Influence of Total vs. Visceral Fat on Insulin Action and Secretion in African American and White Children

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Abstract

GORAN, MICHAEL I., RICHARD N. BERGMAN, AND BARBARA A. GOWER. Influence of total vs. visceral fat on insulin action and secretion in African American and white children. *Obes Res.* 2001;9:423–431.

Objective: To examine whether total body fat (FAT) in general or visceral fat (VFAT) in particular is associated with greater metabolic risk in white and African American children.

Research Methods and Procedures: A total of 68 white and 51 African American children had measures of insulin sensitivity (Si) and acute insulin response (AIR) by a frequently sampled intravenous glucose tolerance test, total body fat by DXA and abdominal fat distribution (visceral vs. subcutaneous) by computed tomography. The influence of FAT and VFAT on insulin parameters were examined by comparing subgroups of children with high or low FAT vs. high or low VFAT and by multiple regression analysis.

Results: In whites, fasting insulin, Si, and AIR were significantly influenced by FAT, but not VFAT (e.g., for Si, 9.8 ± 0.8 in low FAT vs. $4.6 \pm 0.7 \times 10^{-4}$/min/[$\mu$IU/mL[in high FAT, $p < 0.05$; 6.8 ± 0.7 in low VFAT vs. $7.5 \pm 0.8 \times 10^{-4}$/min/[$\mu$IU/mL] in high VFAT, $p > 0.1$). In African Americans, fasting insulin and Si were also primarily influenced by FAT (e.g., for Si, 4.9 ± 0.4 in low FAT vs. $2.8 \pm 0.5 \times 10^{-4}$/min/[$\mu$IU/mL] in high FAT, $p < 0.05$) but not by VFAT, and there were no significant effects of either fat compartment on AIR. In multiple regression analysis, Si was significantly influenced by FAT (negative effect), ethnicity (lower in African Americans), and gender (lower in females), whereas fasting insulin was significantly influenced by VFAT (positive effect), ethnicity (higher in African Americans), and fat free mass (positive effect).

Discussion: Body fat in general is the predominant factor influencing Si, but VFAT may have additional effects on fasting insulin. The lack of major effects of VFAT on Si in children may be explained by lower levels of VFAT or because VFAT affects aspects of whole body insulin action that are not measured by the minimal model.

Key words: insulin secretion, acute insulin response, insulin sensitivity, African American, prepubertal, obesity, body composition, fat distribution

Introduction

In 1947 Vague (1) introduced the concept that the health risks of obesity may be more specific to those with body fat that was distributed in the upper body rather than in the lower body. Subsequent studies, using imaging techniques to directly measure the different compartments of body fat in the upper body, suggested that visceral fat (VFAT), in particular, was more significantly associated with the health risks of obesity (2–4). VFAT is hypothesized to have more significant health risks because it is more metabolically active, more lipolytically sensitive, and releases free fatty acids into the hepatic portal vein that expose the liver to higher levels of free fatty acids, causing increased hepatic glucose production and decreased hepatic insulin extraction. These effects, however, are hypothesized and have not been tested directly.

However, because the different body fat compartments (e.g., total body fat [FAT] vs. subcutaneous fat vs. VFAT) are usually highly correlated with one another (5), it is often difficult to distinguish which component has unique independent effects. Thus, the unique role of VFAT has been challenged (6). For example, the presence of a significant correlation between VFAT and insulin sensitivity (Si) does not necessarily imply that VFAT directly influences Si,

Submitted for publication October 3, 2000.
Accepted for publication in final form May 10, 2001.
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because VFAT may be serving as a surrogate for other body fat compartments with which it is highly correlated. In a previous study using a multiple regression approach that incorporated all available measures of body fat into one model, we showed that VFAT has unique metabolic effects on fasting insulin but not on Si and that this effect was independent of other fat compartments (7). However, regression approaches can be misleading, because the compartment of body fat with the highest correlation is generally selected into the model and may not take into account more subtle differences in correlations. One previous longitudinal study in 30 nondiabetic women studied over 7 years demonstrated convincing evidence that a change, specifically in VFAT rather than in FAT, was associated with a worsening of indices of insulin secretion and action (8). Also, in older, obese, premenopausal women who were matched for FAT, women with high VFAT had a lower glucose disposal per kilogram of lean body mass compared with those with low visceral adipose tissue levels (9). In addition, one other longitudinal study has shown that VFAT, and not any other compartment of body fat, predicted the development of type 2 diabetes in Japanese Americans (10,11), thus supporting a unique role of VFAT in increasing health risk. Thus, studies that identify and examine subjects with distinguishable differences in the degree of fat accumulation in one compartment compared with another may be a more powerful strategy for identifying unique metabolic associations with a particular fat compartment.

