Effect of a Controlled High-Fat Versus Low-Fat Diet on Insulin Sensitivity and Leptin Levels in African-American and Caucasian Women

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African-American women have been shown to be more insulin-resistant than age- and weight-matched Caucasian women, but the reasons for this difference are unclear. The purpose of the present study was to determine whether experimental manipulation of dietary fat intake has differential effects by race on insulin sensitivity (S_I) in 20 African-American and 11 Caucasian women. Additionally, leptin levels before and after 3 weeks of an isocaloric high-fat ([HF] 50% fat, 35% carbohydrate, and 15% protein) or low-fat ([LF] 20% fat, 55% carbohydrate, and 15% protein) diet were compared. African-American and Caucasian women did not differ significantly in the body mass index (BMI) or percentage body fat at baseline. S_I (adjusted for BMI) decreased on the HF diet and increased on the LF diet in both races combined relative to the baseline control (control, 2.42 ± 0.22; HF, 2.29 ± 0.22; LF, 2.75 ± 0.21 × 10^{-4} $min^{-1}/\mu U \cdot mL$; main effect of diet, $P = .04$). There was a 6% decrease in S_I on the HF diet compared with the control in women of both races, while the LF diet increased S_I by 6% in African-American and 20% in Caucasian women. Leptin levels increased by 14% on the HF versus control diet in African-Americans (35.2 ± 3.0 *v* 30.8 ± 3.0 ng/mL, $P < .01$), but did not change with diet in Caucasian women. Glucose and insulin administration had no effect on leptin levels. We conclude that a HF diet consumed over several weeks reduces S_I in healthy women of both races; however, the magnitude of increase in S_I on a LF diet is greater in Caucasian women. The HF diet significantly increased leptin levels in African-American women, although there were no other influences of diet, insulin, or race on serum leptin.

A NUMBER OF STUDIES have shown a relationship between dietary fat intake and insulin resistance. In animal models, high-fat (HF) feeding produces both whole-body and tissue insulin resistance.[1,2] Similarly, in most (although not all) human studies, HF diets produce whole-body insulin resistance even in the absence of significant changes in body weight or composition.[3-5]

Several studies have observed differences in insulin resistance between African-American and Caucasian women that are independent of obesity or a family history of diabetes.[6,7] The decreased insulin sensitivity (S_I) in African-American women may explain, in part, their high rate of type II diabetes, which is twice that of Caucasian women by middle age.[8] The cause of race differences in S_I is unclear, but is likely a combination of genetic and environmental factors. Since diet affects S_I, it is possible that differences in habitual dietary intake or in the metabolic response to dietary macronutrients may partly mediate race differences in S_I. Recently, Mayer-Davis et al[9] reported that S_I correlated with total dietary fat intake in African-Americans, Hispanics, and non-Hispanic whites participating in the Insulin Resistance Atherosclerosis Study. To our knowledge, no study has specifically compared the metabolic response to controlled diets in African-American versus Caucasian individuals.

The purpose of the present study was to determine the effect of controlled HF versus low-fat (LF) diets on S_I in African-American and Caucasian women. We hypothesized that a HF diet would reduce S_I, with a more pronounced reduction in African-American women. We additionally studied the effect of diet on serum leptin, and related leptin to the regional fat distribution and aspects of the insulin resistance syndrome.

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SUBJECTS AND METHODS

Subjects

Twenty African-American and 11 Caucasian premenopausal women were studied. The ethnicity of all four grandparents was confirmed for each subject. The subjects were nonsmokers on no medication (including birth control pills), and in general good health. African-American and Caucasian women were matched for degree of obesity (by body mass index [BMI]) across a range of body weight. We also sought to include women whose S_I from the minimal model was in a moderate range (1.0 to 5.0 × 10^{-4} $min^{-1}/\mu U \cdot mL$). All women had a fasting glucose level less than 110 mg/dL (6.1 mmol/L). Participants provided written informed consent, and the study was approved by the Louisiana State University Institutional Review Board.

