Obese Premenopausal African-American Women With Normal and Impaired Glucose Tolerance Have a Similar Degree of Insulin Resistance but Differ in β-Cell Function

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OBJECTIVE — To determine whether insulin resistance and secretion differ in obese premenopausal African-American women with and without glucose intolerance.

RESEARCH DESIGN AND METHODS — A total of 63 women underwent oral glucose tolerance tests (OGTTs). A total of 48 women underwent frequently sampled intravenous glucose tolerance tests (FSIGTs). Insulin resistance was determined from the insulin sensitivity index (S_I) from the FSIGT. Insulin secretion during the OGTT was determined by $(I_{30\ min} - I_{0\ min})/(G_{30\ min} - G_{0\ min})$ and during the FSIGT by the acute insulin response to glucose (AIRg). The disposition index, the product of AIRg and S_I, was used to determine whether AIRg was adequate to compensate for insulin resistance. Statistical analyses included one-way analysis of variance with Bonferroni corrections for multiple comparisons and regression analyses.

RESULTS — The women were divided into three groups: nonobese glucose tolerant ($n = 32$), obese glucose tolerant ($n = 17$), and obese glucose intolerant ($n = 14$). The BMI of the three groups were 24.8 ± 2.3, 37.8 ± 5.5, and 42.0 ± 7.6 kg/m^2 (mean ± SD), respectively ($P < 0.0001$). The ages of the three groups were 34.9 ± 8.4, 32.1 ± 5.0, and 41.1 ± 6.3 years ($P = 0.011$). S_I was higher in the nonobese women than in the obese glucose-tolerant women (3.99 ± 1.44 vs. 2.66 ± 2.14 l · mU^{-1} · min^{-1}, $P = 0.03$). S_I was similar in the obese glucose-intolerant and obese glucose-tolerant women (2.12 ± 1.27 vs. 2.66 ± 2.14 l · mU^{-1} · min^{-1}, $P = 0.9$). OGTT showed that insulin secretion was lower in the glucose-intolerant than the obese glucose-tolerant women (1.73 ± 1.38 vs. 3.62 ± 2.11, $P = 0.005$). FSIGT showed that AIRg was not significantly lower in glucose-intolerant than in obese glucose-tolerant women (807 ± 665 vs. 1,253 ± 655 mU · l^{-1} · min, $P = 0.078$). The disposition index was lower in glucose-intolerant than in obese glucose-tolerant women (1,324 ± 1,061 vs. 2,656 ± 1,415, $P = 0.014$).

CONCLUSIONS — Obese premenopausal African-American women with and without glucose intolerance have a similar degree of insulin resistance but differ in insulin secretion.

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Abbreviations: AIRg, acute insulin response to glucose; FSIGT, frequently sampled intravenous glucose tolerance test; LBM, lean body mass; NIH, National Institutes of Health; OGTT, oral glucose tolerance test; SAT, subcutaneous abdominal adipose tissue; S_I, insulin sensitivity index; TAT, total abdominal adipose tissue; VAT, visceral adipose tissue.

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

The prevalence of type 2 diabetes in African-American women is rising (1). Glucose intolerance is an intermediate step in the development of diabetes (2). To prevent the progression from glucose intolerance to diabetes, it is critical to understand the characteristics of the glucose-intolerant state. Increased insulin resistance, decreased insulin secretion, and central obesity all contribute to the deterioration of glucose tolerance (2–4). The relative contribution of each of these factors to the development of glucose intolerance in African-American women is unknown.

Obese glucose-intolerant Pima Indians have higher insulin resistance than obese glucose-tolerant Pima Indians (2). In contrast, obese Caucasian women with and without normal glucose tolerance have a similar degree of insulin resistance (5,6). It is unknown whether the severity of insulin resistance differs between obese glucose-tolerant and glucose-intolerant African-American women.

Visceral adipose tissue (VAT) is believed to have a role in the development of insulin resistance (7,8). Therefore, it is paradoxical that African-American women are more insulin-resistant than Caucasian women but have less VAT (9,10).

