Insulin Sensitivity, Insulin Secretion, and Abdominal Fat

The Insulin Resistance Atherosclerosis Study (IRAS) Family Study

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The relationship between insulin sensitivity and overall obesity is well established. However, there remains debate as to which of the fat depots, visceral abdominal tissue (VAT) or subcutaneous abdominal tissue (SAT), is of greater importance. Also, the relationship between fat distribution and insulin secretion is largely unknown. We studied S_I, acute insulin response (AIR), and disposition index (DI), as obtained by minimal model analysis, in 999 Hispanic and 458 African-American men and women as part of the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. VAT and SAT were measured from computed tomography scans performed at the L4/L5 vertebral region. A mixed-model approach was used to determine the relationship between each of the glucose homeostasis measures (S_I, AIR, and DI) versus abdominal fat measures. Mean values were as follows: age, 41 years; S_I, 1.98 $10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$; AIR, 840 pmol $\cdot ml^{-1} \cdot min^{-1}$; BMI, 28.5 kg/m^2; VAT, 100 cm^2; and SAT, 333 cm^2. SAT, VAT, and their joint interaction were each inversely and significantly associated with S_I, adjusting for age, sex, ethnicity, and BMI. SAT, but not VAT, was positively associated with AIR, except when additionally adjusting for S_I, in which case VAT was inversely associated with AIR. VAT and the joint interaction of VAT and SAT were inversely associated with DI. The fat measures explained 27% of the model R^2 for S_I, 16% for AIR, and 16% for DI. Thus, fat distribution is an important determinant of both insulin resistance and insulin secretion. *Diabetes* 52: 2490–2496, 2003

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AIR, acute insulin response; DI, disposition index; IRAS, Insulin Resistance Atherosclerosis Study; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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Insulin resistance is associated with overall obesity and particularly abdominal obesity (1). However, simple measures of body size such as BMI or waist circumference do not adequately describe the distribution of adipose tissue, which now appears to be a major determinant of the variation in insulin resistance. Computed tomography has made it possible to discriminate between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (2). However, there is debate regarding which of these fat depots is more important in determining insulin resistance (3,4). These fat depots differ morphologically and functionally, suggesting that their metabolic impact may differ as well (5).

In normal individuals, as insulin sensitivity declines, the β-cells of the pancreas compensate by secreting more insulin. An additional compensation is reduced first-pass clearance of insulin by the liver. In individuals at risk for type 2 diabetes, the ability to compensate for insulin resistance is compromised. Thus, it is of interest to clearly determine whether overall obesity or obesity in a specific depot is a more important determinant of insulin resistance, because adipose in that depot would provide a greater stress to the β-cells and higher risk for type 2 diabetes.

It is possible to assess the ability of the β-cells to compensate for insulin resistance by exploiting the known hyperbolic relationship between insulin secretion and insulin sensitivity (6). As resistance progresses, normal β-cells will upregulate according to the formula: insulin secretion × insulin sensitivity = constant, where the constant is termed the "disposition index" (DI). It is therefore of interest not only to know the importance of VAT versus SAT vis-à-vis insulin resistance but also the potential for compensation as reflected in the DI.

We sought to examine the relationship between insulin resistance, insulin secretion, DI, and abdominal adiposity in a large epidemiologic cohort in which quantitative assessments of insulin resistance and abdominal fat distribution have been made. Specifically, we wished to determine whether the relationships between abdominal adiposity and glucose homeostasis parameters are independent of overall body mass; whether the relationship differs by ethnicity, sex, or body mass; and whether one or

the other fat depot (VAT or SAT) is more strongly associated with these measures.

RESEARCH DESIGN AND METHODS

The Insulin Resistance Atherosclerosis Study (IRAS) Family Study is designed to explore the genetics of insulin resistance and visceral adiposity (7). Three centers recruited and examined members of large families of Hispanic (San Antonio, TX, and San Luis Valley, CO) or African-American ethnicity (Los Angeles, CA) over a 2.5-year period (2000–2002). Probands were identified from the parent study (the IRAS [8]) as those who had self-reported a large family structure on a family medical history questionnaire 2 years before this study. This collection was supplemented with large non-IRAS families recruited from the general population. Selection was not based on body size or glucose tolerance status.

