Insulin Resistance in Adipocytes of Obese Women: Effects of Body Fat Distribution and Race

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Upper-body obesity (UBO) in white women is associated with increased fatty acid turnover and resistance to the effects of insulin on systemic glucose metabolism. The present study determined whether the abilities of insulin to stimulate glucose transport and suppress lipolysis are impaired in adipocytes from white UBO (W-UBO) women. Because the clinical risks associated with UBO are attenuated in black women, the effects of race on adipocyte insulin sensitivity were assessed. Forty-two healthy, equally obese women were selected for study on the basis of race (black or white) and body fat distribution (UBO or lower-body obesity [LBO]). In white women, both abdominal and gluteal fat cells from the UBO versus LBO group were less responsive to the stimulatory effects of insulin on glucose uptake and less sensitive to the antilipolytic effects of insulin and the adenosine analog, phenylisopropyladenosine (PIA). In contrast, in black women, fat cells from UBO and LBO groups were equally sensitive to the stimulatory effects of insulin on glucose transport and the suppressive effects of insulin and PIA on lipolysis. These in vitro data correlate well with previous clinical findings that UBO in white women but not in black women is associated with insulin resistance and dyslipidemia. Thus, resistance to the antilipolytic effects of insulin and adenosine at the level of adipose tissue may increase systemic lipolysis and play a role in the development or maintenance of peripheral insulin resistance associated with UBO in white women, but not in black women.

HUMAN OBESITY is a predisposing factor for several debilitating diseases including non–insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD). Although many of the obese may eventually develop these illnesses, some do not. This heterogeneity among the obese is related, in part, to the anatomic location of body fat rather than to total body fatness. Observational[1-3] and prospective population[4,5] studies have demonstrated that a preponderance of abdominal fat is a potent independent risk factor for NIDDM and CVD.

Race may be another important factor contributing to the heterogeneity among the obese regarding susceptibility to chronic diseases. Recently, we reported that whereas equally obese white women with increased waist to hip ratios showed a worsening of metabolic complications, increased waist to hip ratios in black women were not associated with additional glucose intolerance, insulin insensitivity, or hypertriglyceridemia (but high-density lipoprotein cholesterol levels were decreased).[6] Consistent with these findings, a recent longitudinal study showed that body mass index (BMI) and upper-body fat distribution were associated with mortality in white women, but they failed to predict mortality in black women.[7] The reasons for the racial dimorphism among the obese that we and others[7-11] have observed remain unclear.

The hallmark of upper-body obesity (UBO), at least among whites, is insulin resistance,[3] which has been documented at the level of muscle[12] and of the liver.[13] Few previous studies have examined whether adipose tissue is also resistant to insulin. Increases in systemic lipolysis in white UBO (W-UBO) women were documented by Jensen et al[14]; however, mechanisms underlying the increased fatty acid turnover are unclear.

Increased lipolytic activity of fat cells in abdominal sites is thought to contribute to the high fatty acid flux in UBO.[3-15] Increases in responsiveness to catecholamines in abdominal versus gluteal fat cells are well documented,[16-18] but few studies have systematically investigated whether body fat distribution per se influences adipocyte metabolism. Furthermore, few studies have addressed regional differences in the regulation of lipolysis by insulin; some have reported increased sensitivity to insulin in abdominal as compared with femoral adipocytes, but others have not.[2,9,19,20] Kissebah et al[2] were the first to show higher rates of basal lipolysis in fragments of abdominal adipose tissue from UBO versus lower-body obesity (LBO) women. However, Landin et al[21] recently observed that the antilipolytic effect of a single high dose of insulin was similar between isolated fat cells from UBO and LBO women.

The present study was designed to determine whether the insulin sensitivities of glucose transport and antilipolysis are impaired in isolated fat cells from W-UBO and black UBO (B-UBO) women of comparable total adiposity. Possible differences in insulin action between abdominal and gluteal fat cells from UBO and LBO women of both races were also examined. In addition, to gain further insight into the mechanisms regulating lipolysis, sensitivity to the antilipolytic effects of adenosine was also assessed.

SUBJECTS AND METHODS

Subject Selection

Forty-two women were selected for study on the basis of race (black or white), age (18 to 45 years), menstrual history (regular menses), ideal body weight (130% to 150%), percent body fat determined by hydrodensitometry (40% to 45%), and body fat

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distribution (UBO or LBO)[6] according to the waist to hip ratio (≤ 0.76 for LBO or ≥ 0.85 for UBO). In calculating percentage body fat with the Siri equation, a different density of fat-free mass (FFM) was used for black (1.105 g/mL) and white (1.100) women, using the data recently reported by Ortiz et al.[22] The subjects were the same as those who participated in an earlier study.[6] They were in good health and had normal glucose tolerance, as previously described in detail.[6]

Four experimental groups were formed as follows: B-UBO, black LBO (B-LBO), W-UBO, and white LBO (W-LBO) groups. These groups were well matched for age, BMI, percent body fat, and percent FFM (Table 1).

The study was approved by the Institutional Review Board of St. Luke's/Roosevelt Hospital Center, and all subjects provided written informed consent.