Another important objective related to VFAT and health risk is to examine whether the association between VFAT and metabolic risk is similar across subgroups of the population who may be more susceptible to obesity-related health risk, such as type 2 diabetes. This is especially important in the African American population, which has a much higher risk of diabetes, despite a lower level of VFAT. This paradox suggests that either the influence of VFAT varies across subgroups of the population or that the greater risk for type 2 diabetes is due to factors unrelated to, and independent of, visceral adiposity. Previous studies that have compared African American children (12) and adults (13) have shown a clearly distinctive profile, at all ages studied, with African Americans having a lower accumulation of VFAT, a higher fasting insulin level, a lower Si, and a greater acute insulin response (AIR) to intravenous glucose. In addition, the lower Si and higher insulin response among African Americans remain highly significant, even after controlling for differences in FAT and VFAT (7).

In the current analysis, we used two separate analytical strategies to examine the effects of visceral relative to total fat mass on insulin action and secretion in a larger sample of children. In the first approach, we identified subgroups with low VFAT and low FAT, low VFAT and high FAT, high VFAT and low FAT, or high VFAT and high FAT. This approach allows testing of the independent effects of visceral vs. total fat in a two-way ANOVA that can isolate which particular compartment of fat has a significant influence on Si, independent of other compartments. Using this design, we examined whether FAT in general and/or VFAT in particular was associated with indices of insulin secretion and action and whether the pattern of these effects was similar in white and African American children. In the second approach, we used multiple regression analysis to identify the factors contributing to variance in insulin action and secretion, similar to the strategy that we used in a recent analysis (7).

Research Methods and Procedures

Subjects

Study subjects were part of an ongoing, longitudinal study on body composition, energy expenditure, and risk factors in children and adolescents. Findings regarding body fat distribution, aerobic capacity, energy expenditure, insulin action, and dietary factors in this cohort have been reported previously (5,7,14,15). Children were recruited by newspaper, radio advertisements, and word-of-mouth. For this study, only those subjects determined by evaluation by a pediatrician of both breast and pubic hair in females and of genitalia in males to be Tanner stage 1 or 2 were included. All children with measures of Si, FAT by DXA, and VFAT by computed tomography scanning were included in this analysis. No child was taking medications known to affect body composition (e.g., Ritalin or growth hormone), diagnosed with syndromes or diseases known to affect body composition or fat distribution (e.g., Cushing's disease, Down's syndrome, 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, and parents provided informed consent before testing.

Protocol

Children were admitted to the General Clinical Research Center in the late afternoon for an overnight visit. On arrival, anthropometric measurements were obtained. A computed tomography scan was conducted in the Department of Radiology at University of Alabama at Birmingham at ~5 PM. The children were served dinner and an evening snack, with all food consumed before 8 PM. 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 8 PM and testing the following morning. Two weeks after testing at the General Clinical Research Center, children returned to the Department of Nutrition Sciences at University

of Alabama at Birmingham for body composition analysis by DXA.

Tolbutamide-Modified, Frequently Sampled, Intravenous, Glucose Tolerance Test

The Si, AIR, and disposition index (DI; product of Si and AIR) were determined using a tolbutamide-modified, frequently sampled, intravenous, glucose tolerance test in the early morning after an overnight fast as reported previously (7). Briefly, a fasting blood sample was drawn, glucose was administered intravenously at time zero (25% dextrose; 11.4 g/m^2), tolbutamide (125 mg/m^2) was injected intravenously at 20 minutes postglucose, and 18 blood samples were collected over 3 hours. Sera were analyzed for glucose (Ektachem DT II System; Johnson and Johnson Clinical Diagnostics, Bridgeview, IL) and insulin (Radioimmunoassay; Diagnostic Products Corp., Los Angeles, CA), and values were entered $\pm$ into the minimal model (MINMOD) computer program (version 3.0) for determination of Si, AIR, and DI, which is the product of Si and AIR and serves as an index of β-cell function (16).