Insulin sensitivity was assessed by the frequently sampled intravenous glucose tolerance test (9) with minimal model analyses (10) as previously described (8). An injection of insulin was used to ensure adequate plasma insulin levels for the accurate computation of insulin resistance across a broad range of glucose tolerance (11). Also, a reduced sampling protocol, requiring 12 plasma samples (12), was used because of the large number of subjects. Glucose in the form of a 50% solution (0.3 g/kg) and regular human insulin (0.03 μ/kg) was injected through an intravenous line at 0 and 20 min, respectively. Blood was collected at −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min for the determination of plasma glucose and insulin concentrations. S_I was calculated by minimal model analysis. Acute insulin response (AIR) was the mean insulin increment in the plasma insulin concentration above the basal in the first 8 min after the administration of glucose. DI was calculated as the product of S_I and AIR.

Abdominal fat mass was measured at the L2/L3 and L4/L5 vertebral region by computed tomography under a common protocol used at each of the three sites. Scans were read centrally at the University of Colorado Health Sciences Center, Department of Radiology, for VAT and SAT. Bowel fat was substracted out from the VAT. The L4/L5 measures were used in these analyses. The SAT and VAT areas at the L2/L3 and L4/L5 regions are very highly correlated: for SAT, the Spearman correlation is 0.95 and for VAT, 0.90. A total of 45 (2.7%) participants were missing the L4/L5 data but had L2/L3 data. For these participants, we imputed the L4/L5 data from the L2/L3 data using a simple linear model.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg. BMI was calculated as weight/height^2 and was used as an estimate of overall adiposity. Overweight was categorized as BMI >25 and ≤30 kg/m^2 and obesity as BMI >30 kg/m^2. Plasma glucose was measured using the glucose oxidase technique on an autoanalyzer. Impaired fasting glucose was defined as fasting glucose ≥110 and <126 mg/dl. Plasma insulin was measured using the dextran-charcoal radioimmunoassay (13), which has a 19% external coefficient of variation. Laboratory measures were performed at the University of Southern California. Ethnicity was obtained by self-report. Data are presented by center instead of ethnicity because of known differences in lineage between the Hispanics in San Antonio, Texas, and San Luis Valley, Colorado (14–16).

Statistical methods. To investigate the joint relationships among the measures of adiposity (VAT, SAT, and VAT/SAT) and the measures of insulin sensitivity and secretion (S_I, AIR, and DI), we computed a three-step series of mixed linear models. The first set of models jointly explored the functional forms (i.e., linear and quadratic) of age and BMI, adjusting for sex and clinic. To minimize collinearity among the predictor variables, the quadratic effects for BMI and age were modeled as the squared deviation from the respective variable's mean. In the case of age, the nonlinear or quadratic term was statistically significant and was retained for subsequent modeling. In the case of BMI, the quadratic term was not statistically significant and was not retained for subsequent modeling. The second set of models tested for the main effects of VAT and SAT. The third set of models tested the two-way interaction between VAT and SAT, adjusting for age, sex, center, and BMI. All models accounted for the potential familial correlation via assuming an exchangeable correlation structure and computing the empirical or sandwich estimator of the variance. Two sets of models are presented here: the best final model for each of S_I, AIR, and DI and a set of stratified models for each (sex and obesity status). Estimation and hypothesis testing was based on maximum likelihood estimates and likelihood ratio tests. To better approximate the model's assumptions (i.e., approximate normality and homogeneity of variance), we transformed S_I to the natural log (S_I + 1) and AIR to the signed square root of the absolute value of AIR; we defined the signed square root of AIR as the square root of AIR if AIR >0, or −1 times the square root of the absolute value AIR if AIR <0. DI was also transformed using the signed square root transformation. VAT, SAT, and VAT/SAT ratio were naturally log-transformed to minimize the influence of extremely large values. These logarithmic transformations had the fortunate consequence of exhibiting linear relationships with the transformed values of S_I, AIR, and DI.

We computed the generalized coefficient of determination, R^2 defined as follows (17):

$$R^2 = 1 - \left\{\frac{L(0)}{L(\beta)}\right\}^{\frac{2}{n}}$$

To provide a measure of the independent effect of each variable in the model, we report the percent change in the R^2 (i.e., the difference between the R^2 from models with and without the variable of interest, divided by the R^2 containing that variable). In the presence of significant interactions, we do not report the tests of significance for the corresponding main effects. The percent change in R^2 for the corresponding main effects of terms involved in the interaction were computed removing both the main effect of interest and the interaction.