Subcutaneous Adipose Tissue Aspirations

Needle aspirations of subcutaneous adipose tissue were performed at 9 AM on subjects that had fasted from 9 PM the evening before. After the skin was disinfected and the subcutaneous tissue was anesthetized (2% Lidocaine; Elkins-Sinn, Cherry Hill, NJ), adipose tissue from an abdominal and a gluteal site was obtained using a blunt-ended needle designed for liposuction (3-mm Spirotri cannulae; Unitech Instruments, Fountain Valley, CA). Aspirations were performed in the abdominal region at a point one third of the distance from the superior anterior iliac crest to the umbilicus and at one of the gluteal regions in the upper lateral quadrant. The interval between aspirations did not exceed 10 minutes.

Isolation of Fat Cells

Aspirated adipose tissue was washed immediately in phosphate-buffered saline (pH 7.4) and then digested with collagenase (1 mg/mL) in Krebs-Henseleit buffer (37°C) containing 25 mmol/L HEPES, 10 mmol/L bicarbonate, 5% albumin (CRG-7; Reheis Pharmaceuticals, Kankakee, IL), and 0.55 mmol/L glucose.[23] After 30 to 45 minutes of digestion with constant agitation at 60 cycles per minute, the fat cells were filtered through nylon mesh (250 μm; Tetko, Briarcliff Manor, NY) and washed four times by flotation with Krebs-Henseleit-bicarbonate-HEPES buffer (37°C) that was free of collagenase and glucose (KHBH-A).

Determination of Fat Cell Size

Diameters of ≥ 200 cells from each fat cell suspension were measured directly using a microscope and ocular micrometer according to the method reported by DiGirolamo et al.[24] The mean cell volume, cell weight (assuming that the density of lipid is equal to that of triolein, 0.915), and cell surface area were then calculated from the mean cell diameters and standard deviations according to the formulae reported by Goldrick[25] and Zinder and Shapiro.[26] In addition, an aliquot of the fat cell suspension was taken for measurement of total lipid content according to Dole's lipid extraction method.[27] The total number of cells per milliliter of suspension was then calculated from the lipid content of the cell suspension divided by the mean fat cell weight.

Table 1. Clinical Characteristics of Study Subjects (mean ± SE)

	Black Women		White Women	
Characteristic	UBO	LBO	UBO	LBO
No.	11	11	10	10
WHR	0.89 ± 0.01	0.72 ± 0.01	0.88 ± 0.01	0.71 ± 0.01
Age (yr)	36 ± 2	37 ± 2	40 ± 1	38 ± 2
BMI (kg/m^2)	33 ± 1	34 ± 1	35 ± 1	32 ± 1
Body fat (%)	44 ± 1	44 ± 1	43 ± 1	44 ± 1
FFM (%)	56 ± 1	56 ± 1	57 ± 1	56 ± 1

Abbreviation: WHR, waist to hip ratio.
Reprinted with permission.[6]

Measurement of Glucose Transport

Rates of basal and insulin-stimulated glucose uptake were measured in vitro according to the method reported by Kashiwagi et al.[23] This assay reflects rates of glucose transport measured directly with 3-*O*-methylglucose.[23] Isolated fat cells suspended in KHBH-A (20,000 to 40,000 cells/mL) were incubated in triplicate with varying concentrations (0, 25, 50, 100, 400, and 16,000 pmol/L) of human insulin (Humulin, Lilly, Indianapolis, IN). After a 15-minute preincubation, a trace amount (300 nmol/L) of [U-^{14}C]-D-glucose (0.1 μCi/mL) was added. The incubation continued at 37°C for 1 hour with continuous shaking. The incubation was terminated by centrifuging an aliquot of the fat cell suspension through silicone oil. Radioactivity associated with the fat cell layer was determined by liquid scintillation spectroscopy. The data are expressed as glucose clearance rate in femtoliters per cell or per cell surface area per second.

Measurement of Lipolysis

Lipolysis in isolated fat cells was measured as described by Berlan and LaFontan[28] and Kather et al.[29] Fat cells were suspended in KHBH-A (10,000 to 20,000 cells/mL) containing glucose (5 mmol/L). To assess the antilipolytic effects of insulin and adenosine, lipolysis in the presence of adenosine deaminase ([ADA] 2 μg/mL) plus various concentrations of insulin (25, 100, and 400 pmol/L) or the nonhydrolyzable adenosine receptor agonist, phenylisopropyladenosine ([PIA] 10 and 100 nmol/L), was determined. Fat cells were incubated with gentle agitation (60 cycles/min) at 37°C for 2 hours. The fat cell suspension was transferred to microcentrifuge tubes, and after a brief 15-second centrifugation, the buffer below the fat cell layer was removed for determination of glycerol. Glycerol was assayed in neutralized perchloric acid extracts of the incubation medium.[30] All data are expressed as net glycerol release per cell and per cell surface area; the amount of glycerol present at the start of incubation was subtracted from all values.

Calculations

The sensitivities of glucose transport and antilipolysis to insulin were defined as the insulin concentrations that produced a half-maximal effect (ED_{50}). For glucose transport, ED_{50} was calculated for each subject from the linear regression of transport rate expressed as a percent of maximal transport versus the log of insulin concentration at 25, 50, 100, and 400 pmol/L, as described by Kashiwagi et al.[23] For antilipolysis, ED_{50} was calculated for each subject from individual dose-response curves, which were linearized using log-logit plots according to the method reported by Bolinder et al.[19]

Responsiveness to insulin was calculated for each subject as the increment in glucose transport over basal at a maximal dose of insulin (16,000 pmol/L), or the decrement in glycerol release from baseline (ADA-stimulated) at a maximal dose of insulin (400 pmol/L).

