The Relationship in African-Americans of Sex Differences in Insulin-Mediated Suppression of Nonesterified Fatty Acids to Sex Differences in Fasting Triglyceride Levels

Anne E. Sumner, Harvey Kushner, Thomas N. Tulenko, Bonita Falkner, and Julian B. Marsh

Insulin is a potent antilipolytic hormone that promotes the deposition of fat and decreases the release of nonesterified fatty acids (NEFA) from adipose tissue. The purpose of this study was to investigate in African-Americans (AAs) sex differences in insulin-mediated suppression of plasma NEFA and fasting triglyceride (TG) levels. Ninety AAs, 44 men and 46 women with a mean age of 34 ± 8 years were classified by body mass index (BMI) into three groups: non-obese (22 men and 18 women), obese (12 men and 10 women), and severely obese (10 men and 18 women). In each BMI group, women versus men had greater percent body fat (non-obese, 30 ± 6 *v* 18 ± 6, $P < .001$; obese, 36 ± 3 *v* 26 ± 2, $P < .001$; and severely obese, 39 ± 4 *v* 29 ± 4, $P < .001$). An oral glucose tolerance test (OGTT) was performed with fasting TG levels and plasma insulin and NEFA concentrations obtained at 0, 30, 60, and 120 minutes. In women, insulin-mediated NEFA suppression was similar in each of the three BMI groups (non-obese, 85% ± 14%; obese, 88% ± 11%; and severely obese, 87% ± 10%; $P = .8$). In men, the percent suppression of NEFA declined with increasing obesity (non-obese, 83% ± 14%; obese, 71% ± 21%; and severely obese, 68% ± 16%; $P = .04$). Changes in NEFA suppression were reflected in the fasting TG levels. TG levels in women were similar in each BMI group (non-obese, 71 ± 39 mg/dL; obese; 69 ± 21; severely obese, 79 ± 30; $P = .7$). In contrast, fasting TG levels for men were higher in the higher BMI groups. Plasma TG levels in men were 87 ± 41 mg/dL for obese, 113 ± 65 for obese, and 169 ± 81 for severely obese ($P = .001$). These data demonstrate sex differences in insulin-mediated NEFA metabolism. In AA women, the maintenance of sensitivity to insulin-mediated suppression of NEFA regardless of the degree of obesity may contribute to the normal plasma TG levels. For AA men, the resistance to insulin-mediated suppression of NEFA in the higher BMI categories may allow more NEFA to be released from adipose tissue into the circulation and available to the liver for synthesis into TG-containing lipoproteins.

CARDIOVASCULAR DISEASE is a major of cause of morbidity and mortality in African-Americans (AAs).[1] Compared with AA women, AA men have a higher prevalence of heart disease, but AA women have a higher death rate from heart disease.[2] In whites, an elevated fasting plasma triglyceride (TG) level appears to be an independent risk factor in women but not in men.[3] But AA men and women have lower fasting plasma TG levels than Caucasians.[4] Therefore, findings in caucasian subjects may not be applicable to AAs. However, both the Coronary Artery Risk Development in Young Adults (CARDIA) Study and Atherosclerosis Risk in Communities (ARIC) Study[4,5] have demonstrated a sex difference in fasting plasma TG levels in both AAs and Caucasians. AA and Caucasian men have higher fasting plasma TG levels than AA and Caucasian women.

Obesity is considered a risk factor for hypertriglyceridemia.[3,6] Adult obesity disportionately affects AA women.[7] In the National Health and Nutrition Examination Survey (NHANES) III phase I cohort, 49% of AA women were obese, compared with 32% of AA men, 33.5% of Caucasian women, and 32% of Caucasian men.[8]

A major factor contributing to the sex difference in obesity in AAs may be sex differences in adipocyte sensitivity to insulin.[9] Insulin is a potent fat-regulatory hormone because insulin both promotes the deposition of fat and inhibits the breakdown of fat by inhibiting lipolysis and the subsequent release of nonesterified fatty acids (NEFA) from adipose tissue into the circulation.[10,11] Adipocyte sensitivity to insulin can be indirectly assessed in vivo by analyzing plasma insulin and NEFA levels obtained during a standard 75-g oral glucose tolerance test (OGTT).[9,12] In response to ingestion of glucose, pancreatic β cells secrete insulin. In response to this acute increase in plasma insulin concentration, adipocyte lipolysis is inhibited and fewer NEFA are released into the circulation. The decrease in the plasma concentration of NEFA during an OGTT is referred to as insulin-mediated suppression of NEFA.[12] The higher the suppression of NEFA during on OGTT, the higher the adipocyte sensitivity to insulin.

