Unique Effect of Visceral Fat on Insulin Sensitivity in Obese Hispanic Children With a Family History of Type 2 Diabetes

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OBJECTIVE — This study aimed to establish whether total fat or central fat was related to measures of insulin in obese Hispanic children with a family history of type 2 diabetes.

RESEARCH DESIGN AND METHODS — Subjects were 32 children aged 8–13 years. Visceral fat and subcutaneous abdominal fat were determined by magnetic resonance imaging at the umbilicus and total body fat was determined by dual-energy X-ray absorptiometry. Insulin sensitivity (S_i) and acute insulin response (AIR) were determined by frequently sampled intravenous tolerance test with minimal modeling.

RESULTS — Mean fasting glucose and insulin, S_i, and AIR (± SD) were 5.3 ± 0.3 mmol/l, 206 ± 105 pmol/l, 11.8 ± 5.7 [$\times 10^{-4}$ min^{-1}/(pmol/l)], and 17,175 ± 9,695 (pmol/l × 10 min), respectively. In multivariate regression analysis, total fat mass was independently and positively related to fasting insulin ($P < 0.01$) and negatively related to S_i ($P < 0.05$) but was not related to AIR. Visceral fat was independently and positively related to fasting insulin ($P < 0.05$) and AIR ($P < 0.01$) and negatively related to S_i ($P < 0.001$).

CONCLUSIONS — These findings support the hypothesis that specific accumulation of visceral fat in addition to overall adiposity in Hispanic children increases the risk of type 2 diabetes.

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The association between obesity and insulin resistance has been well documented, and it has been hypothesized that specific metabolic effects of visceral fat may explain this association (1). Support for a causal role of visceral fat causing insulin resistance has been shown in animal studies in which surgical removal of visceral fat in obese rats reversed insulin resistance (2) and in animal studies in aging rats in which the loss in visceral fat, as a consequence of caloric restriction, resulted in improvement in hepatic insulin sensitivity (S_i) (3).

Visceral fat seems to be metabolically unique compared with subcutaneous abdominal fat. Bjorntorp (4) suggested that visceral fat results in hepatic insulin resistance via a "portal" effect of free fatty acids released by increased omental fat. The increased flux of fatty acids to the liver leads to increased hepatic glucose production (5, 6) and decreased hepatic insulin clearance, which in turn leads to insulin resistance and hyperinsulinemia.

In children as in adults, central fat seems to be related to S_i. However, the precise depot that is associated with S_i is not entirely clear and may differ with obesity status (7–9).

Although the relationship between central fat and S_i has been widely studied in Caucasians, there are very few reports in the Hispanic population. Studies in Hispanic Americans may be important because both children and adults in this subgroup of the population are more obese (10,11), have higher waist-to-hip ratios (12,13), and have higher insulin levels (11) than Caucasians (13). In addition, Hispanic adults have been found to be more insulin-resistant than Caucasians (13) and have greater central distribution of fat (14) at similar levels of adiposity. The Insulin Resistance Atherosclerosis Study, a large multicenter study on atherosclerosis, reported that waist circumference was negatively related with S_i in this ethnic group after adjustment for confounding variables (15). However, there have been no previous studies examining the relationship between S_i and direct measures of body fat distribution. Therefore, it is unclear if the increased insulin resistance in Hispanics is explained by total fat, subcutaneous abdominal fat, or visceral fat.

Therefore, the objective of the present study was to examine whether total body fat or central body fat (visceral fat and subcutaneous abdominal fat) were related to fasting insulin, S_i, and insulin secretion in obese Hispanic children with a family history of type 2 diabetes. We hypothesized that visceral fat would be related to S_i and secretion and that this relationship would be independent of the effect of either total fat or subcutaneous abdominal fat.

RESEARCH DESIGN AND METHODS

Subjects

The present study included 32 children (20 boys and 12 girls) who were recruited through clinics and word of mouth and were required to meet the following inclusion criteria: *1*) Hispanic origin (determined by self-report and based on both parents and both sets of grandparents re-

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Abbreviations: AIR, acute insulin response; DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; S_i, insulin sensitivity.