Total Body Fat and Abdominal Fat

Whole body composition (fat mass and fat free mass) were measured by DXA using a Lunar DPX-L densitometer (LUNAR Radiation Corp., Madison, WI), as described previously (17). Subcutaneous abdominal fat and VFAT were measured by computed tomography scanning with a HiLight/Advantage Scanner (General Electric, Milwaukee, WI) as described previously (5).

Data Analysis

Fat mass (kg) was adjusted for total lean tissue mass, gender, age, and Tanner stage. Children with an adjusted fat mass below the mean were classified as low total fat (coded as 0), and those above the mean were classified as high total fat (coded as 1). VFAT cross-sectional area (cm^2) was adjusted for subcutaneous abdominal fat, total lean tissue mass, gender, age, and Tanner stage. Children with an adjusted VFAT below the mean (low visceral relative to subcutaneous abdominal fat) were classified as low VFAT (coded as 0), and those above the mean (high VFAT relative to subcutaneous abdominal fat) were classified as high VFAT (coded as 1). These adjustments were performed separately in white and African American children. The breakdown of the white and African American sample into the four subgroups (low FAT, low VFAT; low FAT, high VFAT; high FAT, low VFAT; and high FAT, high VFAT) is shown in Table 1.

Pearson correlation analysis was performed to examine the simple relationships between body fat compartments and the major outcome variables. A two-way analysis of covariance was performed to examine the effects of high/low FAT vs. high/low VFAT. The dependent variables examined were fasting glucose, fasting insulin, Si, AIR, and DI. These variables were log-transformed before analysis, but for ease of interpretation, the main effects are presented for the untransformed values. For each dependent measure analyzed, the main effects examined in the model were FAT (low vs. high) and VFAT (low vs. high); age and gender were included as covariates. Main effects of FAT and VFAT were compared using the least square differences.

In the second analytical approach, multiple regression analysis was used, with Si, fasting insulin, or AIR as dependent variables. The independent variables in the model were fat mass, VFAT, race, gender, age, and fat free mass (with Si also included in the model for AIR). The analysis was conducted using the log-transformed values for all those variables that were not normally distributed. All analyses were conducted using SPSS, version 9.0 (SPSS, Chicago, IL). Power analysis calculations for sample sizes were conducted using NCSS (NCSS, Kaysville, UT).

Results

As shown in Table 2, the sample of children in this analysis included 68 white children (10.0 $\pm$ 1.2 years of age; 29 boys and 39 girls) and 51 African American children (9.3 $\pm$ 1.2 years of age; 26 boys and 25 girls) who varied greatly in terms of body composition, abdominal fat distribution, and insulin action and secretion. The African American sample was younger by 0.7 years, had a slightly lower percentage of body fat, and, as we have shown previously (7), they had a significantly lower Si and higher DI. Note that the data in Table 2 are simple crude descriptive statistics and are presented as absolute, unadjusted data.

As previously reported (5), the different compartments of body fat were highly correlated with each other as follows: FAT vs. subcutaneous abdominal fat ($r = 0.97$ in white children and $r = 0.96$ in African American children), FAT vs. VFAT ($r = 0.85$ in white children and $r = 0.85$ in African American children), and subcutaneous abdominal fat vs. VFAT ($r = 0.86$ in white children and $r = 0.78$ in African American children). As shown in Table 3, the univariate correlations between body fat compartments and diabetes risk factors showed three distinct patterns. First, for each risk factor, there were similar correlation coefficients with each body fat compartment. Second, this pattern was similar in both white and African American children. Third, the correlations tended to be lower in the African American group. Within each ethnic group, the correlations between risk factors and obesity factors were not statistically different from each other ($p > 0.2$). For example, we had less than a power of 0.5 to detect the correlations of -0.68 and -0.59 (correlations for Si vs. FAT and VFAT in white children) as significantly different or -0.52 and -0.43 as significantly different (correlations for Si vs. FAT and VFAT in African American children).