RESULTS

The current analysis includes 1,457 individuals: 494 from 42 Hispanic families residing in San Antonio, 505 from 30 Hispanic families residing in the San Luis Valley, and 458 from 60 African-American families residing in the Los Angeles area. The mean number of individuals studied per family was 12 in San Antonio, 24 in San Luis Valley, and 14 in Los Angeles. Family members with diabetes (self-report or fasting glucose >126 mg/dl) were excluded from this analysis.

Participating family members were aged 18–81 years, with an average age of ~40 years (Table 1). Of the subjects, 58% were female. Hispanics were more insulin sensitive than African Americans. African Americans had greater AIR than Hispanics. DI was lowest among Hispanics in San Antonio. The distribution of abdominal fat differed by sex and ethnicity. Women had higher SAT and lower VAT than men. Hispanics had greater VAT than African Americans for similar (or lower, as is the case for women) BMI. The Hispanic cohort from San Antonio had the highest prevalence of obesity: 39% among men and 45% among women. Overall, 8% had impaired fasting glucose, with slightly higher rates observed in African Americans.

SAT and VAT were both inversely associated with S_I after adjusting for BMI and demographic characteristics (Table 2). These associations persisted across ethnicity, sex, and obesity status (Table 3). Furthermore, there was statistical evidence of an interaction (inverse) between SAT and VAT, such that when SAT and VAT are both high, S_I is extremely low. (When the interaction term of SAT and VAT is not included in the model, VAT is the only fat depot statistically associated with S_I). Obesity (BMI ≥30 kg/m^2), but not sex or ethnicity, modified this effect: there was no evidence of an interaction between SAT and VAT among obese subjects (Table 3). Other independent correlates of S_I were age (inversely associated), clinic/ethnicity (Hispanics were more insulin sensitive than the African American referent group), and BMI (inversely associated). Percent change in R^2 was greatest for the joint effect of both fat mass measures and their interaction. The percent change in R^2 associated with dropping these three variables from the model was 27%; the model R^2 was 43.5%. Importantly, BMI explained a relatively small portion of the variance (2.2%). Overall, VAT was a stronger predictor of change in S_I: the beta coefficient for VAT was 73% larger than that for SAT.

SAT, but not VAT, was positively associated with AIR. There was no evidence of a statistical interaction between

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TABLE 1
Descriptive statistics of the IRAS Family Study cohort

	Hispanic (San Antonio)		Hispanic (San Luis Valley)		African American (Los Angeles)	
	Men	Women	Men	Women	Men	Women
n	193	301	216	289	197	261
Age (years)	38.4 ± 14.6	41.5 ± 13.7	40.5 ± 13.6	41.7 ± 12.9	42.7 ± 14.4	40.2 ± 13.1
S_I ($10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	1.89 ± 1.87	2.02 ± 1.83	2.31 ± 1.84	2.33 ± 1.89	1.68 ± 1.20	1.59 ± 1.15
AIR ($pmol \cdot ml^{-1} \cdot min^{-1}$)	821 ± 728	661 ± 581	793 ± 635	835 ± 689	951 ± 855	1,005 ± 778
DI	1,187 ± 1,106	1,055 ± 848	1,527 ± 1,336	1,642 ± 1,449	1,315 ± 1,199	1,440 ± 1,293
BMI (kg/m^2)	29.2 ± 5.2	29.8 ± 6.5	26.9 ± 4.8	27.3 ± 5.4	28.0 ± 4.9	29.7 ± 7.1
SAT (cm^2)	274 ± 128	391 ± 154	252 ± 126	359 ± 140	251 ± 137	406 ± 196
VAT (cm^2)	124 ± 64	105 ± 55	117 ± 56	90 ± 50	96 ± 60	77 ± 47
VAT/SAT ratio	0.48 ± 0.21	0.28 ± 0.12	0.51 ± 0.22	0.25 ± 0.12	0.42 ± 0.22	0.20 ± 0.10
Overweight (%)	39	30	37	34	45	26
Obese (%)	39	45	25	26	29	43
Impaired fasting glucose (%)	7.3	8.0	6.9	6.9	10.7	8.4

Data are means ± SD or %. Population estimates for overweight are (reading left to right) 46, 32, 46, 32, 37, and 30. Population estimates for obesity are (reading left to right) 24, 36, 24, 36, 21, and 39. Population estimates for impaired fasting glucose are (reading left to right) 11.6, 6.3, 11.6, 6.3, 7.7, and 6.4. See text for citations for population estimates.