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

porting to be Hispanic); 2) family history of type 2 diabetes (parent, grandparent, or sibling); 3) aged 8–13 years; 4) BMI above the 85th percentile for age and sex according to the Centers for Disease Control and Prevention charts (16); 5) Tanner stage 1 or 2; and 6) absence of diabetes, established by an oral glucose tolerance test and the diagnosis criteria from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (17). All children in this study were at Tanner stage 2, except for three children who were at Tanner stage 1 determined by physician evaluation. The children were of Mexican-American (n = 25), Central American (n = 3), or mixed Mexican- and Central American (n = 4) descent and lived in the county of Los Angeles. No child was taking medications known to affect insulin resistance or body composition, diagnosed with syndromes of disease known to affect body composition or fat distribution, diagnosed with any major illness since birth, or diagnosed with diabetes. This study was approved by the Institutional Review Board of the Health Science Campus, University of Southern California. Consent was obtained from all parents and children after the nature of the procedures was explained and before testing was commenced. We have not previously reported any data from these children in our previous publications.

Table 1—*Subjects' physical and metabolic characteristics*

	Boys (n = 20)	Girls (n = 12)	Total (n = 32)
Age (years)	10.8 ± 1.7	10.0 ± 1.6	10.5 ± 1.7
Height (cm)	144.2 ± 8.9	139.8 ± 9.6	142.5 ± 9.3
Weight (kg)	56.0 ± 15.1	51.0 ± 14.8	54.1 ± 14.9
BMI (kg/m^2)	26.5 ± 4.6	25.7 ± 4.7	26.2 ± 4.5
Fat mass (kg)	21.0 ± 8.4	20.7 ± 8.6	20.9 ± 8.3
Lean mass (kg)	32.6 ± 6.7	28.3 ± 6.8	31.0 ± 7.0
Percent body fat	36.7 ± 6.6	40.3 ± 6.6	38.0 ± 8.3
Subcutaneous abdominal fat (cm^2)	269.9 ± 110.2	269.2 ± 119.2	269.6 ± 111.7
Visceral fat (cm^2)	48.7 ± 19.0	44.9 ± 18.7	46.8 ± 18.6
Fasting glucose (mmol/l)*	5.4 ± 0.2	5.2 ± 0.3	5.3 ± 0.3
Fasting insulin (pmol/l)	220 ± 105	183 ± 104	206 ± 105
S_i [$\times 10^{-4}$ min^{-1}/(pmol/l)]	10.4 ± 5.3	12.5 ± 6.3	11.8 ± 5.7
AIR (pmol/l × 10 min)	18,613 ± 10167	14,793 ± 8751	17,175 ± 9695

Data are means ± SD. *$P < 0.05$ for sex.

Protocol

Children were admitted to the General Clinical Research Center in the afternoon for an overnight stay. Height and weight were recorded to the nearest 0.1 cm and 0.1 kg, respectively. A whole-body dual-energy X-ray absorptiometry (DEXA) scan was performed to determine whole-body composition using a Hologic QDR 4500W (Bedford, MA). Central fat distribution was measured directly by magnetic resonance imaging (MRI) at the LAC/USC Imaging Science Center. A single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus was analyzed for cross-sectional area of adipose tissue (18). The scan lasted ~2 min and a General Electric 1.5 Signa LX-Echospeed device with a General Electric 1.5-Tesla magnet was used (Waukesha, WI). The children were served dinner and an evening snack; all food was consumed before 8:00 P.M. Consumption of only water was permitted between 8:00 P.M. and testing the following morning.

Insulin-modified frequently sampled intravenous glucose tolerance test

At 6:30 A.M. a topical anesthetic (Emla cream; Aztrozeneca, Wilmington, DE) was applied to the antecubital area of both arms, and at ~7:30 A.M., flexible intravenous catheters were inserted in both arms. Two fasting blood samples were drawn at −15 and –5 min for determination of basal glucose and insulin. At time 0, glucose (25% dextrose, 0.3 g/kg body wt) was administered intravenously. Blood samples were then collected at the following time points: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, 180, and 210 min. Insulin (0.02 units/kg body wt) (Humulin R; Eli Lilly, Indianapolis, IN) was injected intravenously at 20 min. Plasma was analyzed for glucose and insulin and values were entered into the Minmod Millenium 2002 computer program (version 5.7; Richard N. Bergman) for determination of S_i and acute insulin response (AIR) (19–21).

Assay of glucose and insulin

Glucose was measured in duplicate using a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH) and a glucose oxidase kit. Insulin was assayed in duplicate using a specific human insulin enzyme-linked immunosorbent assay kit from Alpco (Wyndham, NH).