Table 1. Descriptive characteristics in white and African American children

	White ($n = 68$)	African American ($n = 51$)	Significant ethnic differences
Gender (girls/boys)	29/39	26/25	NS
Age (years)	10.0 ± 1.2 (7.5–12.2)	9.3 ± 1.2 (7.2–11.9)	$p < 0.05$
Fat mass (kg)	12.7 ± 9.1 (2.1–44.7)	12.1 ± 9.4 (1.7–37.8)	NS
Fat free mass (kg)	25.9 ± 4.9 (16.6–41.4)	26.2 ± 5.3 (14.7–38.2)	NS
% body fat	28.6 ± 11.5 (9.8–53.0)	26.5 ± 12.4 (6.8–50.6)	$p < 0.05$
SAAT (cm^2)	145.2 ± 108.9 (15.2–420.5)	124.4 ± 119.3 (8.8–436.4)	NS
VFAT (cm^2)	47.6 ± 26.6 (15.5–141.5)	34.2 ± 23.9 (7.3–117.5)	NS
Fasting glucose (mg/dL)	94.2 ± 5.6 (83.0–116.0)	93.7 ± 6.3 (77.0–105.0)	NS
Fasting insulin (μIU/mL)	13.8 ± 8.3 (4.0–39.0)	14.6 ± 8.2 (4.0–40.0)	NS
Si ($\times 10^{-4}$/min/[μIU/mL])	7.2 ± 5.0 (0.4–23.1)	3.9 ± 2.6 (0.6–12.1)	$p = 0.05$
AIR (μIU/mL)	782 ± 649 (117–3275)	1811 ± 1320 (457–8668)	NS
DI ($\times 10^{-4}$/min)	3763 ± 2222 (296–11587)	5756 ± 3710 (836–17116)	$p < 0.05$

SAAT, subcutaneous abdominal adipose tissue.

Table 1 shows the breakdown for white and African American samples into the four subgroups with low/high FAT and low/high VFAT. The children in the high FAT group had a ~2-fold higher fat mass, and those in the high VFAT group had ~50% more VFAT in the white sample and 75% more VFAT in the African American sample. As shown in Table 1, this created four subgroups that had markedly different profiles with regard to FAT and VFAT.

Table 4 summarizes the mean unadjusted glucose and insulin parameters in these four subgroups and shows the significant main effects of high/low FAT and high/low VFAT from a two-way analysis of covariance, which adjusted for age and gender. In the white sample, there was no significant effect of fat or VFAT on fasting glucose. For fasting insulin, Si, AIR, and DI, there was a significant effect of fat, but no effect of VFAT, with higher fat related to higher insulin, lower Si, higher AIR, and a lower DI. In the African American sample, there were no significant effects of fat or VFAT on fasting glucose or AIR. For fasting insulin, Si, and DI, there was a significant effect of fat, with higher fat related to higher insulin, lower Si, and lower DI. Figure 1 summarizes the significant main effects for low vs. high FAT and low vs. high VFAT in white and African American children. The data on these plots are the estimated least-square means for the main effects from the

Table 2. Patterns of correlation coefficients between diabetes risk factors and body fat compartments in white and African American children

	Fasting glucose		Fasting insulin		Si		AIR		DI	
	White	African American	White	African American	White	African American	White	African American	White	African American
Total fat mass	NS	NS	0.82	0.67	−0.68	−0.52	0.68	0.40	−0.42	−0.29
% Fat	NS	NS	0.73	0.60	−0.70	−0.53	0.58	0.37	−0.40	−0.31
SAAT	NS	NS	0.79	0.63	−0.70	−0.47	0.65	0.34	−0.41	−0.30
VFAT	NS	NS	0.76	0.68	−0.59	−0.43	0.58	0.39	−0.41	NS

SAAT, subcutaneous abdominal adipose tissue.