Statistical Analysis

All statistical analyses were performed using SAS (Statistical Analysis System, Cary, NC) on an IBM personal computer (Pough-

keepsie, NY). Two-way ANOVAs with repeated measures were performed using the general linear model procedure. Race and body fat distribution were the two main factors in the model, and aspiration site and dose of insulin or PIA were the repeated measures. When significance was detected at the P less than .05 level for either the main effects, repeated-measures effects, or interaction effects, the least-significant difference (LSD) test was applied, as described by Winer,[31] for post hoc analyses. The LSD test with the appropriate mean square error terms was used to determine which two group means were significantly different from each other at P less than .05.

RESULTS

Subject Characteristics

The four experimental groups were well matched for age, BMI, percent body fat, and percent FFM (Table 1).

Fat Cell Size

In LBO women of both races, abdominal fat cells were significantly smaller than gluteal fat cells ($P < .05$; Fig 1). In contrast, average fat cell size was similar between abdominal and gluteal fat cells from UBO women. Comparisons between UBO and LBO women showed that independently of race, abdominal fat cells from UBO women were larger than abdominal cells from LBO women, whereas gluteal cells from UBO and LBO women were similar in average size.

Effect of Insulin on Glucose Transport

Within each group, abdominal and gluteal fat cells had similar rates of glucose transport in the absence and presence of insulin. In isolated fat cells from all four experimental groups, insulin stimulated glucose transport in a dose-dependent manner. In fat cells from W-LBO women, maximal rates of glucose transport in the presence of insulin were threefold greater than baseline. However, the ability of insulin to stimulate glucose transport was greatly attenuated in fat cells from W-UBO women. Fat cells from W-UBO women exhibited significantly lower rates of glucose transport (expressed per cell and per cell surface area) at baseline and at every insulin dose than fat cells from the same region in W-LBO women (Fig 2). Maximally insulin-stimulated glucose transport rates of fat cells from W-UBO women were less than half the rates of cells from W-LBO women. The incremental response (maximal-basal glucose transport) to insulin was significantly decreased in fat cells from W-UBO versus W-LBO women, whereas the half-maximal rates of insulin-stimulated glucose transport (ED_{50}) were similar (Table 2).

In contrast, in black women, basal and insulin-stimulated glucose transport rates (expressed per cell and per cell surface area) of fat cells from UBO and LBO groups were similar (Fig 2). Likewise, ED_{50} values and incremental responses were similar for fat cells from black UBO and LBO groups (Table 2).

The only racial difference in glucose transport was observed between abdominal fat cells from LBO women. In B-LBO women, abdominal cells had significantly lower rates of basal and insulin-stimulated glucose transport than abdominal cells from W-LBO women (per cell and per cell surface area). The ED_{50} and incremental response were also significantly lower in abdominal cells from B-LBO versus W-LBO women (Table 2).

Antilipolytic Effect of Insulin

The antilipolytic effect of insulin was tested under conditions in which basal lipolysis was enhanced by addi-

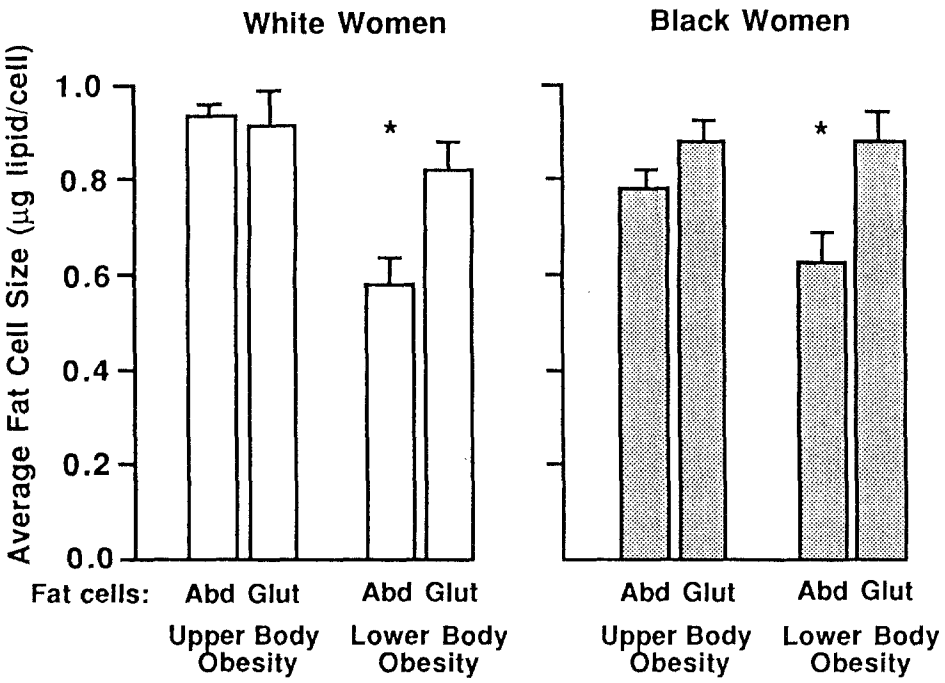

Fig 1. Average fat cell size of isolated subcutaneous fat cells. *Abdominal (Abd) v gluteal (Glut) fat cells, significant difference at $P < .05$ by LSD post hoc analysis.