Much of the NEFA that are released into the circulation from adipose tissue is cleared by the liver, synthesized into TG, and packaged into very–low-density lipoprotein (VLDL) particles. Havel et al[13] found a positive linear correlation between hepatic uptake of NEFA and hepatic secretion of VLDL particles. In the fasting state, the plasma TG level is correlated with the VLDL-TG concentration.

This study was designed using OGTTs to determine in AAs if there are sex differences in insulin-mediated suppression of NEFA, and to relate these sex differences to sex differences in fasting plasma TG levels.

SUBJECTS AND METHODS

Ninety clinically well nondiabetic AAs (46 premenopausal women and 44 men; mean age, 33.9 ± 8 years; age range, 21 to 49) participated in the study. The protocol was approved by the Institutional Review Board of the Allegheny University of the Health Sciences (formerly the Medical College of Pennsylvania and Hahnemann University). The subjects were drawn from a cohort that has been under study since

From the Allegheny University of the Health Sciences (formerly the Medical College of Pennsylvania and Hahnemann University), Philadelphia, PA.

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Address reprint requests to Anne E. Sumner, MD, Institute for Women's Health, Allegheny University of the Health Sciences, 3300 Henry Ave, Philadelphia, PA 19129.

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adolescence in ongoing investigations of blood pressure regulation.[14] No subjects were taking any lipid-lowering agents or antihypertensives. All women were studied during the first 2 weeks of the menstrual cycle. Eight women were on oral contraceptives. All participants had measurements of height, weight, and skinfold thickness (triceps, biceps, subscapular, and suprailiac). From these anthropometric measurements, percent body fat was calculated.[15]

Each subject had a fasting plasma TG assay and a 75-g OGTT (Glucola; Ames Laboratories, Elkart, IN) with blood samples for glucose, NEFA, and insulin concentrations obtained at 0, 30, 60, and 120 minutes. These samples were immediately centrifuged, and the plasma was removed and stored at −80°C.

Fasting plasma TG levels were measured in the Lipid Research Laboratory of the Medical College of Pennsylvania by standard enzymatic methods and an automated analyzer (Hitachi 704; Boehringer Mannheim, Indianapolis, IN). Plasma glucose concentrations were determined by the glucose oxidase method (Glucostat; Yellow Springs Instrument, Yellow Springs, OH). Plasma NEFA were determined by the enzymatic colorimetric method (NEFA C test; Wako, Osaka, Japan). Plasma insulin was determined with a solid-phase radioimmunoassay (Coat-A-Count; Diagnostic Products, Los Angeles, CA).

Statistical Analysis

Two-way ANOVA was used to test for statistically significant differences in means (non-obese *v* obese *v* severely obese, and males *v* females). The test for interaction between obesity groups and gender groups was performed. Differences and correlations were considered statistically significant at $P < .05$. Bivariate correlations among parameters were examined using Pearson correlation coefficients. All values are presented as the mean ± SD unless otherwise stated.

Percent suppression of NEFA was calculated according to the following formula: 100 × ([NEFA] at 0 min − [NEFA] at 120 min)/[NEFA] at 0 min. The total insulin concentration response to the OGTT was defined as the area under the insulin curve as estimated using the trapezoidal rule, which equals 0.5 × insulin at 0 min + insulin at 30 min + 1.5 × insulin at 60 min + insulin at 120 min. The same equation was used to determine the area under the glucose curve during the OGTT. The insulin to glucose ratio at each time point and the area under the curve for the insulin to glucose ratio was used as a measure of the sensitivity to insulin as a glucoregulatory hormone.