S_I Measurement

After 5 to 7 days of the control diet and at the end of 3 weeks of each experimental diet, a frequently sampled intravenous glucose tolerance test (FSIGT) was performed after an overnight fast.[10] Strenuous exercise was prohibited for 48 hours before the test. Following baseline blood sampling, glucose 300 mg/kg (50% dextrose; Abbott Laboratories, North Chicago, IL) was injected, followed by collection of blood samples (4 mL) at 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 minutes. At 20 minutes, an injection of insulin (Humulin 0.03 U/kg; Eli Lilly, Indianapolis, IN) was administered, and sampling continued at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes. Each blood sample was analyzed for glucose and insulin, and the data were used to calculate S_I and glucose effectiveness (S_G) using the minimal model method of Bergman et al.[11] Additionally, the serum leptin level was measured at baseline and 16 and 40 minutes postglucose to determine the effects of glucose and insulin administration on circulating leptin.

Anthropometrics and Body Composition

At screening, height and weight were measured and body composition was determined by dual-energy x-ray absorptiometry (QDR2000; Hologic, Waltham, MA). The minimum waist and maximum hip

circumferences were used to compute the waist to hip ratio. Visceral and subcutaneous abdominal fat areas were obtained from an abdominal computed tomography (CT) scan at the level of the L4-L5 intervertebral space (High-Speed Advantage; General Electric, Milwaukee, WI). Calculation of intraabdominal fat areas from the 1-cm scans was accomplished using software on the CT scanner with a range of −190 to −30 HU. CT scans were only available on 16 African-American and 10 Caucasian women.

Diets

A crossover design was used with diet order randomly assigned. A control "standard American" diet (37% fat, 43% carbohydrate, and 15% protein) was consumed for 1 week before beginning each experimental diet. Initial measurement of S_I ("baseline") was performed at the end of this control diet for the first diet period only. Subjects were assigned to receive either a HF (50% fat, 35% carbohydrate, and 15% protein) or LF (20% fat, 55% carbohydrate, and 15% protein) diet for 3 weeks in random order following 1 week of the control diet. After a 1-month washout period on their habitual diet, participants returned for the second diet period.

All meals were prepared by the Pennington Metabolic Kitchen. Participants were required to consume breakfast and dinner at the Center Monday through Friday, with lunches and weekend meals packed for take-out. Any foods not consumed were weighed. Compliance was assessed daily using a standardized form on which the women recorded any foods not eaten or additional foods consumed. In general, compliance was high and similar between African-Americans and Caucasians (90% *v* 82%, respectively).

The energy content of the diet was individualized for each person with the goal of maintaining body weight throughout the study. Energy requirements were determined based on the resting metabolic rate as measured by indirect calorimetry (2900Z portable metabolic cart; Sensormedics, Yorba Linda, CA) multiplied by a physical activity factor of 1.4. If weight fluctuated by more than 1 kg from week to week, the energy content of the diet was adjusted to return the weight to baseline. Within a given diet period, the mean weight change was 0.08 ± 0.16 kg (maximum change, ±1 kg). The mean weight at the time S_I was measured was 84.0 ± 3.3 kg (baseline), 83.4 ± 3.2 kg (LF), and 84.1 ± 3.4 kg (HF).

The ratio of monounsaturated/polyunsaturated/saturated fat on the control diet was 14:8:15. On the HF diet, this ratio was 18:10:19, and on the LF diet 8:4:7. The ratio of simple to complex carbohydrate was not matched between the diets; simple carbohydrate comprised a greater percentage of total carbohydrate in the LF (59%) versus HF (39%) diet. The macronutrient composition of the study diets, which were designed using Moore's Extended Nutrient Database (MENu), was subsequently confirmed in a food analysis laboratory.

Habitual Dietary Intake

Dietary intake over the past year was estimated using a previously validated food frequency questionnaire.[12] Data on the total energy intake and percentage of energy consumed as fat were analyzed for the present study.

Laboratory Tests

Insulin was analyzed on an automated IMx instrument (Abbott Laboratories, Abbott Park, IL). Glucose (glucose oxidase method) was analyzed on a Synchron CX7 (Beckman, Brea, CA). Serum leptin was determined using a commercially available and previously validated radioimmunoassay[13] kindly provided by Linco Research (St Louis, MO). All samples for leptin were analyzed in a single assay with an intraassay coefficient of variation of 7.8%. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using an autoanalyzer (Synchron CX5; Beckman). The dextran sulfate precipitation method was used for HDL measurement. Low-density lipoprotein was calculated using the Friedewald equation, assuming triglycerides within normal limits.