SAT and VAT on AIR, nor between the adipose tissue measures and ethnicity, sex, or obesity on AIR. However, in obesity-stratified models, there appeared to be a qualitative difference in effect sizes for VAT on AIR, albeit nonsignificant, with a positive borderline significant effect in the nonobese and an inverse (nonsignificant) effect in the obese (Table 3). Other independent correlates of AIR are age (inversely associated), sex (females lower than males), and clinic/ethnicity (Hispanics in San Antonio lowest). Percent change in R^2 was greatest for age (41.6%) and secondly for SAT (16.3%) and clinic/ethnicity (13.8%). When S_I is included in this model as an additional covariate, SAT remains positively and significantly associated with AIR ($P < 0.0001$) and VAT becomes significantly (inversely) associated with AIR ($P = 0.002$).

VAT and the interaction between SAT and VAT were inversely associated with DI. SAT was associated with DI only through the modifying effects of VAT (i.e., no independent SAT effect). This negative interaction term indicates that when SAT and VAT are both high, DI is particularly low. Other independent correlates of DI included age (inversely associated), clinic/ethnicity (Hispanics in San Luis Valley highest), and BMI (inversely associated). None of these factors (sex, ethnicity, or BMI) was found to modify the effect of SAT or VAT on DI. Percent change in R^2 was greatest, and similar, for age (16.5%) and for the joint effect of both fat mass measures and their interaction (16.4%).

The models for S_I, AIR, and DI were repeated with VAT/SAT ratio replacing the individual VAT and SAT measures. VAT/SAT was inversely associated with S_I ($\beta = -0.1869$, $P < 0.0001$) as well as DI ($\beta = -6.3417$, $P < 0.0001$), adjusting for age, sex, ethnicity/clinic, and BMI. In contrast, VAT/SAT was not associated with AIR. When additionally adjusting for VAT and SAT, the VAT/SAT ratio tended to no longer be significant. The sole exception is in the analysis of DI where $P = 0.03$ for VAT/SAT. Thus, the cross-product form of the interaction (as presented in Table 2) is statistically more significant and explains a higher proportion of the variation in S_I and DI than the VAT/SAT ratio.

DISCUSSION

We found a strong independent relationship between both visceral and subcutaneous adiposity with insulin resistance. Increased levels of fat in these depots were significantly associated with lower S_I, the impact of which was enhanced by a significant inverse interaction term. Thus, high levels of fat in both depots lead to substantial insulin resistance. Moreover, the fat measures explained over one-quarter of the model variance (27 of 43.5%), with VAT being a more potent predictor than SAT. The effects were similar across ethnic groups and sex. However, in the obese, there was no statistical evidence of an interaction between VAT and SAT. The relationship between abdominal fat and insulin secretion was quite different: subcutaneous, but not visceral, adiposity was an important correlate of AIR. In this population, age, not fat, explained the greatest proportion of the variance in AIR. When S_I is included in the AIR model, both SAT and VAT (inverse) are significant correlates. Finally, VAT (inverse) and the VAT-SAT interaction explain a similar amount of the model variance in DI compared with age per se (16.5%).

A majority of studies report the singular importance of VAT (vis-à-vis SAT) as inversely related to insulin sensitivity (18–20). But two other studies have appeared that report an equal or stronger association of SAT with insulin sensitivity (3,21). In another study, two functionally different compartments within SAT were examined. Kelley et al. (4) observed a strong correlation of euglycemic clamp–measured insulin-stimulated glucose utilization with both VAT and deep SAT, but not with superficial SAT, suggesting that the deeper compartment is more strongly related to insulin resistance. Cnop et al. (22) reported in 174 individuals a strong inverse relationship between intra-abdominal fat area (VAT) and S_I ($P < 0.001$) but only a borderline significant relationship between SAT and S_I ($P = 0.06$). Importantly, VAT is more effectively depleted by diet-induced weight loss than SAT, with a clear concomitant improvement in insulin sensitivity (23). Thus, although VAT and SAT have been shown in some studies to have cross-sectional relationships with insulin sensitiv-

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ity, VAT appears to have greater clinical importance. In our study, both VAT and SAT were significantly associated with S_I. However, VAT was a more potent predictor: a 20% change in VAT had a similar impact on S_I as did a 30% change in SAT.