The contribution of visceral obesity to insulin secretion is controversial. It is postulated that free fatty acids released by VAT into the portal circulation cause impaired hepatic insulin extraction and hyperinsulinemia (11,12). In glucose-tolerant Caucasian women, a positive association has been reported between acute insulin secretion and VAT (7). The relationship between VAT and insulin secretion in African-American women must be explored.

The purpose of this investigation is to determine whether insulin resistance and secretion differ in African-American

women with and without glucose intolerance.

RESEARCH DESIGN AND METHODS

— A total of 63 premenopausal African-American women participated in a study on cardiovascular risk factors at the National Institutes of Health (NIH) in Bethesda, Maryland. All participants were born in the U.S. and identified both parents as being of African descent. Normal volunteers were recruited by advertisements in newsletters, word of mouth, and the NIH website. The study was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases. All subjects gave informed consent. In women older than 39 years, premenopausal status was confirmed by gonadotropin levels. Women were studied in the follicular phase of the cycle.

Three visits were conducted over 3 months. At visit 1, a medical history and physical examination were performed. For visits 2 and 3, subjects came to the NIH in the morning after a 12-h fast. At visit 2, with the subject supine, a 75-g oral glucose tolerance test (OGTT) (Trutol 75; Custom Laboratories, Baltimore, MD) was performed with glucose and insulin concentrations determined at 0, 30, and 120 min. Abdominal computed tomography and dual X-ray absorptiometry were also performed.

At visit 3, 48 subjects underwent frequently sampled intravenous glucose tolerance tests (FSIGTs). Intravenous lines were placed in the antecubital vein in each arm. At time 0, glucose (0.3 g/kg) was injected intravenously over 1 min. From 20 to 25 min, an infusion of insulin ($4\ mU \cdot kg^{-1} \cdot min^{-1}$) was administered. Glucose and insulin concentrations were determined at –10, −1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min.

Body composition

Computed tomography. A single-slice image using a CT/I scanner (GE Systems, Milwaukee, WI) was obtained with the patient in the supine position with 10-mm collimation at L2–3. For total abdominal adipose tissue (TAT), a region-of-interest cursor was used to trace the periphery of the abdominal cavity. A density mask was made of the resulting region of interest to include pixels with attenuation values from −150 to −50 Hounsefield units. VAT was calculated by tracing the perimeter of the visceral cavity and obtaining a fat-density mask. Subcutaneous abdominal adipose tissue (SAT) was determined by subtracting VAT from TAT.

Dual-energy X-ray absorptiometry. Whole-body composition measurements were performed with a Hologic QDR 4500A dual-energy X-ray absorptiometer (Hologic, Bedford, MA) in the array mode (software version 5.71A). The instrument determines grams of body fat, lean body mass (LBM), and percentage of fat.

Insulin resistance

Insulin resistance was determined from the insulin sensitivity index (S_I) calculated from the insulin-modified FSIGT using the minimal model equations (13). S_I is the incremental change in insulin required to increase fractional glucose disappearance (14).

Insulin secretion

Insulin secretion was measured during the OGTT as the difference in insulin concentration between 30 and 0 min divided by the difference in glucose concentration between 30 and 0 min ($(I_{30\ min} - I_{0\ min})/(G_{30\ min} - G_{0\ min})$) (3). The acute insulin response to glucose (AIRg) during the FSIGT is calculated as the area under the insulin curve for insulin above basal concentration from 0 to 10 min (15). The disposition index, which is the product of AIRg and S_I, was used to determine whether AIRg was adequate to compensate for the degree of insulin resistance (15).

Analytic methods

Glucose was assayed using the glucose oxidase method (Glucostat; Yellow Springs Instrument, Yellow Springs, OH). Insulin was assayed using the double-antibody chemiluminescent sandwich assay (Diagnostic Products, Los Angeles, CA).

Statistical analyses

Data are presented as mean ± SD. One-way analysis of variance with Bonferroni corrections for multiple comparisons were used to compare means between groups. $P < 0.05$ was considered significant. Variables not normally distributed were transformed by log or square root. Multiple regression analyses were performed separately with transformed S_I and AIRg as dependent variables and VAT, SAT, percentage of fat, fat weight, LBM, and age as independent variables. Statistical analyses were performed with STATA 6 software (College Station, TX).