A stepwise multiple linear regression (SPSSPC+ Ver 3.0; SPSS, Chicago, IL) was performed to examine the multiple correlations among variables and the association with plasma TG levels. For men and women separately, it was determined which linear combination of age, BMI, percent body fat, percent suppression of NEFA levels, and NEFA and insulin concentrations correlates with plasma TG levels. The stepwise computer algorithm for the regression equation selects at the first step the highest correlated variable with the dependent variable (plasma TG level). At the second step, the algorithm selects the variable that produces the highest canonical correlation, based on two independent variables, with the dependent variable. Therefore, variables that are highly correlated with the first independent variable entered are not entered into the regression. The computer algorithm was continued until there were no additional statistically significant ($P < .05$) increases in the prediction of the single dependent variable on the best linear combination of independent variables. There were some highly correlated independent variables such as BMI and percent body fat. The algorithm is not disrupted or negated by this multicolinearity, but once one of a set of highly correlated parameters is entered into the model, it is usually the strongest correlate with the dependent variable and there is no additional predictive value for others.

RESULTS

Men and women were divided into three categories by BMI according to criteria set by the National Center for Health Statistics[16] (Table 1). Men were defined as non-obese for a BMI of less than 27.8 kg/m^2, obese for BMI ≥ 27.8 but less than 31.1 kg/m^2, and severely obese for BMI of 31.1 kg/m^2 or greater.[7] For women, the criteria were non-obese for BMI less than 27.3 kg/m^2, obese for BMI ≥ 27.3 but less than 32.2 kg/m^2, and severely obese for BMI of 32.2 kg/m^2 or greater.[7] Within each BMI group, women had significantly greater percent body fat (Fig 1A) and peripheral fat as measured by the triceps skinfold (Fig 1B).

Men had higher plasma glucose concentrations at each time point except 120 minutes, and a higher area under the glucose curve (Table 2). Fasting insulin concentrations were higher in men than in women, but there were no sex differences in insulin concentration at any other time point, in the area under the insulin curve or in the insulin to glucose ratio at any time point, or in the area under the insulin to glucose curve (Table 2). There were also no sex differences in NEFA concentrations (Table 2). There were significant sex differences during the OGTT in percent suppression of NEFA. Women suppressed NEFA concentration during the OGTT by 86.5% ± 11.6%, versus 76.4% ± 18.1% for men ($P = .002$). Figure 2 illustrates in men and women the decrease in NEFA concentration during the OGTT. Figure 3A demonstrates that when the population was subdivided into three groups, non-obese, obese, and severely obese, women maintained sensitivity to insulin-mediated suppression in every BMI group, but with increasing BMI, men had significantly less suppression of NEFA (Fig 3A).

There were significant sex differences in fasting plasma TG concentration. For men, fasting TG levels were higher in the higher BMI groups (Fig 3B). For women, TG levels did not change with BMI group (Fig 3B). Examination of Fig 3A and B simultaneously demonstrates that women showed greater sup-

Table 1. Population Characteristics

	Men (n = 44)			Women (n = 46)			2-Way ANOVA (*P*)		
	Non-obese (n = 22)	Obese (n = 12)	Severely Obese (n = 10)	Non-obese (n = 18)	Obese (n = 10)	Severely Obese (n = 18)	Men *v* Women	BMI	Interaction
Age (yr)	31 ± 4	32 ± 3	31 ± 4	31 ± 3	32 ± 3	32 ± 3	.5	.7	.9
Weight (kg)	75 ± 10	91 ± 5	120 ± 24	65 ± 7	80 ± 9	106 ± 19	<.001	<.001	.8
BMI (kg/m^2)	23 ± 3	30 ± 1	40 ± 8	24 ± 2	30 ± 1	40 ± 8	.7	<.001	.9
Central fat index†	1.5 ± .4	1.6 ± .5	1.6 ± .5	.9 ± .3	1.2 ± .3	1.2 ± .4	<.001	.04	.34

*Two-way ANOVA was used to determine statistical differences between gender and obesity groups with a test for interactive effects.
†Ratio of subscapular skinfold thickness to triceps skinfold thickness.

