Rapid Publications

Leptin: A Significant Indicator of Total Body Fat but Not of Visceral Fat and Insulin Insensitivity in African-American Women

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The recently cloned adipose tissue hormone leptin has been proposed to be involved in the neuroendocrine regulation of adiposity and its metabolic sequelae. Visceral fat is known to predict reduced insulin sensitivity and associated adverse metabolic profiles. In this study, we report the first evaluation of the relationships between leptin levels and total body fat, visceral fat, and insulin sensitivity in a cohort of premenopausal African-American women. Thirty-four subjects were analyzed for total fat mass and visceral fat by dual-energy X-ray absorptiometry and computerized axial tomography, respectively. Insulin sensitivity (S_I) was assessed using Bergman's minimal model. Results showed that fasting leptin levels strongly correlated with total body fat mass ($r = 0.797$, $P < 0.001$). Correlations of leptin with visceral fat ($r = 0.54$, $P < 0.001$) and S_I ($r = -0.419$, $P = 0.02$) were dependent on total body fat. In conclusion, leptin levels reflect total body fat mass, and although visceral fat is known to predict reduced insulin sensitivity independently, leptin did not. Our data thus suggest that diverse mechanisms are responsible for the regulation of total body versus visceral fat distribution, with its metabolic and health risks. *Diabetes* 45:1635–1637, 1996

In Caucasian women, abdominal body fat localization is a predictor of a cluster of adverse metabolic profiles, including glucose intolerance, dyslipidemias, hypertension, and their cardiovascular risks (1–3). This relationship is independent of and additive to that due to degree of overweight and is mediated by a close link with visceral fat. The mechanisms underlying the adverse metabolic profiles are dependent on the close association of visceral fat with insulin resistance and adaptive hyperinsulinemia (4,5).

African-American women have the highest incidence of obesity and obesity-related morbidities, including NIDDM (6). As in Caucasians, body fat distribution appears to predict the frequencies of these morbidities (7–10). Our preliminary data in African-American women indicate a close link between visceral fat and adverse metabolic profiles (A.D., M.I.H., and A.H.K., unpublished observations).

Recent studies have identified the soluble factor leptin (the *ob* gene product), which is synthesized and secreted by adipose tissue and which is claimed to signal satiety and its associated hormonal adjustments, including insulin secretion (11). The present study was undertaken in a cohort of healthy premenopausal African-American women in whom total body and visceral fat were determined, along with insulin sensitivity. The aim was to evaluate the relationship of these measurements to plasma leptin levels and consequently address the potential prediction of obesity-related risks in this ethnic group.

RESEARCH DESIGN AND METHODS

Subjects. We recruited 34 healthy African-American women, selected to be premenopausal, 20–45 years of age, and to have a wide range of BMIs (kg/m^2) and waist-to-hip ratios (WHRs). Laboratory studies were performed to confirm normal kidney, liver, and thyroid function. An oral glucose tolerance test was also done to exclude diabetes. All subjects had maintained stable body weight for at least 2 months before testing and were not on any medications. Subjects were stabilized on an isocaloric diet consisting of 50% carbohydrate, 30% fat, and 20% protein, with 300 mg/day cholesterol. Metabolic studies were performed during the first 10 days after menstruation. Studies were performed at the General Clinical Research Center. Study participants signed a written consent approved by the Human Research Review Committee of the Medical College of Wisconsin.

Procedures

Anthropometric measurements. Measurements of BMI and WHR were performed by a single investigator. Fat distribution within the abdomen (visceral fat) was determined by computerized tomography (CT). Three contiguous slices were measured, with the center slice at the midplane of the fourth lumbar vertebra. The mean of three readings was used for analysis (12). Total body fat mass was determined by dual-energy X-ray absorptiometry (DEXA) (13). Whole-body scans were taken from a Norland scanner with the patient in a supine position.

Insulin sensitivity. The insulin-modified intravenous glucose tolerance test (minimal model) was used to assess insulin sensitivity (14). After a 12-h overnight fast, cannulae were placed in both antecubital veins. A bolus of 50% glucose solution (0.3 g/kg) was injected at time 0, and a bolus (0.05 U/kg) of regular human insulin (Eli Lilly, Indianapolis, IN) was given at 20

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Received for publication 3 July 1996 and accepted in revised form 21 August 1996.

CT, computerized tomography; CV, coefficient of variation; DEXA, dual-energy X-ray absorptiometry; S_I, insulin sensitivity index; WHR, waist-to-hip ratio.