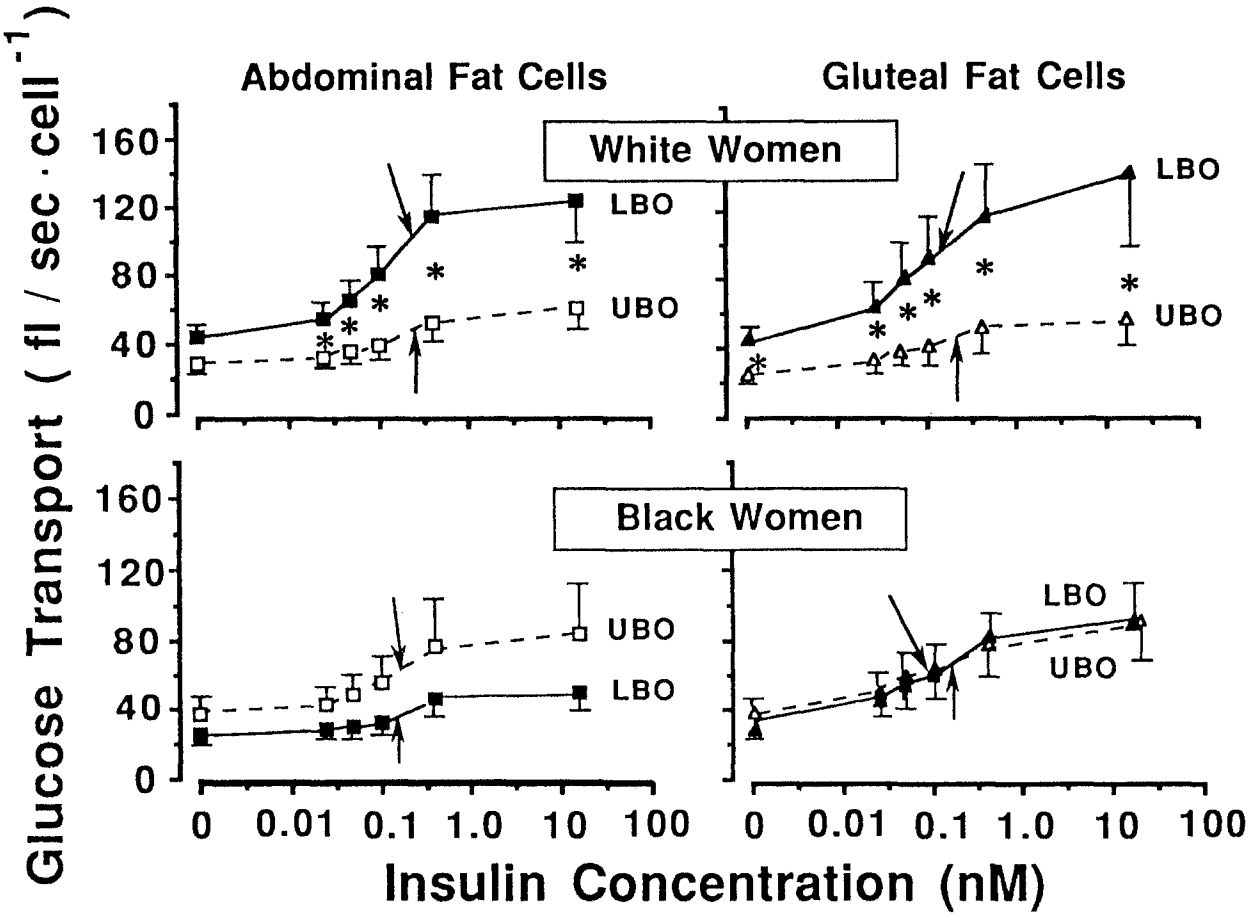

Fig 2. Glucose transport in isolated fat cells. Insulin dose-response curves for glucose transport expressed per cell (fL glucose/s · cell^{-1}) are given for abdominal and gluteal fat cells from UBO (---) and LBO (—) women. Arrows indicate the average ED_{50}, which was calculated from individual dose-response curves. Two-way ANOVA with repeated measures was performed. When significance was detected at $P < .05$, the LSD post hoc analysis was applied. *UBO *v* LBO, significantly different at $P < .05$ by LSD analysis.

tion of ADA, which removes endogenous adenosine, a potent antilipolytic compound that accumulates in the medium during fat cell incubations.[32] Rates of ADA-stimulated lipolysis (expressed per cell or per cell surface area) were similar in gluteal and abdominal fat cells from W-UBO and W-LBO women (Table 3). Likewise, rates of ADA-stimulated lipolysis were similar in gluteal fat cells from B-UBO and B-LBO women. However, rates of ADA-stimulated lipolysis (per cell and per cell surface area) in abdominal fat cells from B-LBO women were significantly ($P < .01$) lower than in abdominal cells from B-UBO women (Table 3).