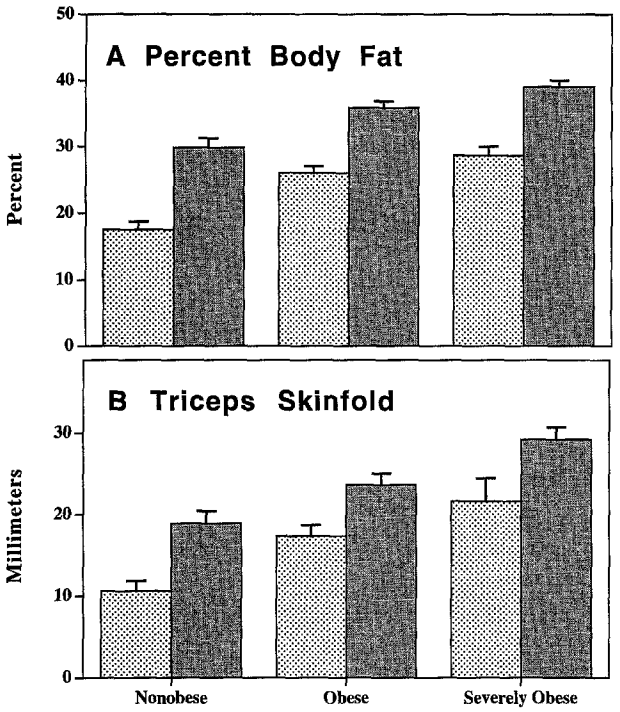

Fig 1. (A) Percent body fat. The number of men (▨) and women (▩) in each group is provided in Table 1. Men *v* women, $P < .001$. (B) Triceps skinfold. Men *v* women, $P < .001$. Data are the mean ± SE, analyzed by 2-way ANOVA.

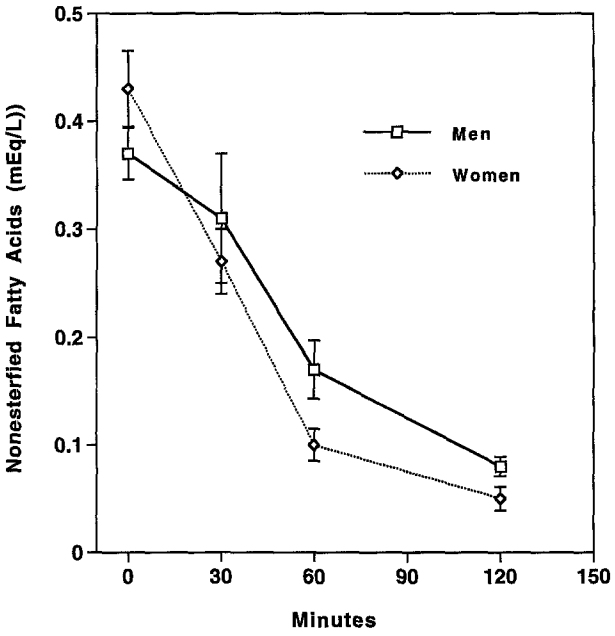

Fig 2. NEFA concentrations for men (n = 44) and women (n = 46) during the OGTT.

pression of NEFA and lower TG levels, whereas in men lower suppression of NEFA was strongly associated with higher TG levels.

Table 3 provides Pearson correlation coefficients between fasting plasma TG and BMI, percent body fat, 0- and 120-minute NEFA levels, percent change in NEFA, and 0- and 120-minute insulin concentrations. In both men and women, fasting plasma TG level correlated significantly with 0- and 120-minute insulin concentrations. But it is only in men that fasting plasma TG concentration correlated with BMI ($r = .37$, $P < .05$), percent body fat ($r = .4$, $P < .01$), and percent change in NEFA ($r = -.31$, $P < .05$).