Table 3. Subgroups of subjects with high/low FAT vs. high/low VFAT

	Low total, low visceral	Low total, high visceral	High total, low visceral	High total, high visceral
White subjects				
Sample size	24 (10/12)	11 (6/5)	15 (6/9)	18 (7/11)
Adjusted fat mass (kg)	8.8 ± 2.2 (3.4–12.4)	9.2 ± 2.7 (3.0–12.5)	17.5 ± 4.2 (13.8–29.0)	16.7 ± 3.4 (13.5–25.4)
Adjusted VFAT (cm^2)	41.1 ± 4.6 (32.3–47.2)	54.6 ± 7.1 (47.6–73.7)	37.3 ± 12.1 (8.9–47.2)	59.9 ± 12.6 (48.1–97.3)
African American subjects				
Sample size	15 (8/7)	12 (6/6)	12 (6/6)	12 (6/6)
Adjusted fat mass (kg)	8.3 ± 1.7 (6.0–11.2)	6.9 ± 3.2 (1.4–10.8)	16.7 ± 2.2 (13.5–19.4)	18.3 ± 3.4 (13.5–27.5)
Adjusted VFAT (cm^2)	27.9 ± 4.5 (18.8–34.1)	41.5 ± 4.5 (35.1–52.4)	21.8 ± 10.1 (2.3–33.8)	46.6 ± 13.2 (35.0–78.2)

ANOVA and are adjusted for age and gender (the additional adjusting for Tanner stage did not change the findings), and the significant main effects are indicated, where $p < 0.05$ in the two-way analysis of covariance model.

The results of the multiple regression analysis are shown in Table 5. For Si, the significant factors in the model were fat mass (negative effect), ethnicity (lower in African Americans), and gender (lower in females), with no significant contribution from VFAT, fat free mass, or age. When analysis was conducted by separate ethnic group, the only significant variable in the model for whites was fat mass, and none of the variables were significant in African Americans. For fasting insulin, the significant factors in the model were VFAT (positive effect), fat free mass (positive effect), ethnicity (higher in African Americans), and gender (higher in females), with no significant contribution from fat mass or age. When analysis was conducted by separate ethnic group, the only significant variable in the model for

Table 4. Influence of high and low total fat and high and low VFAT on glucose and insulin parameters

	Low total, low visceral	Low total, high visceral	High total, low visceral	High total, high visceral	Significant main effects in 2-way ANOVA
White subjects					
Fasting glucose (mg/dL)	92.6 ± 5.1	94.0 ± 5.7	95.7 ± 7.4	95.0 ± 4.4	None
Fasting insulin (μIU/mL)	11.8 ± 7.5	9.5 ± 3.4	16.2 ± 8.0	17.2 ± 10.4	Total fat (VFAT, $p = 0.09$)
Si ($\times 10^{-4}$/min/[μIU/mL])	9.5 ± 4.8	10.3 ± 5.8	4.2 ± 3.4	4.7 ± 3.3	Total fat
AIR (μIU/mL)	669 ± 433	458 ± 262	1042 ± 821	914 ± 802	Total fat
DI ($\times 10^{-4}$/min)	4843 ± 2497	3738 ± 1403	3071 ± 1738	2915 ± 2133	Total fat
African American subjects					
Fasting glucose (mg/dL)	93.4 ± 4.8	93.7 ± 7.6	93.7 ± 4.8	94.1 ± 8.5	None
Fasting insulin (μIU/mL)	11.1 ± 4.2	12.5 ± 6.2	14.4 ± 7.1	21.5 ± 10.9	Total fat (VFAT, $p = 0.12$)
Si ($\times 10^{-4}$/min/[μIU/mL])	6.0 ± 3.2	4.1 ± 1.9	2.9 ± 1.7	2.3 ± 1.5	Total fat (VFAT, $p = 0.1$)
AIR (μIU/mL)	1447 ± 538	1533 ± 1010	1589 ± 641	2765 ± 2193	None
DI ($\times 10^{-4}$/min)	7875 ± 4259	5887 ± 4317	3907 ± 1807	4828 ± 2604	Total fat