One potential explanation for our findings of independent effects of both VAT and SAT on S_I, as well as an important interaction between the two, is that our study had much greater statistical power with a sample size of 1,457. Most earlier studies had sample sizes below 100 participants. Also, logarithmic transformation for both our important dependent (VAT and SAT) and independent variables (S_I) may have detected subtle relationships not observed with nontransformed variables. Also, we included an interaction term in our model (VAT by SAT), which previous reports did not, because adequately powered tests of interactions require large sample sizes, such as in this study.

Few studies have reported the relationship between abdominal fat and insulin response per se. We observed that participants with high levels of SAT are able to compensate insulin resistance with increased secretion, consistent with compensation for skeletal muscle insulin resistance. But two studies have found a positive association between visceral fat and AIR. Sumner et al. (24) observed a significant positive relationship between VAT (but not SAT) and AIR in 49 healthy obese and nonobese women ($r^2 = 0.48$, $P = 0.014$), adjusting for SAT, fat weight, lean body mass, percentage of fat, and age. Cruz et al. (25) reported a significant positive association between magnetic resonance imaging–assessed VAT and AIR in 32 obese Hispanic children with a positive family history of type 2 diabetes. Goran et al. (26), in a study of 119 children, did not observe an independent effect of VAT on AIR. Both Cruz et al. and Goran et al. modeled this relationship in the presence of S_I in the model. Our results are contrary in that we found an association between SAT, but not VAT, and AIR, except in the presence of S_I. In the presence of S_I, both SAT (positively) and VAT (inversely) are associated with AIR. Although we transformed our variables to better approximate model assumptions, it is unlikely that these transformations would lead to such contradictory findings.

This is the first report of the relationship between adipose tissue distribution and DI. DI describes the ability of insulin response to compensate for insulin resistance. Thus, DI is a measure of β-cell functionality (6). We found that both age and the joint effect of the fat measures explained an equal proportion of the variability in β-cell function, as reflected in DI (16%). VAT (inverse) was the primary fat depot associated with DI. Importantly, BMI, a measure of overall obesity, explained only a small proportion of the variability in DI. Thus, obesity in a specific depot (in this case, VAT) is a more important determinant of DI and may explain its ability to predict risk for type 2 diabetes (27). It is unclear why DI should be better determined by visceral than by subcutaneous fat. However, there may be an association of the hepatic responses to risk factors for insulin resistance: reduced liver sensitivity to insulin (which may be secondary to adipocyte resistance), reduced first-pass clearance of insulin by the liver (28), and deposition of liver triglycerides. Possibly,

TABLE 2
Summary of models for S_I, AIR, and DI

	S_I* (model R^2 = 43.5)			AIR* (model R^2 = 11.6)			DI* (model R^2 = 26.3)		
	β ± SE	*P*	Percent change in R^2	β ± SE	*P*	Percent change in R^2	β ± SE	*P*	Percent change in R^2
Age	0.0006 ± 0.0011	<0.0001	10.6	−0.2303 ± 0.0315	<0.0001	41.6	−0.2101 ± 0.0439	<0.0001	16.5
Linear	−0.0004 ± 0.0001			0.0013 ± 0.0012			−0.0071 ± 0.0019		
Quadratic	0.0150 ± 0.0293	0.5839	0.05	−2.4395 ± 0.8883	0.0018	6.1	−1.8651 ± 1.1406	0.0833	0.8
Sex (F vs. M)									
Ethnicity/clinic									
African American (Los Angeles)									
Hispanic (San Antonio)	0.2052 ± 0.0366	<0.0001	5.7	−5.3888 ± 1.0895	<0.0001	13.8	−1.2041 ± 1.3076	0.0150	2.2
Hispanic (San Luis Valley)	0.2181 ± 0.0387			−3.0265 ± 1.1575			2.4949 ± 1.4139		
BMI (kg/m^2)	−0.0134 ± 0.0043	0.0002	2.2	−0.0657 ± 0.0968	0.4386	0.4	−0.5349 ± 0.1507	<0.0001	4.0
Log SAT (cm^2)	−0.1996 ± 0.0526	†		5.4969 ± 1.1613	<0.0001	16.3	1.5534 ± 1.8960	†	
Log VAT (cm^2)	−0.3456 ± 0.0333	†	27.0‡	0.5247 ± 0.9301	0.5271	0.3	−8.7357 ± 1.2202	†	16.4‡
SAT by VAT interaction	−0.1334 ± 0.0278	<0.0001					−3.4585 ± 0.9874	0.0009	

*S_I was natural log, and AIR and DI were square root–transformed (retaining sign). †*P* values not computed for main effects when interaction term is included in the model. ‡The percent change in R^2 associated with dropping both fat measures and their interaction. The percent change in R_2 for dropping the interaction term only was 3.7 for S_I and 2.9 for DI. The percent change in R_2 is relative to the overall R_2.