We performed a stepwise multiple linear regression analysis to examine the predictability of plasma TG as a function of age, BMI, percent body fat, 0- and 120-minute insulin levels, 0- and 120-minute NEFA levels, percent suppression of NEFA, and sex. In the first regression equation, sex and insulin and NEFA concentrations were statistically significant predictors of TG levels. Since the ANOVA also showed a significant effect of gender, regression models were repeated for men and women separately (Table 4). The regression models are highly different for men and women. For women, the only significant correlate of plasma TG is the 0-minute insulin. For men, the 120-minute plasma insulin level, 120-minute NEFA concentration, and percent suppression of NEFA are significant correlates of plasma TG level, and together account for 47% of the variance (R^2) in male plasma TG levels, which is a highly statistically significant predictability.

The correlation coefficient for percent change in NEFA with the 0- and 120-minute NEFA values was .26 and −.73, respectively. The correlation between 120-minute NEFA and percent change in NEFA was large, but not large enough to exceed the limits of the computer algorithm. The last variable to be entered into the regression for males was percent change in NEFA, which in part seems to represent this high correlation with the 120-minute NEFA value that was already entered into

Table 2. Metabolic Variables by Sex and BMI

	Men (n = 44)			Women (n = 46)			2-Way ANOVA (*P*)		
	Non-obese (n = 22)	Obese (n = 12)	Severely Obese (n = 10)	Non-obese (n = 18)	Obese (n = 10)	Severely Obese (n = 18)	Men *v* Women	BMI	Interaction
0-min glucose (mg/dL)	91 ± 8	100 ± 9	99 ± 7	86 ± 7	90 ± 7	91 ± 7	<.001	.001	.5
0-min insulin (U/mL)	7.9 ± 11	13.7 ± 10	23.4 ± 12	6.7 ± 3	9.3 ± 5	14.4 ± 7	.02	<.001	.2
0-min NEFA (mEq/L)	.37 ± .16	.37 ± .18	.37 ± .19	.51 ± .27	.34 ± .08	.41 ± .26	.15	.3	.3
120-min NEFA (mEq/L)	.05 ± .05	.09 ± .06	.11 ± .05	.07 ± .11	.04 ± .03	.05 ± .04	.07	.63	.02
Glucose area*	543 ± 64	559 ± 86	602 ± 71	494 ± 91	479 ± 72	557 ± 87	.002	.005	.7
Insulin area*	225 ± 179	346 ± 129	534 ± 227	258 ± 198	305 ± 123	510 ± 231	.9	<.001	.7
Ins/Glu area†	1.6 ± 1.2	2.3 ± .8	3.3 ± 1.2	1.9 ± 1.3	2.5 ± 1	3.6 ± 1.6	.3	<.001	.9

*Area under the curve calculated as 0.5 × variable at 0 min + variable at 30 min + 1.5 × variable at 60 min + variable at 120 min.
†Insulin to glucose ratio.