RESULTS

— Of the 63 women studied, 49 were glucose tolerant and 14 were glucose intolerant (16). All glucose-intolerant women were obese (BMI ≥ 30 kg/m^2). Of the 49 glucose-tolerant women, 17 were normal weight (BMI 18.5–24.9 kg/m^2), 15 were overweight (BMI 25.0–29.9 kg/m^2), and 17 were obese (BMI ≥ 30 kg/m^2). Insulin sensitivity and secretion were not different between the normal and overweight women. Therefore, they were combined into one group and identified as nonobese. The final three groups were *1*) nonobese and glucose tolerant ($n = 32$); *2*) obese and glucose tolerant ($n = 17$); *3*) obese and glucose intolerant ($n = 14$).

The subjects' ages, body composition, and OGTT data are listed in Table 1. The glucose-intolerant women were older than the two groups of glucose-tolerant women. Body size measurements were not significantly different between the obese glucose-tolerant and glucose-intolerant women.

Insulin resistance

The obese glucose-tolerant and glucose-intolerant women had a similar degree of insulin resistance (Fig. 1). The two groups of obese women were more insulin resistant than the nonobese women.

Insulin secretion

Compared with the nonobese women, the obese glucose-tolerant women had a greater insulin response to a glucose challenge (Table 1, Fig. 2). The glucose-intolerant women had a lower insulin response than the obese glucose-tolerant women. However, the difference in AIRg between the obese glucose-tolerant and glucose-intolerant women was not significant ($P = 0.078$). The relationship of AIRg to S_I is shown in Fig. 3. The disposition index was lower in the obese glucose-intolerant women than in the obese glucose-tolerant women (1,324 ± 1,061 vs. 2,656 ± 1,415, $P = 0.014$).

Relationship of VAT area to insulin sensitivity and secretion

The *P* values from the multiple regression analyses with S_I as the dependent variable

Table 1—*Age, body composition, and OGTT data*

	Nonobese glucose tolerant (n = 32)	Obese glucose tolerant (n = 17)	Obese glucose intolerant (n = 14)	P (overall model)
Age (years)	34.9 ± 8.4a	32.1 ± 5.0a	41.1 ± 6.3b*	0.011
BMI (kg/m^2)	24.8 ± 2.3a	37.8 ± 5.5b‡	42.0 ± 7.6b‡	<0.0001
Percent fat	31.0 ± 4.6a	42.1 ± 3.5b‡	44.8 ± 4.7b‡	<0.0001
VAT (cm^2)	27.2 ± 18.1a	73.4 ± 33.1b‡	103.9 ± 53.3b‡	<0.0001
SAT (cm^2)	139.7 ± 54.2a	429.0 ± 134.5b‡	498.7 ± 176.4b‡	<0.0001
Fasting glucose (mmol/l)	4.6 ± 0.4a	4.8 ± 0.5a,b	5.1 ± 0.6b†	0.002
Fasting insulin (pmol/l)	37.8 ± 15.6a	69.0 ± 35.4b†	69.6 ± 43.2b†	0.0005
$I_{30\ min} - I_{0\ min}/G_{30\ min} - G_{0\ min}$	2.23 ± 2.25a	3.62 ± 2.11b†	1.73 ± 1.38a	0.004

Data are means ± SD. Analyses are one-way analysis of variance with Bonferroni corrections for multiple comparisons. *Values not sharing the same letter are significantly different. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

and VAT, SAT, percentage of fat, fat weight, LBM, and age as independent variables demonstrate that only VAT was significantly related to S_I (Table 2). A similar analysis was performed with AIRg and the independent variables cited above. VAT was not significantly related to AIRg.

Age

The multiple regression analyses revealed that age was not a risk factor for either insulin resistance or secretion (Table 2).

CONCLUSIONS — Glucose intolerance in premenopausal African-American women is not associated with an extra increment in insulin resistance beyond the insulin resistance caused by obesity. Because African-American women have a high prevalence of both obesity and glucose intolerance (1), it is encouraging that glucose intolerance is not associated with a further deterioration in insulin sensitivity.