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TABLE 3
Summary of effect sizes for adipose tissue variables in sex- and obesity-stratified models of S_I, AIR, and DI, adjusted for age, sex, ethnicity/clinic, and BMI

	Sex-stratified models				Obesity-stratified models			
	Male		Female		Nonobese (BMI <30 kg/m^2)		Obese (BMI ≥30 kg/m^2)	
	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*
S_I								
Log SAT	−0.2353 ± 0.0700	†	−0.0953 ± 0.0895	†	−0.3281 ± 0.0510	†	−0.2316 ± 0.0674	†
Log VAT	−0.3811 ± 0.0551	†	−0.3539 ± 0.0395	†	−0.3580 ± 0.0418	†	−0.4673 ± 0.0632	†
Interaction*	−0.1870 ± 0.0359	<0.0001	−0.1167 ± 0.0468	0.01	−0.1653 ± 0.0328	<0.0001	0.0536 ± 0.1083	0.62
AIR								
Log SAT	5.1575 ± 1.9600	0.01	3.5354 ± 1.4711	0.02	3.7407 ± 0.9254	<0.0001	5.6776 ± 2.2482	0.01
Log VAT	0.1756 ± 1.7244	0.92	1.2827 ± 1.1378	0.26	1.7151 ± 0.9367	0.07	−1.8919 ± 1.8134	0.30
DI								
Log SAT	1.3647 ± 3.0768	†	0.9500 ± 2.7243	†	−2.2459 ± 2.0444	†	0.0189 ± 2.6138	†
Log VAT	−10.122 ± 1.9501	†	−8.1781 ± 1.5737	†	−7.3042 ± 1.4470	†	−14.260 ± 2.0399	†
Interaction*	−4.3875 ± 1.6767	0.009	−3.7647 ± 1.2140	0.002	−2.7243 ± 1.4754	0.07	−2.8562 ± 3.9918	0.47

*SAT by VAT interaction. †*P* values not computed for main effects when interaction term is included in the model.

increased DI reflects an hepatic event such as reduced first-pass insulin clearance. Regardless of mechanism, this relationship may help to explain ability of DI to predict type 2 diabetes (29).

Ethnicity did not modify the associations between abdominal fat and S_I (or AIR) in this study. This is consistent with a previous finding from the IRAS, which included equal numbers of African Americans, Hispanics, and Caucasians; the relationship between waist circumference and S_I did not differ by ethnicity (30). Similarly, Goran et al. (26), who studied Caucasian and African-American children, did not observe significant ethnic differences in the relationships between abdominal fat measures and S_I (or AIR).

In our study, ethnicity remained a significant independent predictor of insulin sensitivity, insulin secretion, and DI, even with adjustment for abdominal fat, with African Americans being more insulin resistant and having a greater AIR than Hispanics, and Hispanics in San Luis Valley having a greater DI. Factors other than abdominal fat distribution, such as environment or genetics, must be involved in variation in these measures of glucose homeostasis across these ethnic groups. A Caucasian sample was not included in our study with which to compare these measures. However, the IRAS cohort, from which the current study probands were derived, has been studied with respect to ethnic differences in frequently sampled intravenous glucose tolerance test–derived insulin resistance and insulin secretion (31). Compared with Caucasians, African Americans and Hispanics were more insulin resistant and had a greater AIR—differences that were not completely explained by lifestyle measures (physical activity, percent calories from fat, and fiber) or adiposity (waist-to-hip ratio). It is not known whether a more precise assessment of abdominal adiposity, such as a computed tomography scan, would explain more of the variation in these measures.

Sex did not modify the associations between abdominal fat and S_I (or AIR or DI) in this study. Although it is well established that the sexes differ considerably in fat deposition, it is of interest to determine whether there is also a different effect of fat distribution on insulin sensitivity and insulin secretion between men and women. Our findings are quite consistent with others who report similar correlations between abdominal fat and insulin sensitivity between men and women (21).