Statistical Analysis

Comparisons between groups were performed using an unpaired Student's *t* test. The effects of diet on S_I and S_G were assessed using a two-factor repeated-measures ANOVA based on the maximum-likelihood method with diet and race as factors. Comparisons of the effects of dietary treatment and time point during the FSIGT on leptin were performed using a three-factor repeated-measures ANOVA with diet, race, and time as factors. Post hoc multiple comparison testing was performed using a Tukey adjustment. Simple and multiple linear regression were used to assess the relationships between leptin and metabolic risk factors. Since serum leptin was not normally distributed, Spearman nonparametric correlation coefficients were used. An alpha level less than .05 was considered significant.

RESULTS

Characteristics of the subjects are shown in Table 1. There was no difference at baseline between African-American and Caucasian subjects for the BMI (which was matched in recruiting), percentage body fat, or waist to hip ratio. As previously reported,[6] the abdominal visceral fat area tended to be smaller in African-American women; however, the differences were not significant. There were also no significant differences in S_I, S_G, fasting insulin, or fasting glucose, presumably because the subjects were preselected to avoid extremely high or low S_I values. Fasting leptin tended to be higher in African-American women, but this difference was not statistically significant. At baseline, the dietary intake of total energy and percentage of energy from fat were not different between the two groups based on the food frequency questionnaire.

The effects of the dietary interventions on S_I and S_G are shown in Fig 1. There was a significant main effect of diet on S_I ($P = .04$), which decreased on the HF diet ($2.29 \pm 0.22 \times 10^{-4}$

Table 1. Baseline Characteristics (mean ± SD) of 20 African-American and 11 Caucasian Women Participating in the Dietary Study

Variable	African-American	Caucasian
Age (yr)	36.6 ± 1.4	34.4 ± 1.8
BMI (kg/m²)	31.9 ± 1.6	30.2 ± 1.0
Percent body fat	42.0 ± 1.3	44.2 ± 1.9
Waist to hip ratio	0.80 ± 0.01	0.79 ± 0.01
Visceral fat area (cm²)*	97.5 ± 10.1	100.9 ± 12.3
Subcutaneous fat area (cm²)*	433.4 ± 45.6	415.4 ± 33.1
S_I (10^{-4} $min^{-1}/\mu U \cdot mL$)	2.26 ± 0.35	2.67 ± 0.30
S_G ($min^{-1} \times 100$)	2.55 ± 0.22	2.57 ± 0.16
Fasting glucose (mmol/L)	5.2 ± 0.2	5.2 ± 0.1
Fasting insulin (pmol/L)	52.2 ± 8.4	40.8 ± 7.2
Fasting leptin (ng/mL)	34.9 ± 5.4	25.5 ± 3.9
Energy intake		
MJ/d	8.7 ± 0.9	7.4 ± 0.5
kcal/d	2,082 ± 216	1,762 ± 119
Percent of energy intake as fat	38.6 ± 2.3	38.4 ± 2.2

NOTE. Data are the mean ± SEM. None of the differences are statistically significant by Student's *t* test ($P > .05$).

*Abdominal fat area from CT scan was only available for 16 African-American and 10 Caucasian women.