TABLE 1
Subject characteristics

	Mean ± SE	Range
Age (years)	33.2 ± 5.8	22–46
Weight (kg)	81.3 ± 21.2	51.1–124.3
BMI (kg/m^2)	30.2 ± 7.5	17.4–41.8
WHR	0.82 ± 0.05	0.72–0.95
Fasting plasma glucose (mmol/l)	5.16 ± 0.49	4.1–6.7
Fasting insulin (pmol/l)	104.4 ± 136.2	25.8–854.4

TABLE 2
Relationship of anthropometric variables to S_I in African-American women

Measurement	r value
BMI	0.57*
WHR	0.57*
Total fat mass (DEXA)	0.59*
Visceral fat volume (CT)	0.68*

*$P < 0.01$.

min. Blood samples were taken at the following times: –15, –5, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 24, 30, 40, 50, 70, 100, 120, and 180 min; and they were analyzed for glucose and insulin.

Plasma leptin levels. After an overnight fast, blood samples were drawn at –30, –15, and 0 min for leptin. Blood samples were spun and stored at –70°C before leptin assay.

Analytical procedures. Plasma glucose was measured by the glucose oxidase method with a Beckman analyzer (Brea, CA). Plasma insulin and leptin concentrations were measured in triplicate using solid-phase ^{125}I-radioimmunoassays (Linco Research, St. Charles, MO), and samples for quality control were included in each assay. The commercial leptin assay has recently been detailed (15). At low serum leptin concentrations (4.9 µg/l), our intra- and interassay coefficients of variation (CVs) were 6.2 and 13.8%, respectively, while at higher leptin concentrations (25.6 µg/l), the intra- and interassay CVs were 5.5 and 8.8%, respectively. Insulin sensitivity index (S_I) was determined using the MINMOD computer program of R. Bergman, version 3.0 (16).

Statistical analyses. Simple linear correlations and Pearson's partial correlations were performed using the Stata program, Windows version 4.0 for IBM.

RESULTS

Thirty-four female African-American subjects were studied. Their characteristics are shown in Table 1. Their BMIs ranged from 22 to 46 kg/m^2 and WHRs from 0.72 to 0.95. Fasting plasma glucose and insulin levels ranged from 4.1 to 6.7 mmol/l and 25.8 to 854.4 pmol/l, respectively.

Table 2 shows the relationship between the anthropometric measurements and the insulin sensitivity index (S_I). In this cohort, S_I varied between 1.2 and 38.4 x 10^{-4} min^{-1} per pmol/l. Both BMI and WHR were significantly correlated with S_I and remained so when corrected for each other ($r = 0.515$, $P < 0.01$, and $r = 0.48$, $P < 0.01$, respectively). The DEXA-measured total fat mass and the CT-measured visceral fat volume were also significantly correlated with S_I. The correlation between S_I and visceral fat also remained significant when adjusted for total body fat mass ($r = 0.44$, $P < 0.05$).

Table 3 shows the relationship of total body and visceral fat mass to plasma leptin levels. In this cohort, fasting plasma leptin levels ranged from 1.4 to 57.1 ng/ml and were significantly correlated with BMI ($r = 0.719$, $P < 0.001$). The DEXA-determined total body fat mass, however, was a stronger correlate of the plasma leptin level ($r = 0.797$, $P < 0.001$; Fig. 1*A*). When the relationship between total fat mass and leptin was corrected for BMI, it remained significant ($r = 0.471$, $P = 0.01$). The total fat mass thus appears to explain the relationship between BMI and leptin, but BMI only explains part of the relationship between whole body fat mass and leptin.

The CT-determined visceral fat (visceral fat) volume was also correlated with plasma leptin levels ($r = 0.542$, $P < 0.001$; Fig. 1*B*). Furthermore, S_I was also significantly correlated with plasma leptin levels ($r = –0.419$, $P < 0.05$; Table 3). When adjusted for influences of total body fat mass, the relationships between leptin levels and either visceral fat or S_I were no longer discernible.

DISCUSSION

Our study shows that in African-Americans, as in Caucasians, fasting plasma leptin levels are correlated with BMI (17). More importantly, leptin levels are strongly correlated with the more precise measurements of total body fat mass. The close association between body fat mass and leptin levels indicates the latter's relationship to energy balance and is in accordance with its proposed role as a satiety factor (11,17). The mechanism responsible for regulation of energy balance and satiety thus appears to involve similar pathways in both African-Americans and Caucasians. Furthermore, our results show that obesity in African-Americans, as in the majority of Caucasians, is accompanied by leptin resistance rather than leptin deficiency (18).

