) was associated with greater visceral fat and lower S_i. African-American ethnicity was associated with less visceral fat, lower S_i, and lower TG. Greater visceral fat was associated with higher fasting insulin and TG. Lower S_i was associated with higher fasting insulin. Higher TG was associated with lower HDL-C.

TABLE 4
Multiple linear regression models for risk factors, including SAAT as an independent variable to test for unique contributions of visceral fat

Variables	Parameter estimate ± SE	P
Dependent variable: log fasting insulin (model R^2 = 0.68)		
Independent variables		
Log SAAT	–0.002 ± 0.152	0.989
Log visceral fat	0.427 ± 0.114	<0.001
Log S_i	–0.391 ± 0.077	<0.001
Sex (M = 1, F = 2)	0.029 ± 0.039	0.452
Ethnicity (Caucasian = 1, African-American = 2)	–0.011 ± 0.050	0.831
Dependent variable: log TG (model R^2 = 0.35)		
Independent variables		
Log visceral fat	0.310 ± 0.141	0.032
Log SAAT	0.116 ± 0.188	0.541
Log S_i	0.019 ± 0.095	0.843
Sex (M = 1, F = 2)	0.048 ± 0.048	0.316
Ethnicity (Caucasian = 1, African-American = 2)	–0.081 ± 0.062	0.197
Dependent variable: log HDL-C (model R^2 = 0.30)		
Independent variables		
Log visceral fat	–0.092 ± 0.074	0.221
Log SAAT	–0.019 ± 0.051	0.713
Log S_i	–0.052 ± 0.051	0.318
Log TG	–0.147 ± 0.073	0.049
Sex (M = 1, F = 2)	–0.045 ± 0.026	0.085
Ethnicity (Caucasian = 1, African-American = 2)	0.013 ± 0.032	0.682
Dependent variable: log S_i (model R^2 = 0.56)		
Independent variables		
Log visceral fat	–0.185 ± 0.184	0.321
Log SAAT	–0.494 ± 0.116	<0.001
Sex (M = 1, F = 2)	–0.012 ± 0.067	0.857
Ethnicity (Caucasian = 1, African-American = 2)	–0.320 ± 0.068	<0.001

$P < 0.05$ is considered significant.

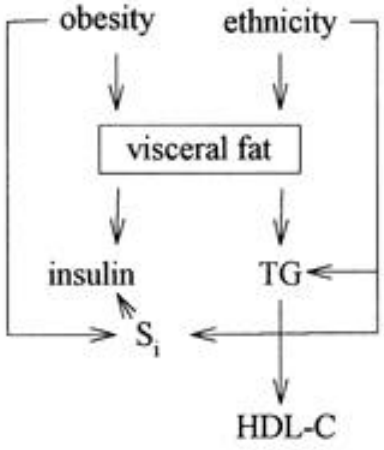

FIG. 2. Relationships between obesity, visceral fat, S_i, and lipids in prepubertal African-American and Caucasian children. Ethnicity and visceral fat were independently related to risk factors (insulin resistance, fasting insulin, TG); total fat was independently related to S_i; and ethnicity was independently related to visceral fat.

DISCUSSION

The primary findings of this study were as follows. *1*) Visceral fat was related to concentrations of both TG and fasting insulin, independent of total fat and SAAT; however, no such relationship existed between visceral fat and S_i. The relationships between visceral fat and risk factors did not differ with ethnicity. *2*) S_i was not independently related to lipid concentrations. These observations suggest that both obesity and visceral fat accumulation may confer unique health risks on prepubertal children. Associations observed in adults between visceral fat and S_i and between S_i and lipids were not observed in prepubertal children, perhaps suggesting that these associations develop with age, sexual maturation, or establishment of disease.

The first objective of the study was to determine if visceral fat was independently related to metabolic risk factors in prepubertal children. We found that visceral fat was related to both TG and fasting insulin, independent of both total fat and SAAT (Tables 3 and 4), suggesting that the influence of visceral fat is unique in children, as it is in adults. The relationship between visceral fat and fasting insulin was independent of S_i, which often is inversely correlated with visceral fat in adults (13,14). One potential mechanism through which visceral fat may affect fasting insulin is through an effect on hepatic insulin extraction. Exposure of the liver to free fatty acids may decrease hepatic insulin clearance (30,31). Thus, mobilization of free fatty acids from visceral fat may result in elevated fasting insulin.

Despite having independent associations with both TG and fasting insulin, visceral fat was not independently associated with S_i. This is somewhat surprising, in light of the strong association of these factors in adults, including African-Americans with type 2 diabetes (32) (but some studies show an association of S_i with SAAT but not visceral fat [33,34]). In our study population, total fat and SAAT, but not visceral fat, were independently associated with S_i. Thus, although more obese children were more insulin resistant, visceral fat made no independent contribution to this risk.

The second objective of the present study was to determine if S_i was independently related to TG and HDL-C in prepubertal children. We found that S_i was not independently related to TG and that visceral fat was the only physiological variable uniquely related to TG. As expected based on the known ability of elevated TG to decrease HDL-C (35), HDL-C was inversely associated with TG. Thus, our data suggest that early in obesity-related metabolic disturbances, elevated TG and insulin resistance are not causally related to each other; elevated TG occurs secondary to visceral obesity, whereas insulin resistance is primary a consequence of peripheral obesity.