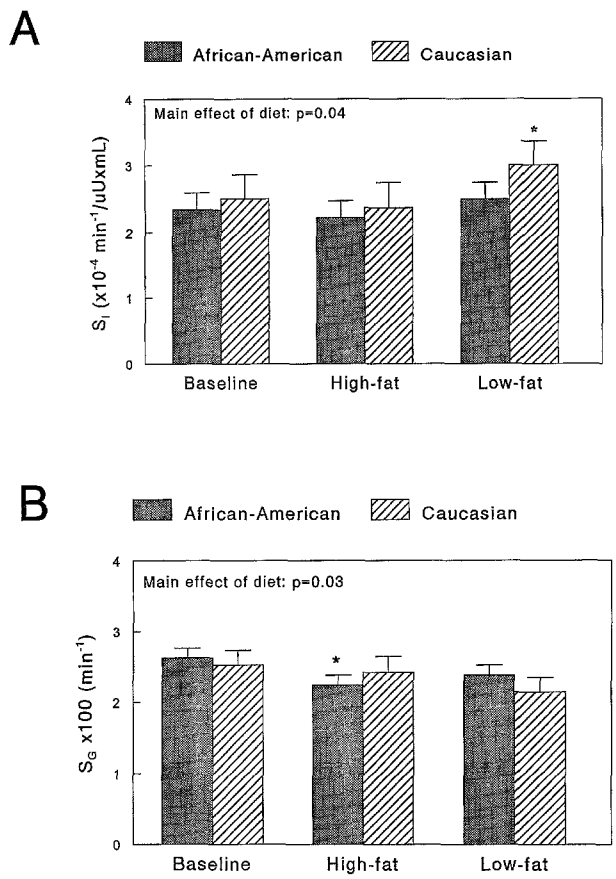

Fig 1. (A) Effect of diet on S_I in 20 African-American and 12 Caucasian women. *High-fat *v* low-fat diet significantly different in Caucasians (P = .04). (B) Effect of diet on S_G. *High-fat *v* baseline diet significantly different in African-Americans (P = .007).

$min^{-1}/\mu U \cdot mL$) and increased on the LF diet ($2.75 \pm 0.21 \times 10^{-4}$ $min^{-1}/\mu U \cdot mL$) across women of both races relative to the baseline control ($2.42 \pm 0.22 \times 10^{-4}$ $min^{-1}/\mu U \cdot mL$). Expressed as the percentage change, S_I decreased by 6% in both African-American and Caucasian women on the HF diet, but increased by 6% in African-Americans versus 20% in Caucasians on the LF diet (not statistically significant). In post hoc multiple-comparison analysis, the difference between the LF and control diet was significant in Caucasian women (P = .04) but not in African-American women. When both races were combined, the LF diet was significantly different from both the control and HF diets.

S_G decreased slightly on both experimental diets compared with the control diet (main effect of diet, P = .03), a difference that was significant in African-American women for the HF versus control diet (P = .007; Fig 1B).

There was a significant increase in serum leptin on the HF diet in African-American women, but otherwise, leptin was not altered by diet treatment (Table 2). Serum leptin levels were stable following glucose and insulin injection during the FSIGT.

Spearman nonparametric correlation coefficients were used to assess relationships between fasting leptin and anthropometric and metabolic variables in 28 women for whom complete leptin data were available. As expected,[14] leptin was positively correlated with both the BMI (r = .69, P = .0001) and percent fat (r = .80, P = .0001). Leptin was also positively correlated with both the visceral (r = .54, P = .007) and subcutaneous (r = .69, P = .0002) fat area by CT scan. Leptin was negatively correlated with S_I (r = −.42, P = .03) and S_G (r = −.49, P = .008) and positively correlated with fasting insulin (r = .45, P = .04). Leptin was not significantly correlated with fasting glucose, blood pressure, or serum lipids, and African-American and Caucasian women had similar correlation values (data not shown). Stepwise multiple regression indicated that the largest variance in leptin (72%) was explained by a model including both the BMI and percent fat. In separate models, the BMI explained more of the leptin variance than percent body fat (64% *v* 48%, respectively). S_I was not independently predictive of leptin when the BMI or percent fat were also included in the model.

DISCUSSION

The reasons for diminished insulin sensitivity in African-American compared with Caucasian women are unclear. The present study tested the hypothesis that the metabolic effects of high dietary fat intake are more deleterious in African-American versus Caucasian women. Our data showed that increased dietary fat reduces insulin sensitivity to a similar degree in women of both races. This suggests that if dietary fat plays a role in race differences in insulin sensitivity, it is more likely due to a difference in the absolute level of dietary fat intake rather than a difference in the metabolic response to dietary fat. It is important to note that the changes in insulin sensitivity in response to diet were independent of weight and presumably body composition changes.

Several studies have suggested that fat intake is higher among both African-American children and adults,[15,16] although this has not been confirmed by other studies.[17] It is known that a low socioeconomic status is associated with a greater intake of dietary fat,[18] and in the US population in general, minorities are disproportionately represented in the poorer classes. Although we did not collect specific data on income from our subjects, the majority were either employed or full-time students, and most of them would be considered middle class. Data on habitual food intake from the food frequency questionnaire in the present study did not show any significant differences for either

Table 2. Leptin Levels (ng/mL) Following HF or LF Diet and Glucose and/or Insulin Injection During the FSIGT

Parameter	African-American	Caucasian
Diet (fasting level)		
Control	30.8 ± 3.0	32.3 ± 4.3
HF	35.2 ± 3.0*	33.0 ± 4.1
LF	32.8 ± 3.0	30.1 ± 4.1
FSIGT (on control diet)		
Fasting	31.4 ± 3.3	31.9 ± 4.9
Postglucose only	30.0 ± 3.3	32.1 ± 4.9
Postglucose and insulin	31.1 ± 3.3	33.0 ± 4.9

NOTE. Data are the mean ± SEM adjusted for BMI.