Statistical analysis

Sex differences in physical and metabolic characteristics were examined using a general linear model. Variables that were not normally distributed (weight, total fat mass, BMI, fasting insulin, and AIR) were log transformed. Univariate linear regression analysis was performed to assess the separate contribution of total fat mass, visceral fat, or subcutaneous abdominal fat (independent variables) on each measure of insulin (dependent variable: log fasting insulin, S_i, or log AIR). Multivariate linear regression analysis was used to establish the independent contribution of visceral fat on *1*) log fasting insulin, *2*) S_i, or *3*) log AIR after adjustment for either total fat mass or subcutaneous abdominal fat. The correlation coefficient between total fat mass and subcutaneous abdominal fat was very high (0.94). Therefore, these two variables were entered separately into each regression model. For these analyses, the dependent variable was either log fasting insulin, S_i, or log AIR and the independent variable was visceral fat, whereas total fat or subcutaneous abdominal fat mass was entered as covariates in addition to sex. In addition, in the model in which log AIR was the dependent variable, S_i was entered as an additional covariate. For this analysis, independent variables were not log transformed. All analyses were performed using SPSS version 9.0 (SPSS, Chicago, IL) with a type I error set at $P < 0.05$.

RESULTS

Physical and metabolic characteristics of subjects

There were no statistically significant differences in age, height, weight, or body composition between boys and girls, al-

Table 2—*Univariate regression analysis to explore the contribution of total fat mass or central fat on measures of insulin*

Model	Dependent variable	Model R^2	β ± SEE	*P*
Total fat mass*				
Model 1	Log fasting insulin	0.46	0.04 ± 0.01	<0.001
Model 2	S_i	0.50	−0.07 ± 0.01	<0.001
Model 3	Log AIR	0.44	0.03 ± 0.01	<0.05
Subcutaneous abdominal fat*				
Model 1	Log fasting insulin	0.46	0.003 ± 0.001	<0.001
Model 2	S_i	0.49	−0.001 ± 0.001	<0.001
Model 3	Log AIR	0.22	0.002 ± 0.001	<0.01
Visceral fat*				
Model 1	Log fasting insulin	0.44	0.02 ± 0.004	<0.001
Model 2	S_i	0.61	−0.03 ± 0.01	<0.001
Model 3	Log AIR	0.54	0.02 ± 0.004	<0.001

*Total fat mass, subcutaneous abdominal fat, and visceral fat were entered separately into each regression model (1–3) as the independent variable. β, parameter estimate; SEE, standard error of the estimate.

though boys tended to have higher lean tissue mass ($P = 0.09$) and lower fat mass. Boys had higher fasting glucose and insulin than girls, but only the former reached statistical significance ($P < 0.05$). There were no statistically significant differences in S_i and AIR by sex (Table 1). Data from boys and girls were combined for all other analyses.

Univariate linear regression analysis to assess the contribution of total body fat and central fat on insulin measures

Regression analysis indicated that total fat mass, subcutaneous abdominal fat, and visceral fat were significantly and positively related to log fasting insulin and log AIR and negatively related to S_i (Table 2, models 1–3).

Multivariate linear regression analysis to assess the contribution of visceral fat on insulin measures after adjustment for total fat mass

Results from the multivariate regression analysis indicated that visceral fat remained significantly and positively related to log fasting insulin ($P < 0.05$) and log AIR ($P < 0.01$) and strongly and negatively related to S_i ($P < 0.001$) (Table 3) after adjustment for total fat mass. Total body fat remained significantly related to log fasting insulin and S_i but not to log AIR (Table 3). The statistical significance of the relationship between visceral fat and S_i was stronger than for total fat mass and S_i, whereas the opposite was true for log fasting insulin (Table 3).

Multivariate linear regression analysis to assess the contribution of visceral fat on insulin measures after adjustment for subcutaneous abdominal fat

Results from the multivariate regression analysis indicated that visceral fat remained significantly and positively related to fasting insulin ($P < 0.01$) and AIR ($P < 0.01$) and strongly and negatively related to S_i ($P < 0.001$) after adjustment for subcutaneous abdominal fat. Subcutaneous abdominal fat remained significantly related to log fasting insulin ($P < 0.05$) and S_i ($P < 0.05$) but not to log AIR. Overall, the statistical significance of the relationship between subcutaneous abdominal fat and measures of insulin was weaker than for visceral fat and insulin measures.

CONCLUSIONS — The primary purpose of this study was to identify whether visceral fat was uniquely associated with fasting insulin, S_i, and AIR. Our results demonstrate for the first time that in obese Hispanic children with a family history of type 2 diabetes, directly measured visceral fat (assessed by MRI) is strongly and positively related to fasting insulin and AIR and negatively related to S_i (assessed by the insulin-modified intravenous glucose tolerance test). These relationships were independent of total body fat mass or subcutaneous abdominal fat.