Insulin resistance and body fat distribution

The anatomical location of adipose tissue may dictate the extent to which obesity contributes to insulin resistance. Except for one small study in Pima Indians (17), VAT has universally been associated with increased insulin resistance (7–9,18,19). VAT contributes to the development of insulin resistance because free fatty acids released from VAT into the portal circulation increase hepatic glucose production and decrease hepatic insulin extraction (11,12,20). In our investigation, VAT was the only body composition measure that was significantly associated with insulin resistance. However, VAT has two components: intraperitoneal and retroperitoneal. In this study, we could not determine the relative contributions of each of these depots to insulin resistance.

It is controversial whether SAT participates in the development of insulin resistance. Goodpaster et al. (21) found that SAT was as strongly associated with insulin resistance as visceral fat. Lovejoy et al. (9) concluded that SAT contributed to insulin resistance in African-American women but not in Caucasian women. Other investigations have not shown a relationship between SAT and insulin resistance (4,7,8,19). Likewise, we found no association between insulin resistance and SAT. Recently, there has been a focus on the metabolic activity of the two components of SAT, deep SAT, and superficial SAT (22). We examined SAT as a single entity; therefore, we cannot determine whether either component of SAT contributes to insulin resistance.

Another fat depot that may be a source of circulating free fatty acids and may contribute to the development of insulin resistance is truncal fat. Significant associations between truncal fat and insulin resistance have been reported (19,23).

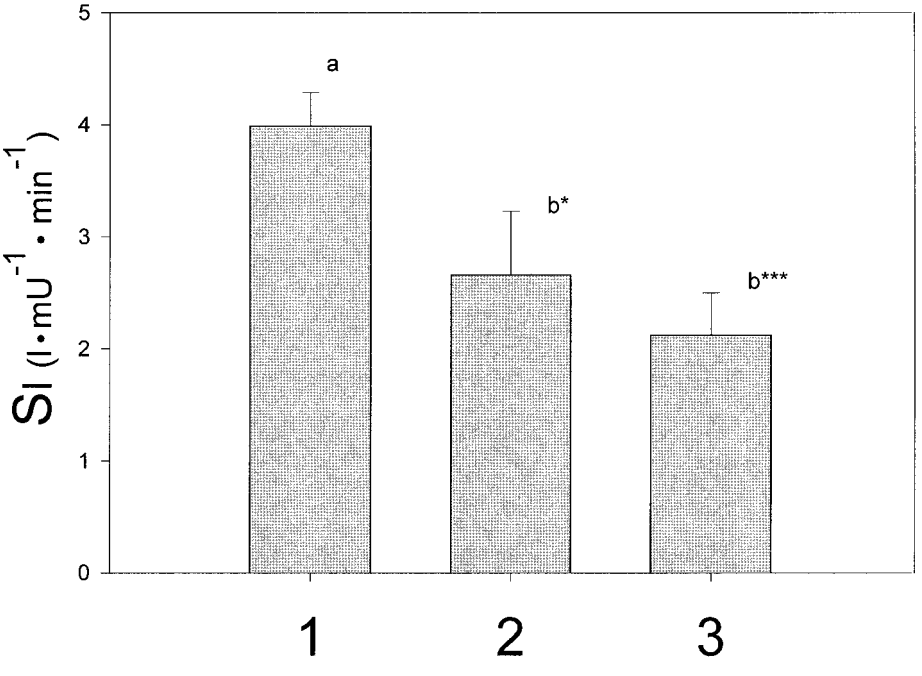

Figure 1—S_I *in* 1*) nonobese glucose-tolerant women,* 2*) obese glucose-tolerant women, and* 3*) obese glucose-intolerant women. Data are means ± SEM and analyzed by one-way analysis of variance with Bonferroni corrections for multiple comparisons. Columns not sharing the same letter are significantly different.* *P < 0.05, **P < 0.01, ***P < 0.001.