Our study showed that, as in Caucasians, visceral fat is a strong predictor of insulin resistance, the hallmark of the adverse metabolic profile in abdominal obesity (4). The poorer correlation between body fat distribution and the metabolic profile that has been observed in previous studies (19) might thus be due to less precise measurements rather than to racial and/or genetic effects. Details of this part of our study and their implications will be addressed elsewhere.

Leptin levels predict neither size of visceral fat nor insulin sensitivity in African-American women. This suggests that in contrast to total body fatness, visceral fat and body fat distribution are probably determined via different mechanisms that do not involve the leptin pathways. Insulin sensitivity, the functional defect linked to visceral fat and its associated adverse metabolic complications, is also independent of the leptin levels.

TABLE 3
The relationship of leptin levels to anthropometric or metabolic variables in African-American women

	Unadjusted r	r adjusted for total fat mass
Total fat mass	0.797*	
Visceral fat volume	0.542*	0.03
S_I	–0.419†	0.04

*$P < 0.001$, †$P < 0.05$.

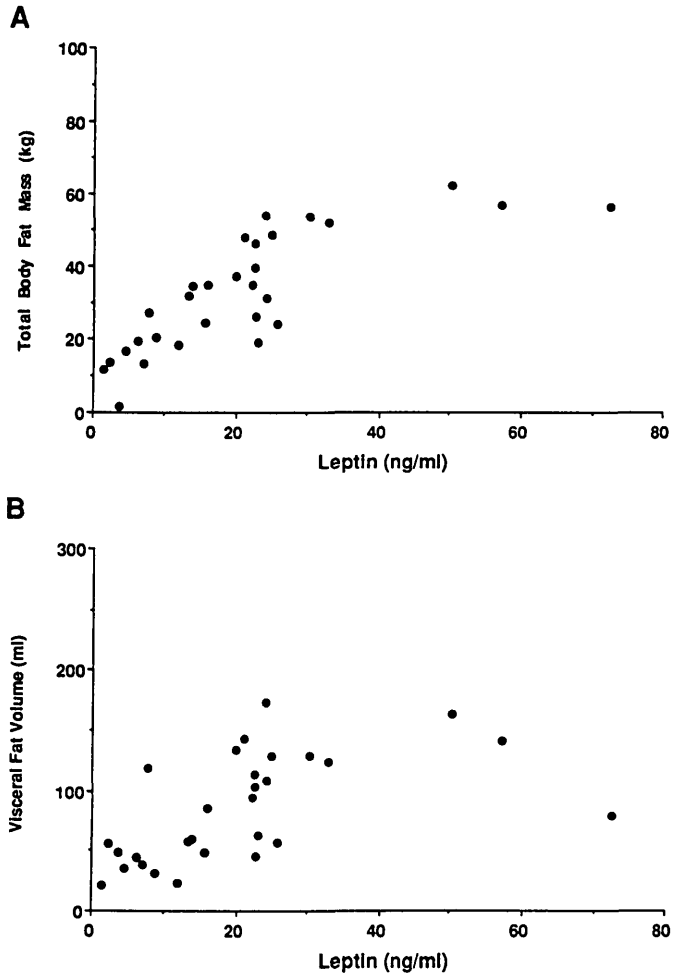

FIG. 1. *A:* **correlation between leptin levels and total body fat. Total body fat, assessed in 34 African-American women by DEXA as described in METHODS, was correlated with fasting plasma leptin levels ($r = 0.797$, $P < 0.001$).** *B:* **correlation between leptin levels and visceral fat. Visceral fat, assessed in 30 African-American women by CT as described in METHODS, was correlated with fasting plasma leptin levels ($r = 0.542$, $P < 0.001$).**

Visceral fat is the most metabolically active adipose tissue depot. Its enhanced lipolysis and consequent high–free fatty acid flux are closely linked to the mechanisms underlying the adverse metabolic profile, including insulin resistance, glucose intolerance, reduced hepatic insulin extraction, dyslipidemia, and possibly hypertension (20).

In conclusion, our study suggests that diverse mechanisms may be responsible for the regulation of obesity levels and body fat distribution, along with their associated metabolic and health risks. Defining those mechanisms should help research aimed at unraveling the genetics and biology of the obesity phenotypes.

ACKNOWLEDGMENTS

These studies were supported by National Institutes of Health grant HL-34989 and General Clinical Research Center grant RR-00058.

We express our gratitude to Jackie Marks and Don Martinson for their assistance in performing the leptin assays. We also wish to thank Keryl Jones for her assistance in recruiting and in helping to perform the clinical studies, and we thank David Nevin, MD, for his helpful suggestions in preparing the manuscript.

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