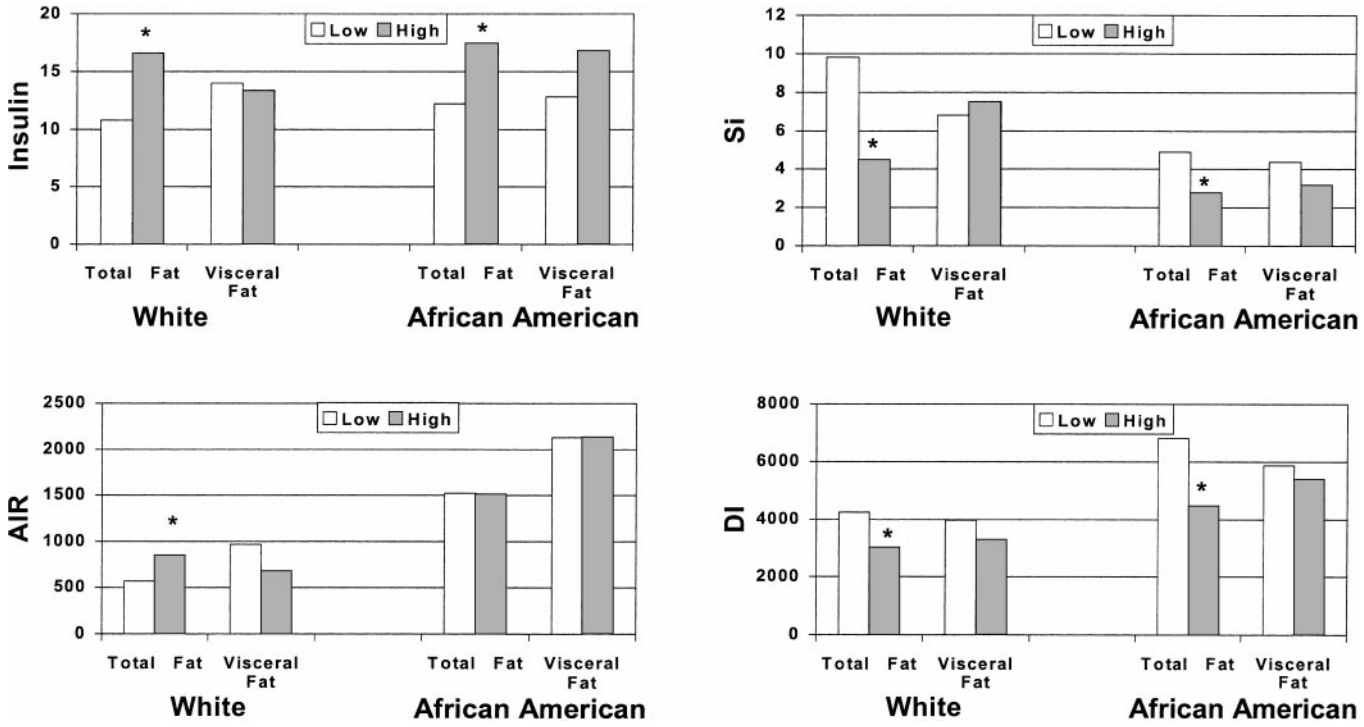

Figure 1: Comparison of least square means for insulin parameters in children with low/high FAT and low/high VFAT. "Insulin" is fasting insulin concentration (μIU/mL); "Si" is Si $\times$ 10^{-4}/min/(μIU/mL); "AIR" is the AIR (μIU/mL); and "DI" is the DI $\times$ 10^{-4}/min from the product of Si and AIR. Data shown are the comparison of the main effects of FAT and the main effects of VFAT from a 2-way analysis of covariance (*significant main effect).

whites was fat mass, and the only significant variable in the model for African Americans was VFAT. For AIR, the significant factors in the model were ethnicity (higher in African Americans) and Si (negative effect), with no significant contribution from the other variables. When analysis was conducted by separate ethnic group, Si was the only significant variable affecting AIR in both whites and African Americans.

Discussion

The primary purpose of this study was to identify whether FAT in general and/or VFAT in particular had unique

Table 5. Multiple regression analysis for Si, Fasting Insulin (INS), and AIR

Independent variable	Dependent variable = Si Parameter estimate (p value in model)	Dependent variable = INS Parameter estimate (p value in model)	Dependent variable = AIR Parameter estimate (p value in model)
Fat mass	$-0.45 + 0.15$ ($p = 0.003$)	NS ($p = 0.09$)	NS ($p = 0.29$)
VFAT	NS ($p = 0.16$)	$0.32 + 0.11$ ($p = 0.005$)	NS ($p = 0.27$)
Fat-free mass	NS ($p = 0.29$)	$0.64 + 0.31$ ($p = 0.04$)	NS ($p = 0.21$)
Ethnicity	$-0.31 + 0.06$ ($p < 0.001$)	$0.09 + 0.04$ ($p = 0.01$)	$0.26 + 0.06$ ($p < 0.001$)
Gender	$-0.14 + 0.06$ ($p = 0.01$)	$0.08 + 0.03$ ($p = 0.02$)	NS ($p > 0.5$)
Age	NS ($p > 0.5$)	NS ($p = 0.24$)	NS ($p = 0.32$)
Si	—	—	$-0.45 + 0.08$ ($p < 0.001$)
Intercept	$5.96 + 1.96$ ($p = 0.003$)	$-2.89 + 1.15$ ($p = 0.01$)	$0.47 + 1.6$ ($p > 0.5$)
Model R^2	0.56	0.56	0.64