Insulin produced a dose-dependent suppression of ADA-stimulated lipolysis (80% to 90%) in isolated fat cells from all four experimental groups (Fig 3). The only site difference in lipolytic rates was observed between abdominal and gluteal fat cells from B-LBO women. In B-LBO women, abdominal fat cells versus gluteal ones were less sensitive and less responsive to the antilipolytic effects of insulin (Table 2). Within all other groups (W-UBO, W-LBO, and B-UBO), abdominal and gluteal fat cells had comparable

Table 2. Insulin Sensitivity (pmol/L) of Glucose Transport and Antilipolysis (mean ± SE)

	White Women		Black Women	
Site	LBO	UBO (n = 10)	LBO	UBO (n = 11)
Glucose transport ED_{50}				
Abdominal	157 ± 27	193 ± 24	159 ± 25	147 ± 26
Gluteal	140 ± 32	172 ± 57	144 ± 28	102 ± 18
Antilipolysis ED_{50}				
Abdominal	37 ± 5*	95 ± 15	75 ± 14†‡	54 ± 10§
Gluteal	28 ± 5*	90 ± 18	43 ± 11	60 ± 13

NOTE. Two-way ANOVA with repeated measures was performed with race and body fat distribution as the two main effects and biopsy site as the repeated measure. When significance was detected at $P < .05$ for either the main effects, repeated-measure effects, or any interaction effects, the LSD test was used for post hoc analysis. Symbols represent significant differences between groups at $P < .05$ by LSD analysis. Comparisons within race and between race compare fat cells of similar type.

*LBO *v* UBO (within-race).

†Abdominal *v* gluteal (within-group).

‡B-LBO *v* W-LBO.

§B-UBO *v* W-UBO.

Table 3. Antilipolytic Effect of PIA (mean ± SE)

	White Women				Black Women			
	LBO		UBO		LBO		UBO	
Stimulus	Abd	Glut	Abd	Glut	Abd	Glut	Abd	Glut
ADA stimulated	239 ± 34	284 ± 38	263 ± 43	225 ± 45	110 ± 18*†‡	229 ± 39	293 ± 51	343 ± 53§
10 nmol/L PIA	117 ± 21†	211 ± 34	230 ± 35	181 ± 33	69 ± 10†	168 ± 26	182 ± 27	234 ± 41
100 nmol/L PIA	31 ± 5†	42 ± 6	63 ± 14	57 ± 9	27 ± 6†	47 ± 10	31 ± 9†§	55 ± 18

NOTE. To assess the antilipolytic effects of PIA, ADA 2 μg/mL was added to all incubations to stimulate lipolysis. Lipolysis is expressed per cell in nmol glycerol released/10^5 cells/2 h.

Abbreviations: Abd, abdominal fat cells; Glut, gluteal fat cells; ADA, adenosine deaminase; PIA, phenylisopropyladenosine.

*LBO *v* UBO (within-race).

†Abd *v* Glut (within-group).

‡B-LBO *v* W-LBO.

§B-UBO *v* W-UBO.

lipolytic rates over the entire dose-response curve and similar sensitivities and responses to insulin.

Both gluteal and abdominal adipocytes from W-UBO versus W-LBO women were significantly less sensitive but equally responsive to the antilipolytic effects of insulin (Table 2 and Fig 3). In black women, there was no effect of body fat distribution on sensitivity or responsiveness of antilipolysis to insulin (Table 2 and Fig 3).

In abdominal but not in gluteal fat cells, insulin suppression of lipolysis was affected by race. In UBO, abdominal fat cells from white women versus black women were less sensitive but equally responsive to the antilipolytic effects of insulin (Table 2 and Fig 3). A converse effect of race was observed in LBO. Abdominal fat cells from W-LBO women were significantly more sensitive and more responsive to the antilipolytic effect of insulin as compared with abdominal cells from B-LBO women. However, this phenomenon may be a function of the lower rates of ADA-stimulated lipolysis