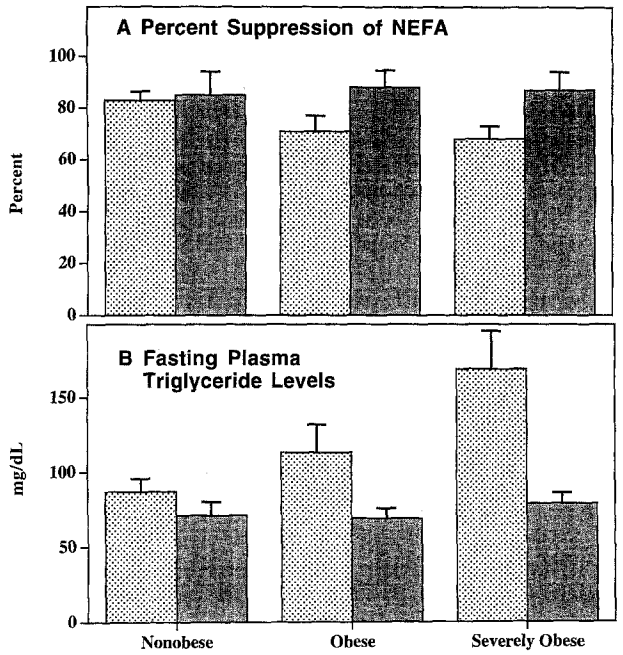

Fig 3. (A) Percent suppression of NEFA during the OGTT. Men *v* women, $P \pm .001$; among BMI groups, $P = .18$; sex × BMI interaction, $P < .05$. (B) Fasting plasma TG concentration. Men *v* Women, $P < .001$; among BMI groups, $P < .01$; sex × BMI interaction, $P < .01$. Data are presented and analyzed as described for Fig 1. (▨) men; (▩) women.

the model. Regression analyses without the percent change had two terms instead of three in the model for the males, that is, no other parameters were entered into the model in place of percent change.

DISCUSSION

AA women have lower plasma TG levels than AA men.[5] This sex difference may be secondary to greater adipocyte sensitivity to insulin in women. By indirect assessment of adipocyte sensitivity to insulin by measuring percent suppression of NEFA during an OGTT, women compared with men had significantly greater percent suppression of NEFA ($P = .001$). The metabolic basis for the high sensitivity of AA women to insulin-mediated suppression of NEFA may be related to their high peripheral body fat content. Using the triceps skinfold, as a measure of peripheral fat, AA women compared with AA men have significantly higher amounts of peripheral fat ($P = .001$; Fig 1B). In Caucasians, comparative studies of peripheral and central fat by adipose tissue biopsy have demonstrated that peripheral fat is more sensitive to insulin's antilipolytic effect.[17] The adipocytes of AAs are probably metabolically similar to the adipocytes of Caucasians. Therefore, the high peripheral body fat content in AA women compared with AA men is consistent with the observed sex differences in sensitivity to insulin-mediated suppression of NEFA.

Table 3. Pearson Correlation Coefficients of Fasting Plasma TG by Sex

Parameter	Correlation With Plasma TG (*r*)	
	Men	Women
BMI	.37*	.05
% body fat	.4†	.27
0-min NEFA	.25	−.11
120-min NEFA	.55*	.12
% change in NEFA	−.31*	−.28
0-min insulin	.49†	.4†
120-min insulin	.45†	.36*

*$P < .05$.
†$P < .01$.

Obesity is considered a risk factor for hypertriglyceridemia.[3,6] Yet in our study, AA women in all three BMI groups, non-obese, obese, and severely obese, had normal TG levels (Fig 3B). At the same time, women in all three BMI groups had a high degree of insulin-mediated suppression of NEFA (Fig 3A). The primacy of insulin in determining plasma TG levels in women is demonstrated both by the Pearson correlation coefficients (Table 3) and the stepwise multiple regression analysis with plasma TG as the dependent variable (Table 4). In both analyses in women, plasma insulin concentrations were the only significant correlate or independent variable. In AA women, the high degree of insulin-mediated suppression of NEFA in all three BMI groups suggests that in all groups smaller amounts of NEFA are mobilized from adipose tissue and available in the circulation for clearance by the liver and synthesis into VLDL-TG.

AA men showed the usual association of increased fasting plasma TG with increased BMI (Table 2). For AA men, plasma TG correlated significantly with BMI ($r = .37$, $P < .05$) and percent body fat ($r = .4$, $P < .01$; Table 3). Obese and severely obese men compared with non-obese men had decreased insulin-mediated suppression of NEFA during the OGTT (Fig 2A). This finding suggests that in obese AA men, more NEFA are released from adipose tissue into the circulation and available for hepatic uptake and synthesis into VLDL-TG. The positive correlation in men of plasma TG with 120-minute NEFA ($r = .55$, $P < .01$) and inverse correlation of plasma TG with percent change in NEFA ($r = .31$, $P < .05$) are consistent with this relationship (Table 3). The multiple linear regression analysis showing a significant association between fasting plasma TG and 120-minute NEFA and percent change in NEFA also supports this relationship (Table 4).