metabolic effects on risk factors for type 2 diabetes in children using two different analytical strategies. In addition, we examined whether these effects were different in African American children who, compared with white children, have less VFAT, higher fasting insulin, lower Si, and higher AIR. Using the most advanced measurement techniques possible in a large sample of the pediatric population and a careful and systematic analytic strategy, our major finding was that in both white and African American children, Si was significantly influenced primarily by FAT, whereas fasting insulin was significantly influenced primarily by VFAT. This finding is in agreement with a previous analysis from this cohort in a smaller sample using a regression approach (7).

Our general findings are in agreement with a previous analysis from this cohort in a smaller sample (7), but they extend the observations in several important ways. First, in the current study, we present data in a much larger sample (119 subjects vs. 61 subjects), which allowed for a more detailed analysis with greater statistical power. Essentially, we verified the multiple regression analysis showing that total fat mass was the main determinant of fasting insulin and that VFAT had unique metabolic effects on fasting insulin but not on Si. With the larger sample size of 120 children, we had a power of >0.95 to detect a significant increment in the model R^2 of 0.05 with the inclusion of VFAT to the model, compared with a power of <0.8 with the 61 subjects from the previous analysis. These calculations assume α of 0.05, a regression model with five controlling variables, and an incremental R^2 of 0.5. Moreover, the larger sample size afforded the opportunity to conduct separate analysis in African American and white children separately, which we believe is important, based of the fact that these groups have distinctively different patterns of body fat (lower VFAT in African Americans) and indices of insulin secretion and action (lower Si and higher AIR in African Americans). Moreover, the larger sample size was advantageous because it allowed us to devise an alternative analytical strategy in which subgroups of children were identified that had high and low FAT and high and low VFAT.

Our findings, which failed to detect a significant effect of VFAT on Si, support the view of Seidell and Bouchard (6) who challenged the hypothesis that VFAT is the specific fat depot influencing health risk and cautioned that data implicating VFAT could be confounded. The important confounders that were discussed included total fat, subcutaneous abdominal fat, fat free mass, smoking, alcohol consumption, physical activity, diet, and sex steroid hormones. We controlled for the body composition factors through the analytical strategy that compared high and low levels of various fat compartments and through specific covariates, and because our study was performed on children, the potential influences of some environmental factors (e.g., smoking, alcohol, and stress) and some hormonal factors (sex steroids) were also reduced. However, the finding that different aspects of body fat may affect different aspects of insulin action and secretion warrants additional investigation.

It is widely discussed that abdominal obesity increases risk for type 2 diabetes, but it has yet to be confirmed whether this effect is due to subcutaneous fat or VFAT in the abdominal region and whether this effect is mediated through low Si or high fasting insulin. Our data tend to support the fact that body fat in general may influence Si, whereas VFAT may influence fasting insulin. However, we cannot discount the possibility that VFAT may become more significant later in life as VFAT accumulates in greater absolute and relative amounts. As discussed by Frayn (18), there are three potential hypotheses that might explain the link between VFAT and risk for type 2 diabetes. The first hypothesis relates to the mechanical effects of excess adipose tissue within the abdominal cavity that might exert harmful pressure and compression of the organs within the abdominal cavity. However, there is no supporting evidence for or against this notion. The fact that we do not see any effects of VFAT in children, whereas other studies have shown effects in adults, may lend support to this hypothesis. The second hypothesis relates to the possibility that visceral adipose tissue may secrete or express a factor that influences systemic metabolism, and there is some evidence to suggest that visceral adipose tissue may overexpress certain factors. This hypothesis is supported by the fact that leptin, for example, is more highly expressed in, and secreted from, subcutaneous compared with visceral adipose tissue (19). Other adipose-produced cytokines may influence insulin resistance, such as interleukin 6 and tumor necrosis factor α (20), and there is evidence to suggest that interleukin 6 is more highly secreted from visceral compared with subcutaneous adipose tissue (21). In light of the current findings, it would be interesting to examine whether there are differences in the secretory and expression products of VFAT derived from African American vs. white subjects, and whether this secretion is age-dependent. The third potential hypothesis linking visceral adipose tissue to risk for type 2 diabetes relates to the effects of free fatty acids released from visceral adipose tissue into the hepatic portal vein with direct exposure to the liver, termed the portal theory (18). This hypothesis is attractive because it has been shown that visceral adipose tissue is more lipolytic and more sensitive to lipolytic stimulation (22), and these effects may be more pronounced in African Americans. As discussed by Frayn (18), the greater lipolysis in visceral adipose tissue implies a greater turnover of lipid in this depot, otherwise VFAT eventually would be depleted. Increased exposure of the liver to free fatty acids increases hepatic glucose production that could result in glucose intolerance (23). In addition, free fatty acids may interfere