Multiple studies have shown that the central body fat depots are more strongly linked to insulin resistance, type 2 diabetes, and cardiovascular disease than the peripheral (gluteal/subcutaneous) fat de-

Table 3—*Multivariate regression analysis to examine the contribution of visceral fat on insulin measures after adjustment for total body fat mass*

Dependent variable	Independent variables	β ± SEE	*P*
Model 1 $R^2 = 0.57$			
Log fasting insulin	Sex	−0.18 ± 0.13	NS
	Total fat mass	0.03 ± 0.001	<0.01
	Visceral fat	0.01 ± 0.01	<0.05
Model 2 $R^2 = 0.67$			
S_i	Sex	0.10 ± 0.18	NS
	Total fat mass	−0.03 ± 0.01	<0.05
	Visceral fat	−0.02 ± 0.01	0.001
Model 3 $R^2 = 0.59$			
Log AIR	Sex	0.14 ± 0.15	NS
	S_i	−0.23 ± 0.15	NS
	Total fat mass	−0.02 ± 0.01	NS
	Visceral fat	0.01 ± 0.01	<0.01

β, parameter estimate; SEE, standard error of the estimate.

pots (1). Several investigators have suggested that the visceral fat depot is more closely associated with the metabolic disturbances of obesity than the subcutaneous abdominal fat depot. However, most of these studies have been conducted in Caucasians of European descent (1), and much less is known regarding the relationship between directly measured central fat and disease risk in other ethnic groups. This question is of great interest because the prevalence of type 2 diabetes affects certain minority groups disproportionately (22). For instance, in the U.S., the rate of type 2 diabetes in Mexican-Americans is two times higher than in Caucasians (23). In addition, both Hispanic children (12) and adults (13) deposit more fat in the central abdominal region than Caucasians, and Hispanic adults are more insulin resistant (13). The Insulin Resistance Atherosclerosis Study has previously hypothesized that the greater degree of insulin resistance and type 2 diabetes in Hispanics in the U.S. may be due to the greater degree of adiposity (13) and to the preponderance of central fat (14), because waist circumference was associated with insulin resistance in this ethnic group (13,15). However, there have not been any previous studies using accurate measures of body fat and body fat distribution to substantiate this hypothesis. In addition, results from a prospective study in Mexican-Americans demonstrated that abdominal obesity, measured indirectly through anthropometry, predicted both hyperinsulinemia and the development of type 2 diabetes in this ethnic group (24).

Our current findings are in agreement with previous reports linking central adiposity to insulin resistance and type 2 diabetes in Hispanics, but these observations are extended to show that in Hispanic children, visceral fat contributes independently to S_i and insulin secretion assessed through AIR. Nevertheless, it is important to note that our findings are specific to Hispanic children, and generalization to the adult population remains to be tested. In addition, in the current study, overall adiposity and peripheral central fat made independent and separate contributions to S_i although they were overall weaker in strength.

The nature of the relationship between central fat and S_i has not been adequately explained. It is possible that an unknown common factor produces both insulin resistance and the central pattern of regional adiposity and that central obesity does not cause insulin resistance. Alternatively, some biochemical feature in central fat may directly influence systemic S_i. The most attractive hypothesis linking central fat with insulin resistance is the increased liberation of fatty acids from visceral fat depots into the portal circulation and consequently to the liver (4). The mechanisms that bring about this high lipolytic capacity in visceral adipocytes include a greater sensitivity to lipolytic effect of catecholamines (25) and less sensitivity to the antilipolytic action of insulin (26). The increased flux of fatty acids to the liver is believed to increase hepatic glucose production (5,6), which leads to glucose intolerance, and to stimulate hepatic VLDL-triglyceride secretion, which leads to hypertriglyceridemia (4). Finally, fatty acids have been shown to interfere with hepatic insulin removal (27,28), thus leading to hyperinsulinemia. Fatty acids released from visceral adipose tissue and delivered into the portal vein might, therefore, have a particularly important role in bringing about many of the features of insulin resistance. This hypothesis is still under debate, and there are some who would argue that subcutaneous abdominal fat is more important in determining the relationship between central fat and insulin resistance (29). Furthermore, the relative importance of central fat deposition in determining the relationship between overall adiposity and S_i differ across the life span.