The third objective of our study was to determine if ethnic differences existed in the relationship between visceral fat and risk factors in prepubertal children. ANCOVA with fasting insulin and TG as dependent variables showed no significant interaction between visceral fat and ethnicity. Thus, for a given increment in visceral fat, we would expect the change in fasting insulin and TG to be similar in African-American and Caucasian children. The reduction in the magnitude of the ethnic difference in TG after adjusting for visceral fat ($P < 0.01$, Table 1, to $P < 0.05$, Table 5) suggested that the higher TG in the Caucasian group was due primarily to greater absolute visceral fat. Likewise, the ethnic difference in HDL-C (lower in Caucasians, Table 1) disappeared after adjusting for TG and other variables (Tables 3 and 4; only TG was independently related to HDL-C). Because visceral fat was the main determinant of TG, and TG of HDL-C, we can assume that the ethnic difference in HDL-C had its origins in the greater visceral fat of the Caucasian children.

The interaction between total body fat and ethnicity was also examined. The only dependent variable to which total fat was independently related was S_i. No significant total fat × ethnicity interaction was found for S_i. Thus, for a given increment in total fat, we would expect the change in S_i to be similar in African-American and Caucasian children (Fig. 1). Therefore, both total and visceral adiposity appear to confer similar risks to children of both ethnic groups. This conclusion agrees with data from adults indicating a similar relationship between visceral fat and S_i in black versus white women (14).

The regression model for S_i indicated independent effects of both total fat and ethnicity (Table 3). After adjusting for total fat, S_i was lower in African-American than Caucasian children (Table 5). This is the first study to demonstrate an independent effect of African-American ethnicity on insulin sensitivity in prepubertal children. No significant ethnic difference in insulin sensitivity between African-American (n = 12) and Caucasian (n = 11) prepubertal children was found in a previous study conducted with hyperglycemic clamps (36). However, the group mean for insulin sensitivity was higher in Caucasian children (21.6 ± 2.8 vs. 17.4 ±

TABLE 5
Insulin, insulin sensitivity, and triglycerides in African-American and Caucasian children

	African-American	Caucasian
Fasting insulin (pmol/l)*	75 ± 5	60 ± 5‡
Insulin sensitivity ($\times 10^{-5}$ min^{-1} · pmol^{-1} · l)†	0.50 ± 0.05	0.86 ± 0.11§
Triglyceride (mmol/l)*	0.50 ± 0.03	0.63 ± 0.06‡

*Adjusted for log visceral fat. †Adjusted for log total fat. ‡$P < 0.05$; §$P < 0.001$.

2.7 mg · kg^{-1} · min^{-1} per μU/ml; $P > 0.05$), suggesting that, with a larger sample size, the difference may have been statistically significant. These observations suggest that the lower S_i observed in African-American versus Caucasian adults (37,38) has its origins in childhood. The physiological cause of the ethnic difference in S_i is not clear. Data from our study suggest that ethnic differences in physical activity (hours per week) and physical fitness (maximal oxygen consumption) do not account for differences in insulin sensitivity and insulin secretion (C-Y. Ku, B.A.G., G.R. Hunter, and M.I.G., unpublished observation). It will be important to determine both the cause of the ethnic difference in S_i and if lower S_i in African-American children elevates risk for development of type 2 diabetes.

Insulin sensitivity in this study was determined by use of minimal model analysis of glucose and insulin data from a tolbutamide-modified frequently sampled intravenous glucose tolerance test. In adults, estimates of insulin sensitivity derived with this method correlate well with those determined by euglycemic clamp (r = 0.84) (39). The minimal model method was selected for use in this study because of concern that reduced hepatic insulin clearance observed in both adult (37) and adolescent (40) African-Americans (versus Caucasians) may confound use of simpler proxy indicators of insulin sensitivity (such as fasting insulin). As determined with the minimal model, S_i reflects glucose disappearance due to both peripheral glucose uptake and decreased endogenous glucose production (41). Without use of isotope-labeled glucose, these two components cannot be individually quantified. It will be of interest to determine the relative contribution of glucose uptake and glucose production to ethnic differences in insulin sensitivity.

Lower insulin sensitivity often is reflected in greater fasting insulin. This was true in the present study as well; insulin sensitivity and visceral fat were the only independent variables to emerge as significantly related to fasting insulin (Table 3). Thus, after adjusting for visceral fat, African-American children had greater fasting insulin (75 ± 5 vs. 60 ± 5 pmol/l, adjusted mean ± SE, $P < 0.05$; Table 5), reflecting their lower insulin sensitivity. When adjusted only for insulin sensitivity, however, fasting insulin in African-American children was lower (63 ± 4 vs. 79 ± 6 pmol/l, $P < 0.05$). These observations indicate that lower visceral fat among African-Americans effectively counteracted the influence of lower insulin sensitivity on fasting insulin, resulting in an absence of an ethnic difference in unadjusted fasting insulin values (Table 1).

In our study population, Caucasian children had absolutely more visceral fat than African-American children. This difference remained significant after adjusting for total body fat, age, and sex ($P < 0.01$; data not shown), similar to what has been reported previously from analyses with this subject population (15). Greater visceral fat in Caucasian versus African-American adult women has been demonstrated as well (12–14). Perhaps greater visceral fat in Caucasians, present even in childhood, may be a factor contributing to the greater incidence of syndrome X in Caucasian adults.

In conclusion, our study indicated that visceral fat is metabolically unique in children, being associated with elevated TG and fasting insulin independent of total fat and SAAT. There was no significant influence of visceral fat on S_i or S_i on lipids (after adjusting for total fat or SAAT) as is generally observed in adults, however, suggesting that such associations develop with progression of age, visceral obesity, or insulin resistance. Longitudinal observations will be required to determine if the observed associations between visceral fat and risk factors ultimately increase disease risk or incidence. African-American children had lower S_i values than Caucasian children, after adjusting for confounding factors. The physiological reason for ethnic differences in S_i in both children and adults is unknown.

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