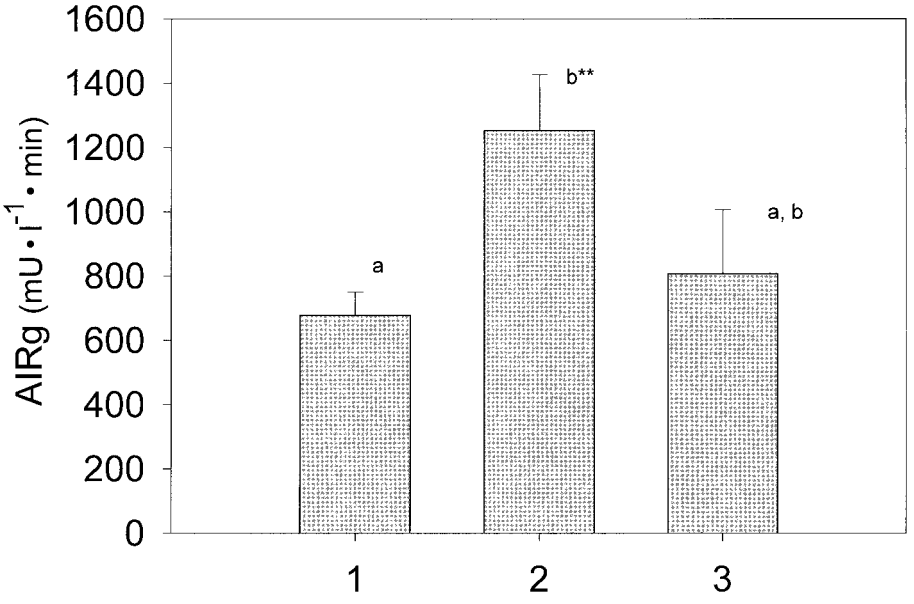

Figure 2—*Acute insulin response to glucose (AIRg). Data are presented and analyzed as described for Fig. 1. The difference between women in groups 2 and 3 did not reach significance with* P = *0.078.*

Table 2—*P* value from multiple regression of S_I* or AIRg* on body composition measures and age

	P
Insulin sensitivity index (S_I), $R^2 = 0.44$	
Age	0.92
Fat weight	0.57
LBM	0.3
Percentage of fat	0.26
SAT	0.23
VAT	<0.01
Acute insulin response to glucose (AIRg), $R^2 = 0.24$	
VAT	0.43
SAT	0.12
Fat weight	0.1
Age	0.07
Percent fat	0.05
LBM	0.02

*Analyses performed after square root transformation to normalize data

Truncal fat is calculated as the sum of five skinfolds: subscapular, midaxillary, suprailiac, umbilicus, and abdomen (19). We did not measure all five skinfolds, but we did measure three: subscapular, suprailiac, and abdomen. With this abbreviated measure of truncal fat, we found that truncal fat was a strong determinant of insulin resistance ($P = 0.001$) (data not shown). However, in multiple regression analyses with S_I as the dependent variable and all three skinfold measurements as independent variables, only the abdominal skinfold measurement was a significant determinant of insulin resistance ($P < 0.001$). The correlation coefficient between the abdominal skinfold thickness and VAT area was $R = 0.75$, $P < 0.0001$. These analyses suggest that the abdominal skinfold may be a surrogate measure of VAT.