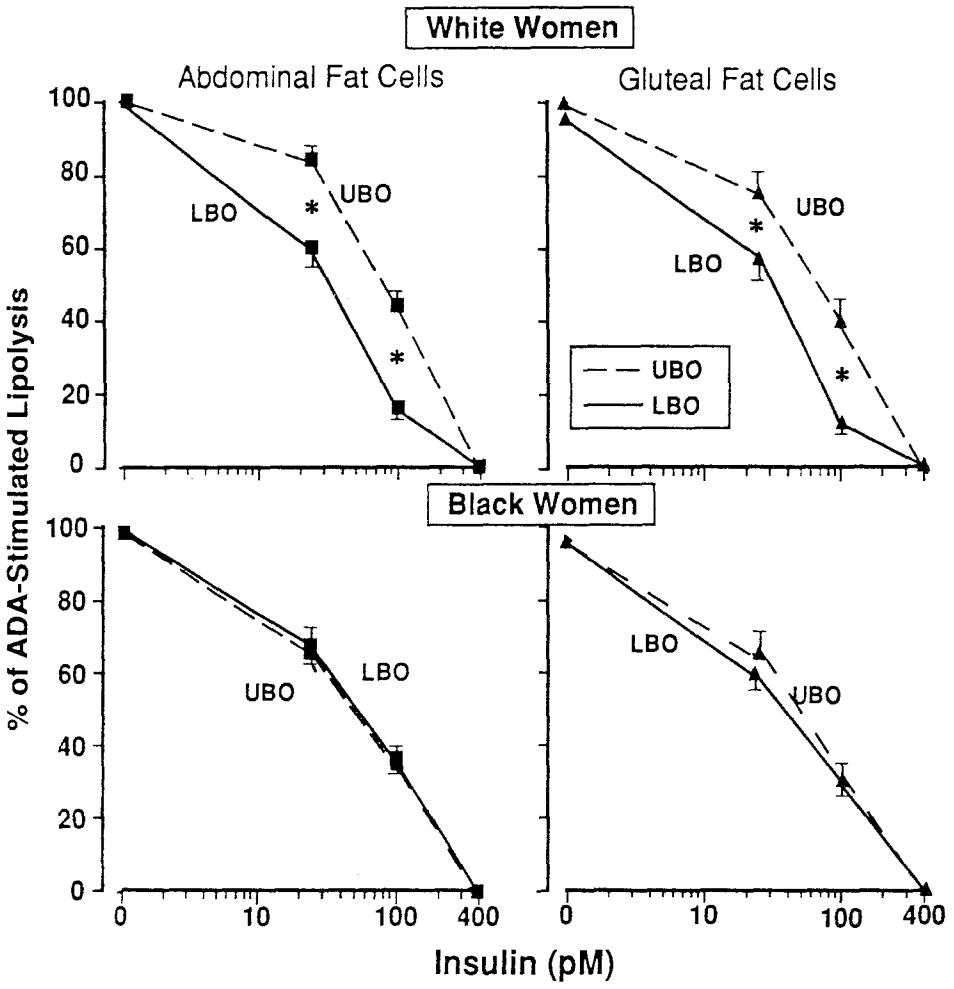

Fig 3. Antilipolytic effect of insulin. Insulin dose-response curves for antilipolysis are shown. Data are expressed as a percent of ADA-stimulated lipolysis [(lipolysis at a given insulin dose − lipolysis at the maximal insulin dose of 400 pmol/L)/(ADA-stimulated lipolysis − lipolysis at the maximal insulin dose) × 100]. *UBO *v* LBO, significantly different at $P < .05$ by LSD post hoc analysis.

observed in abdominal adipocytes from B-LBO women (Table 3).

Antilipolytic Effect of PIA

In isolated fat cells from all four groups, the adenosine analog PIA suppressed ADA-stimulated lipolysis (Table 3). In white women, PIA was less effective in suppressing lipolysis in abdominal fat cells from the W-UBO group versus the W-LBO group (Fig 4). At 10 nmol/L PIA, lipolysis of abdominal fat cells from W-UBO women was not suppressed, whereas lipolysis of abdominal fat cells from W-LBO women was suppressed to 39% of ADA-stimulated rates. Gluteal fat cells from white women were also less sensitive to PIA, although these differences were less marked than in abdominal fat cells (Fig 4). In black women, PIA was equally effective in suppressing lipolysis in abdominal and gluteal fat cells from UBO women versus LBO women.

Rates of lipolysis in the presence of a maximal dose of PIA were affected by race. In abdominal adipocytes from W-UBO women, lipolysis in the presence of 100 nmol/L PIA was twofold greater than that of abdominal cells from B-UBO women (Table 3). Rates of PIA-suppressed lipolysis did not differ between gluteal fat cells from white and black women.

Site differences were observed in the ability of PIA to suppress lipolysis (Table 3). For LBO women of both races, abdominal fat cells had significantly lower lipolytic rates than gluteal fat cells in the presence of 10 and 100 nmol/L PIA. Likewise, for B-UBO women, abdominal fat cells showed significantly lower lipolytic rates at the highest PIA dose tested than gluteal fat cells. However, for W-UBO women, abdominal fat cells had comparable lipolytic rates in the presence of 10 and 100 nmol/L PIA versus gluteal ones.

DISCUSSION

We have observed that UBO in white women is associated with resistance to the effects of insulin on adipocyte glucose uptake and decreased sensitivity to antilipolytic effects of insulin and adenosine. In contrast, adipocytes from B-UBO women do not exhibit alterations in glucose