We did not compare AA women with Caucasian women. However, in studies in which both AA and Caucasian women participated, AA women compared with Caucasian women have lower fasting TG levels.[4,18,19] Dowling and Pi-Sunyer[19] found that when upper-body obese AA women were compared with upper-body obese Caucasian women, the Caucasian women had fasting TG levels that were 76% higher than the AA Caucasian women. This significant racial difference in TG levels might be explained by racial differences in upper-body fat distribution. Conway et al[18] found, by examining abdominal body fat content with computed tomography, that when AA and Caucasian women had similar waist to hip ratios, Caucasian women had significantly more visceral fat. This difference in visceral fat content may be a significant factor in determining racial differences in fasting TG levels, because visceral fat is more resistant to insulin than central subcutaneous fat. Bolinder et al[20] found, in in vitro studies of omental and subcutaneous adipose tissue obtained by biopsy during elective abdominal

Table 4. Predictors of Elevated Plasma TG Levels by Stepwise Multiple Regression Analysis

Step	Parameter	Slope	SE Slope	β	SE (β)	*t*	*P*	R^2
Males (n = 44)								
1	120-min NEFA	947.1	238.0	0.82	.20	3.98	.0003	.55
2	120-min insulin	0.30	0.11	0.32	.12	2.64	.012	.64
3	% change NEFA	−153.6	71.6	−0.43	.20	2.15	.038	.69
Females (n = 46)								
1	0-min insulin	1.76	0.7	0.36	.14	2.51	.016	.36

NOTE. Dependent variable was plasma TG; independent variables were age, BMI, % body fat, 0- and 120-min NEFA and insulin concentrations, and % change in NEFA.

surgery, that omental adipocytes were significantly more resistant to insulin's antilipolytic effects than abdominal subcutaneous adipocytes. In our study, obese and severely obese women versus non-obese women had significantly higher central fat indices (Table 1). However, women in all three groups were equally sensitive to insulin-mediated suppression of NEFA. This maintenance of sensitivity to insulin could be because central fat in AA women appears to be predominantly distributed subcutaneously rather than intraabdominally.[18]

In contrast to our findings, obese AA women in large epidemiological studies such as the ARIC and CARDIA Studies have higher fasting TG levels than non-obese AA women.[5,21] In a combined analysis of AA and Caucasian women in the CARDIA Study, a positive association was seen between fasting TG and percent body fat.[21] However, there was no analysis or discussion of differences between AAs and Caucasians, men or women. A subsequent combined analysis of the CARDIA and ARIC data showed that AA women with a higher BMI had higher fasting TG concentrations. However, in that analysis diabetics were not excluded.[5] The association between diabetes, obesity, and elevated fasting TG is well established[3] and could have altered the relationship between fasting TG and obesity in AA women. Diabetics were excluded from the present study. Alternatively, it is also possible that we did not find an association between obesity and fasting plasma TG levels because our sample size was much smaller.

We examined sex differences during the OGTT for insulin's action as a glucoregulatory hormone. Men compared with women had higher plasma glucose concentrations at each time point except 120 minutes. In terms of insulin concentration, there were no sex differences for the area under the insulin curve. There were also no sex differences for insulin's action as a glucoregulatory hormone, because the insulin to glucose ratio at each time point and the area under the insulin to glucose ratio curve were statistically similar (Table 2). Therefore, sex differences in insulin's action as a glucoregulatory hormone do not explain sex differences in insulin-mediated suppression of NEFA or fasting TG levels.

Insulin promotes the deposition and simultaneously inhibits the mobilization of fat. The normal plasma TG levels in obese and severely obese AA women may be secondary to the low release of NEFA from adipose tissue into the circulation. Therefore, the necessary substrate for hepatic synthesis of VLDL-TG is only available in low concentration. In obese and severely obese AA men, the resistance to insulin-mediated NEFA suppression may allow greater liberation of NEFA from adipose tissue, greater uptake by the liver, and greater hepatic synthesis and secretion of VLDL-TG. Obesity is a risk factor for hypertriglyceridemia and heart disease in Caucasian women.[3] Our findings suggest that obesity may not be a risk factor for hypertriglyceridemia in AA women.

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