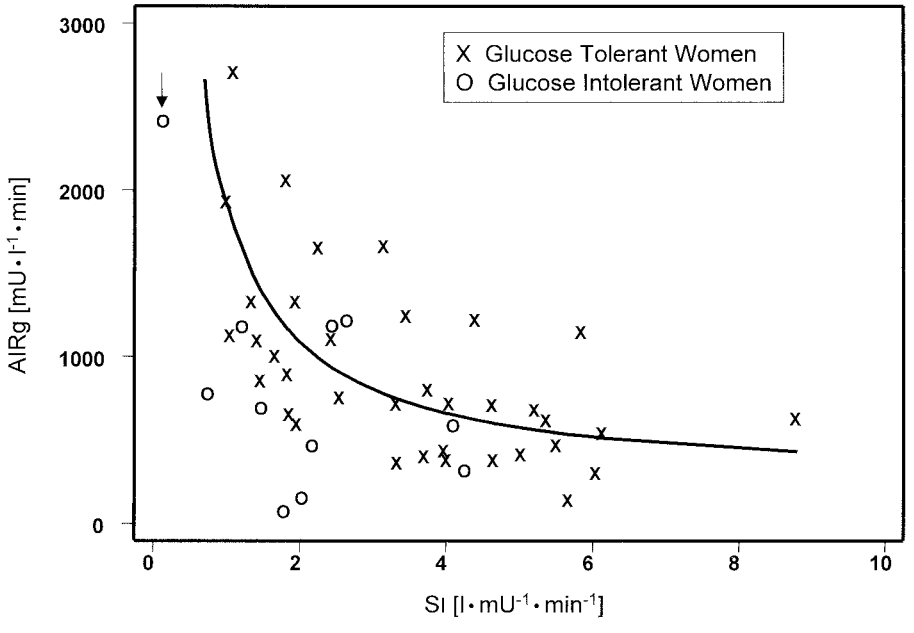

Figure 3—*Insulin secretion versus insulin sensitivity. The equation for the hyperbolic curve for the normal women is AIRg = 237 (±143) +1,700 (±323)/S_I (coefficient ± SD of coefficient). The subject identified by the arrow is discussed in the text.*

Insulin secretion and body fat distribution

Using the OGTT measure of insulin secretion, the obese glucose-intolerant women had lower insulin secretion than the obese glucose-tolerant women. However, AIRg was not significantly lower in the obese glucose-intolerant women than in the obese glucose-tolerant women ($P = 0.078$). This situation was clarified when the relationship between S_I and AIRg was plotted. In the normal glucose-tolerant women, the relationship between AIRg and S_I was hyperbolic. The values for glucose-intolerant women were predominantly below or to the left of the curve determined by the glucose-tolerant women. Similarly, the disposition index was lower in the obese glucose-intolerant women than in the obese glucose-tolerant women. Overall, the glucose-intolerant women were unable to secrete adequate amounts of insulin to overcome their insulin resistance. Even the glucose-intolerant woman with the highest AIRg (2,397 $l \cdot mU^{-1} \cdot min^{-1}$) had inadequate

insulin secretion for her degree of insulin resistance. This subject is identified by an arrow in Fig. 3.

We found no relationship between VAT area and insulin secretion. This is because the obese glucose-tolerant and glucose-intolerant women had similar VAT areas but different levels of insulin secretion. However, in glucose-tolerant women, a positive association between VAT and insulin secretion has been reported (7). With only the glucose-tolerant women in our study, we performed multiple regression analyses with VAT, SAT, fat weight, LBM, percentage of fat, and age as independent variables and AIRg as the dependent variable (data not shown). We, too, found that VAT had a significant effect on AIRg ($R^2 = 0.48$, $P = 0.014$). However, when we performed the analyses with the glucose-tolerant and glucose-intolerant women combined (Table 2), it was the factors related to overall body size, such as percentage of fat and LBM, that affected insulin secretion and not VAT. Therefore, when only obese glucose-tolerant women were studied, the association observed between VAT and insulin secretion may have been secondary to the simultaneous occurrence of insulin hypersecretion and increased VAT.

Age

Age does not seem to affect insulin resistance. The evidence for this is that the glucose-intolerant women were older than the obese glucose-tolerant women, but S_I did not differ. The relationship between age and insulin secretion is unclear. The multiple regression analyses with age as an independent variable and AIRg as the dependent variable yielded a *P* value for the effect of age on AIRg of 0.07. If our study population had been larger, age may have become significantly associated with decreased insulin secretion. Other investigations have examined the effect of age on insulin secretion, and the results conflict (8,24–26). Therefore, the issue remains unresolved.

Insulin resistance is similar in obese glucose-tolerant and glucose-intolerant African-American women. For obese glucose-intolerant African-American women, insulin secretion is inadequate to compensate for their degree of insulin resistance. Identifying ways to increase insulin secretion may be beneficial.

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