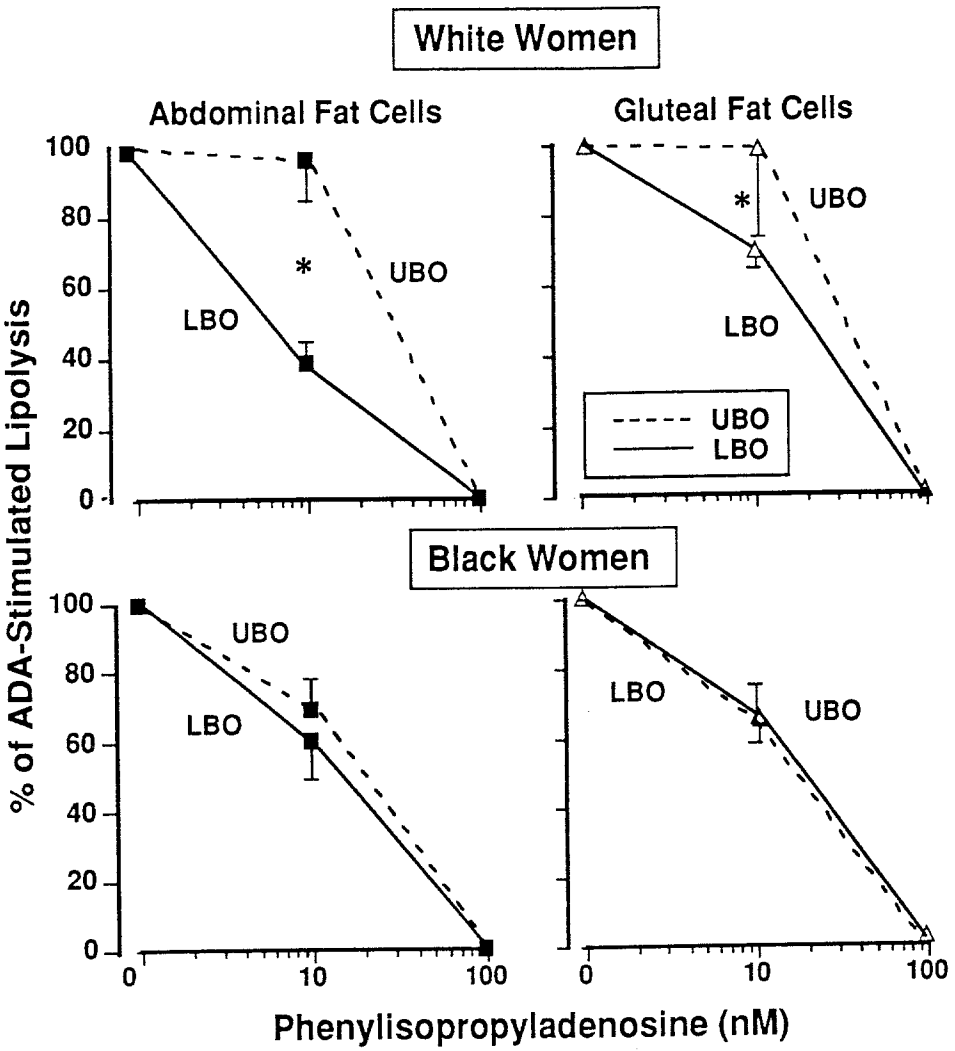

Fig 4. Antilipolytic effect of PIA. PIA dose-response curves for antilipolysis are shown. Data are expressed as a percent of ADA-stimulated lipolysis. *UBO *v* LBO, significantly different at $P < .05$ by LSD post hoc analysis.

transport or antilipolysis versus B-LBO women. These findings suggest that the elevated systemic lipolysis previously observed by Jensen et al[14] in W-UBO women is due at least in part to resistance to the antilipolytic effects of insulin and adenosine. It will be important to confirm that systemic lipolysis is not influenced by UBO in black women.

The literature remains controversial as to whether individuals with NIDDM or those at risk for NIDDM such as UBO individuals are resistant to insulin action at the level of adipose tissue.[20,23,33-35] Some investigators report no differences in the antilipolytic effect of insulin in the various forms of insulin resistance, including obesity, starvation, hyperinsulinemia, and NIDDM.[20] Others have reported that the insulin sensitivities of glucose transport and antilipolysis were decreased in adipocytes from moderately and morbidly obese subjects versus lean controls.[23] Recently, in agreement with the present results, decreased sensitivity to insulin's antilipolytic effect was demonstrated in vitro in fat cells from obese subjects with impaired glucose tolerance.[34] In contrast, in diabetic American Indians,[35] adipocyte sensitivity to the antilipolytic effect of insulin was unaffected, whereas the sensitivity of glucose transport to insulin was impaired. Some of these discrepant findings may reflect heterogeneity among the subjects studied in terms of genetic background and body fat distribution. As we have shown,[6] within the obese nondiabetic, glucose-tolerant population of white women but not of black women, those with an abdominal distribution manifest marked insulin resistance of antilipolysis, whereas those with the same total body fatness but with a gluteofemoral distribution exhibit a relative sensitivity to insulin action of antilipolysis and glucose transport. Whether obesity per se influences adipocyte insulin sensitivity in black women will require further studies.

Garvey et al[36] have recently demonstrated that compared with lean controls, abdominal adipocytes from obese subjects show a 34% decrease in expression of the insulin-sensitive glucose transporter GLUT4, whereas abdominal adipocytes from subjects with NIDDM show a 78% decrease. These decreases in the expression of GLUT4 were associated with parallel decreases in insulin-stimulated glucose transport. The present data extend these findings and suggest that there is heterogeneity in the degree of impairment of adipocyte glucose transport among equally obese subjects. The further decrease in adipocyte glucose transport that we have observed in W-UBO women with normal glucose tolerance may be an early change in the pathogenesis of NIDDM.

Analyses of dose-response curves for glucose transport and antilipolysis suggest that different cellular alterations are responsible for the insulin resistance of these two pathways in adipocytes from W-UBO women. For glucose transport, we observed a decreased responsiveness without a concomitant change in sensitivity, which suggests defects in post–insulin receptor binding events similar to those observed in patients with NIDDM.[37] In contrast, decreased sensitivity with no change in responsiveness was observed for insulin's antilipolytic effect.[38,39] Thus, it is likely that alterations in coupling of the insulin receptor to distal steps regulating lipolysis are affected.