*Significantly different from control diet in African-American women (P < .01).

total energy intake or percentage of energy from fat between African-American and Caucasian women. However, this study with a relatively small number of subjects was not powered to detect race differences in self-reported dietary intake.

It is interesting that although there were no race differences in the response of S_I to the HF diet, Caucasian women tended to have a greater increase in S_I in response to the LF diet than African-American women. Overall, the changes in S_I were small (Fig 1), and thus, although the effects of diet were statistically significant, the issue of whether they were biologically meaningful must be considered. The percent changes in S_I are comparable to those previously reported with dietary interventions.[3] However, as reviewed by Finegood,[19] even the 20% increase in S_I in Caucasian women on the LF diet is less than the percent change observed with athletic training or in pathological states such as obesity and diabetes, which typically cause a 50% or greater change in S_I. Although it is difficult to assess the predictive value of changes in S_I in terms of diabetes risk independent of changes in insulin secretion, the longitudinal population data from Martin et al[20] showed that a decrease in S_I of 1 to 1.5 units was associated with a 10% to 20% increased incidence of subsequent diabetes. Thus, even relatively small absolute changes in S_I may have clinically significant consequences.

Although the present study was not designed to assess the mechanisms by which dietary fat alters whole-body insulin sensitivity, other investigators have addressed this question. Several decades ago, Randle et al[21] proposed that elevated fatty acids may play a causal role in the development of insulin resistance by competing with glucose for oxidation. Competition and subsequent deterioration of the body's ability to dispose of glucose occurs when either circulating[22] or intramuscular[23] triglycerides are elevated, either of which could occur with habitual consumption of HF diets. Oakes et al[24] recently reported that elevated local lipid oxidation (assessed by muscle long-chain fatty-acyl coenzyme A) accounts almost totally for the impairment in insulin-stimulated oxidative glucose metabolism in muscle and the increased gluconeogenesis in liver in HF-fed rats. Nevertheless, there are still a number of unresolved questions regarding the mechanisms of dietary fat–induced insulin resistance.

Glucose effectiveness has also been shown to be an important predictor of glucose tolerance,[20,25] and one study suggested that S_G decreased with high dietary fat intake.[26] The present results confirm a main effect of diet on S_G, although the change was in the same direction with both HF and LF diets compared with the control. The reasons for this finding are unclear, but do not support a consistent effect of diet on S_G.

Studies in rats have suggested that a HF diet increases expression of the *ob* gene within 2 weeks.[27] Our results show that following 3 weeks of a HF or LF diet (a length of time sufficient to change insulin sensitivity), serum leptin was not substantially altered. However, it is interesting that African-American women had a 14% increase in serum leptin on the HF diet compared with the control diet (in the absence of weight changes). This increase in leptin may have biological significance, and larger populations consuming controlled diets need to be studied to determine whether our effect of diet in African-Americans can be replicated.

Leptin levels in humans have been shown to be independently associated with insulin resistance in some studies[28] but not others.[29] The present data do not confirm an effect of insulin sensitivity independent of the BMI or percentage body fat, suggesting that obesity per se is the primary factor in the constellation of metabolic factors. It is likely that the difference between studies regarding the lack of an independent effect of S_I on leptin is methodological, depending on whether a study is cross-sectional or specifically recruits individuals matched for percentage body fat.[28] The present data also confirm other studies demonstrating that acute insulin administration does not alter leptin levels in humans.[28,30]

In summary, the present data show that 3 weeks of dietary intervention has a significant effect on S_I, with a HF diet decreasing and a LF diet increasing S_I. Decreases in S_I in response to the HF diet were similar in African-American and Caucasian women. However, the LF diet improved S_I to a greater extent in Caucasian women (20% *v* 6% above control). Furthermore, our results showed that HF feeding increases serum leptin levels significantly in African-Americans but not Caucasians, a finding that requires further study.

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