with hepatic insulin extraction (24), which may contribute to increased circulating insulin levels. However, there is no substantive in vivo evidence at this time in support of the free fatty acid hypothesis.

It is important to note that our findings are specific to children, and generalization of our findings to the adult population remains to be tested. The physiology and metabolic activity of body fat and VFAT may be different in children and adults, and the lower absolute mass of total and VFAT in children vs. adults, and the longer term sustained effects of adiposity in adults may affect relationships between adiposity and indices of insulin secretion and action. Thus, comparative studies across the lifespan may be informative. Regardless of the generalization of these findings, the distinct effects that we have observed in children emphasize that the influence of body fat on diabetes risk factors is apparent at an early age and, therefore, is unlikely to be a function of long-term sustained exposure to environmental or physiological factors.

Several limitations of our study should be noted. First, the minimal model technique that was used in this study measures whole body Si and cannot differentiate between hepatic and peripheral Si. This may be important because VFAT may have a specific effect on hepatic Si. Second, our findings are derived from a cross-sectional analysis. Longitudinal and mechanistic studies are needed to clarify issues regarding the cause-and-effect nature of VFAT and Si. The only longitudinal study that we are aware of that has related VFAT to onset of diabetes was in Japanese Americans (10,11). VFAT was a significant risk factor for the onset of type 2 diabetes, independent of the influence of fasting insulin, insulin secretion, and family history. However, in that study, there was no measure of whole body fat, so there remains some uncertainty as to whether the effect of VFAT was independent of, or related to, an effect of FAT. Previous studies that have suggested a unique influence of VFAT on development of type 2 diabetes have been in Japanese Americans (10), Pima Indians (25), and African Americans (7,13), which suggest that the influence of VFAT may be most apparent in subgroups of the population who are more susceptible to type 2 diabetes. Finally, additional studies may be needed in larger samples to achieve a greater stratification across groups because the separation above and below the mean may not be sufficient to detect nonlinear relationships. Also, studies in subjects who are specifically recruited to meet criteria of high/low FAT vs. high/low VFAT are likely to have greater power. Finally, no single study can be conclusive about the difficult questions that we are examining. Our primary goal was to separate the potential effects of total FAT and VFAT on insulin action and secretion, and other factors, such as physical activity, dietary factors, and hormonal status, may mediate the relationship between body fat and insulin action and secretion.

In conclusion, the influence of body fat on Si in children is explained primarily by the effects of FAT, but VFAT may have separate effects on fasting insulin. Larger studies in the adult population are needed to examine whether these findings are applicable across the age spectrum and more detailed mechanistic studies are needed to examine the potential differential effects of FAT vs. VFAT on metabolism in African American vs. white subjects.

Acknowledgments

This study was supported by the U.S. Department of Agriculture (MIG), the National Institute of Child Health and Development (MIG: R29 HD 32668 and R01 HD/HL 33064), the National Institute of Aging (BAG: K01AG00740), and by General Clinical Research Center Grant M01-RR-00032. We thank Tena Hilario, who coordinated this project, the staff of the General Clinical Research Center, and the children and their families who participated in this study.

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