In previous studies from our ongoing cohort of lean and obese African-American and Caucasian prepubertal children in Alabama, we repeatedly failed to detect an independent relationship between visceral fat (assessed by computed tomography) and S_i (assessed by the tolbutamide-modified intravenous glucose tolerance test). In that cohort, S_i was significantly influenced primarily by total fat (assessed by DEXA), whereas fasting insulin was significantly influenced by visceral fat (8,30). Besides the obvious differences in ethnic background, the Alabama study and our current study in Hispanic children differ in several respects, such as obesity status and family history for type 2 diabetes. In the Alabama cohort, we recruited a heterogeneous group of male and female children of African-American and Caucasian descent with varying degrees of adiposity, at Tanner stage 1, between the ages of 7 and 10 years. In the current study, subjects were homogenous with respect to ethnicity (Hispanic), family history of type 2 diabetes, and BMI higher than the 85th percentile for age and sex), and all except three children were at Tanner stage 2 of development. Therefore, factors such as ethnicity, obesity status, and family history of diabetes may explain some of the differences in the association between visceral fat and S_i between studies.

We have previously suggested that the lack of association between visceral fat and S_i in prepubertal children might be due to their relatively low visceral fat accumulation (reviewed by M.I.G.; 9,30) and hypothesized that such an association might only be evident in more obese children (9). Support for this view was provided by a study in predominantly Caucasian adolescents girls, in which it was shown that visceral fat (assessed by MRI) was negatively correlated with S_i (assessed by euglycemic clamp) in obese girls but not in nonobese girls. It is interesting to note that the visceral fat cross-sectional area in the obese girls was twofold higher than in the nonobese girls (7) and, in fact, several fold higher than in our cohort of prepubertal children from Alabama (8,30). Surprisingly, visceral fat area in our Hispanic cohort was not strikingly different from what we had previously reported in African-American and Caucasian children of similar age from our Alabama cohort. Visceral fat area was 46.8 ± 16.8 (assessed by MRI), 34.2 ± 23.9, and 47.6 ± 26.6 cm^2 (assessed by computed tomography) in Hispanic, African-American, and Caucasian children, respectively (30). This suggests than in the current cohort of Hispanic children, the clear association between S_i and visceral fat may not be due to high visceral fat but some other underlying factor. One such factor might be family history of type 2 diabetes. Interestingly, several studies in adults have shown that family history of type 2 diabetes was associated with lower visceral fat content despite altered plasma glucose and insulin after an oral glucose tolerance test (31,32). It is possible that in the current cohort of Hispanic children, family history of type 2 diabetes may decrease the threshold of abdominal fat above which a decrease in S_i may become evident and thus allow for the detection of a relationship in these children, despite the fact that their visceral fat

area does not seem to be significantly increased.

Alternatively, the relationship between visceral fat and insulin resistance may be ethnic specific. For instance, the Pima Indians of Arizona (a population with the highest reported prevalence of type 2 diabetes in the world) have, like Hispanics, a central pattern of fat distribution (33). However, in this ethnic group, directly measured visceral fat (assessed by MRI) was not related to glucose disposal rate during a hyperinsulinemic-euglycemic clamp (34). Furthermore, the visceral fat accumulation did not explain the differences in insulin action and secretion between Pima Indians and Caucasians (33). Unfortunately, whether our current findings are specific to Hispanic ethnicity or are an effect of family history of type 2 diabetes cannot be established from the current study.

In general, our results suggest that in addition to peripheral adiposity, the specific accumulation of visceral fat in Hispanic children may further decrease S_i and insulin response to glucose in these children as they go through puberty, a period already characterized by physiological hyperinsulinemia and insulin resistance (35). We hypothesize that the additional burden of insulin resistance during puberty may tip the balance from a state of compensated hyperinsulinemia with normal glucose levels to inadequate insulin secretion, hyperglycemia, and type 2 diabetes. Our findings could therefore have serious implications in the context of the increasing prevalence of obesity among Hispanic American children and the new report of an increase in the incidence of type 2 diabetes in children during the pubertal transition (36), especially among certain ethnic minorities, including Hispanic Americans (17). Our results suggest that the implementation of type 2 diabetes prevention strategies aimed at a reduction in of body fat alone may not be sufficient to improve S_i in this ethnic group. Strategies may need to be focused on specific reduction of visceral fat and/or improvement of insulin resistance.

In conclusion, visceral fat was independently and negatively related to S_i and positively related to insulin secretion in obese Hispanic children with a positive family history for type 2 diabetes. This relationship was independent of overall adiposity and subcutaneous abdominal fat. Total body fat or subcutaneous abdominal fat also contribute to insulin resistance in this ethnic group. The specific accumulation of visceral fat, in addition to overall body fat, in Hispanic children may therefore increase risk of developing type 2 diabetes during adolescence.

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