Metabolic differences between subcutaneous abdominal and gluteal fat cells are well documented.[16-18] Abdominal fat cells are more lipolytically responsive to catecholamines as compared with femoral or gluteal fat cells. In contrast to the results reported by Smith et al,[16] the present results confirm previous reports[19,20,39] that the sensitivity of antilipolysis to insulin is similar between these two subcutaneous sites. Furthermore, it is clear that this lack of a site effect in insulin action is independent of body fat distribution. In contrast to the lack of site differences in insulin effects, regional differences in sensitivity to the antilipolytic effect of adenosine were observed. For black women and W-LBO women, PIA was more effective in suppressing lipolysis in abdominal fat cells than in gluteal ones. However, for W-UBO women, this site difference was not evident; PIA-suppressed lipolysis was comparable between abdominal and gluteal fat cells. These findings are in contrast to a previous study by Wahrenberg et al,[18] in which sensitivity of antilipolysis to PIA was similar in abdominal and gluteal fat cells from lean men and women. Adenosine suppresses lipolysis by binding to its receptor and inhibiting adenylyl cyclase via inhibitory G-protein.[29] In contrast, insulin's antilipolytic effect is due to a stimulation of cyclic guanosine monophosphate–inhibited phosphodiesterase.[29,40] Thus, it is likely that regional differences in lipolysis observed in vivo in UBO[41] are due to alterations in multiple steps in the lipolytic cascade.

Antilipolytic effects of insulin were determined under conditions in which endogenous adenosine was removed. Although rates of ADA-stimulated lipolysis were similar in adipocytes from W-UBO and W-LBO women, it is possible that levels of cyclic adenosine monophosphate varied, potentially modulating sensitivity to insulin under these in vitro conditions.[42] Thus, additional studies will be required to dissect the mechanisms modulating sensitivity to insulin antilipolysis in UBO.

One other site difference in fat cell metabolism was observed. In B-LBO women, abdominal fat cells had a decreased capacity for glucose transport and a decreased capacity to mobilize fat versus gluteal fat cells. These abdominal fat cells were metabolically sluggish in the basal state and under all hormonal conditions as compared with all other fat cells studied. These differences are not merely secondary to the smaller size of these cells, since they were the same size as abdominal adipocytes from W-LBO women, which were more active metabolically.

UBO influenced subcutaneous fat cell morphology to the same extent in healthy, premenopausal black women as it did in white women. Abdominal fat cells from UBO women were nearly twofold larger than abdominal fat cells from LBO women, independent of race. Neither we nor Landin et al[21] could confirm the observation of Kissebah et al[2] that abdominal adipocytes from UBO women are larger than gluteal ones. The reason for the discrepancy is unclear. Nevertheless, it appears that an enlarged abdominal girth in women of either race is due in part to a significant

hypertrophy of subcutaneous abdominal fat cells. Fat cell morphology but not its metabolism was influenced by UBO in black women.

Although abdominal fat cells from B-UBO women were hypertrophied to the same extent as those from W-UBO women, they were not more resistant to the effects of insulin on glucose transport or antilipolysis as compared with fat cells from B-LBO women. It therefore appears that the association between UBO and insulin resistance at the level of adipose tissue is dependent on race. These in vitro findings are consistent with our in vivo results in which the same B-UBO women did not the manifest glucose intolerance, peripheral insulin resistance, or altered plasma lipids as W-UBO women of similar total adiposity.[6] A recent longitudinal study by Stevens et al[7] supports our findings of racial dimorphism in UBO. Abdominal girths were examined as predictors of all-cause mortality and coronary heart disease mortality during 25 to 28 years of follow-up evaluation in black and white women in the Charleston Heart Study. The risk of all-cause mortality was greater in white women with larger abdominal girths independently of BMI. In contrast, abdominal girths were not predictive of mortality in black women. Thus, although fat patterning predicted mortality in white women, it failed to do so in black women. To account for the racial differences in our clinical study, we previously speculated that black women may have smaller amounts of intraabdominal (visceral) fat for a given waist to hip ratio than equally obese white women.[6] Support for this hypothesis has recently been provided in a study of weight loss in black and white women.[43] Given that the metabolism of visceral fat cells is thought to be tightly linked to metabolic abnormalities, further studies should assess lipolysis in vivo in black women.

In summary, we have shown that UBO is associated with insulin resistance at the level of adipose tissue independent of total adiposity but dependent on race. The present in vitro results are consistent with our previous in vivo findings,[6] which showed that an upper-body fat distribution does not exacerbate the metabolic abnormalities associated with obesity in black women as it does in white women. The data support the hypothesis that resistance to the antilipolytic effects of insulin and adenosine in W-UBO women contributes to the accelerated flux of free fatty acids observed in vivo by Jensen et al.[14] Increased fatty acid availability may contribute to the decreased peripheral glucose utilization, hyperinsulinemia, and increased hepatic triglyceride synthesis that are the hallmarks of UBO.[3,15] Thus, heterogeneity among the obese regarding susceptibility to NIDDM and CVD may be related at least in part to the degree of insulin resistance at the level of adipose tissue.

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