On the other hand, obesity did modify the associations between abdominal fat distribution and S_I in this study. Although the main inverse effects of SAT and VAT on S_I persisted across obesity status, the SAT by VAT interaction was not observed in the obese group. A previous report in 36 women suggested that the association of fat distribution with insulin sensitivity differed across body size, with an inverse association between VAT and insulin sensitivity observed only in obese, but not nonobese, women (32). Our findings show conclusively that the strong inverse relationships between VAT and insulin sensitivity, and SAT and insulin sensitivity, persist across a range of body sizes. However, the further dampening of S_I in individuals with high levels of SAT and VAT was not observed in obese subjects. This finding may simply reflect a floor effect such that low levels of S_I in obese subjects cannot be further lowered because the distribution is bounded by zero. Obesity also modified the association between VAT and AIR. In the combined cohort, no effect of VAT on AIR was observed. However, a borderline positive effect of VAT on AIR was observed in the nonobese, and a nonsignificant inverse effect was observed in the obese. We are unable to explain such divergent findings; they may have occurred by chance.

The mechanisms underlying the relationship between VAT and SAT and insulin resistance are unclear. Arner (33) has suggested that the flux of lipid from the visceral fat depot to liver might account for hepatic insulin resistance ("portal theory"). In a canine model, development of insulin resistance occurred concomitant with visceral adiposity because of a modestly elevated fat content in the diet but without increased calories (28). Mittelman et al. (28) suggested that flux of free fatty acid from visceral depot to liver ("visceral-hepatic axis") causes primary insulin resistance of the liver. In addition, Johnson et al. (34) have shown that subcutaneous adipocytes of women with visceral adiposity exhibit insulin resistance and an increased rate of lipolysis. This would contribute to in-

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creased peripheral insulin resistance. Finally, both SAT and VAT secrete a host of factors that could induce or worsen insulin resistance, such as tumor necrosis factor-α, interleukin-6, or resistin (35). Adiposity has been shown to also be associated with decreased adiponectin (36), which could play a role in regulating insulin sensitivity. One or more of these factors may be important.

The mechanisms underlying the relation between increased SAT and insulin secretion are unclear and are further complicated by the impact of the associated insulin resistance on β-cell function. Our data show that the effect of SAT on AIR was maintained and the effect of VAT on AIR was enhanced (inversely) when S_I was included in the regression model. Nonetheless, age had the greatest impact on the variance in AIR. The relationship between age and AIR may reflect a decline of insulin secretory capacity as a function of aging (37). General and visceral adiposity have been shown to be associated with impaired β-cell function possibly due to chronic elevation of free fatty acids and lipotoxicity. Another interesting facet is that increased free fatty acids secondary to expanded VAT and SAT impair hepatic insulin clearance, resulting in increased peripheral insulin levels that could be falsely interpreted as increased insulin secretion.

The strengths of this study are its extensive standardized phenotypes, including computed tomography–measured abdominal fat and directly measured insulin sensitivity, and the large number of participants from two minority populations. The family study design may be considered a limitation. However, we have adjusted for the lack of independence among measures by using a mixed-model approach. There may remain concern that the sample is not representative of the general population. The prevalence of obesity, overweight, and impaired fasting glucose may be one gauge of the representativeness of the sample. We compared these rates to those reported for national samples. Rates of obesity are high in Hispanic participants from San Antonio relative to national estimates and low in Hispanic participants, particularly women, from San Luis Valley (38). The difference between these Hispanic samples and national estimates likely reflects differences in the unique Hispanic populations from which these samples arose (14–16). Men from Los Angeles have higher rates of overweight and obesity when compared with the population estimates. The impaired fasting glucose rates are higher in African-American men and women and lower in Hispanic men relative to the population estimates (39). Regardless of these differences, tests of the relationship between abdominal adiposity and measures of insulin resistance and secretion are expected to be valid.

In summary, we observed an association of both VAT and SAT and their joint interaction with insulin resistance. Although VAT was shown to be a more potent correlate of S_I, SAT was also independently associated with S_I, and together explained a large portion of the variation in insulin sensitivity. We also observed an association of SAT with increased AIR, contrary to several other reports indicating the sole importance of VAT on insulin secretion. However, the effect was minor relative to age in explaining variation in insulin secretion. Finally, VAT was inversely associated with DI, along with an interaction between SAT and VAT. In conclusion, we observed that the various fat depots are associated with measures of glucose homeostasis. These findings have important implications for the risk of type 2 diabetes (27) and prevention of diabetes through weight loss programs focused on abdominal fat (23).

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