Leptin concentration in women is influenced by regional
distribution of adipose tissue\textsuperscript{1-3}

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ABSTRACT Leptin concentrations in humans are increased
with obesity, and women have higher leptin concentrations than
men. This sex difference reflects the greater fat mass of women.
However, there is evidence that factors other than the size of the
adipose tissue mass contribute to serum leptin concentrations. This
study was undertaken to determine whether anthropometric factors
influenced leptin concentrations in our population. Leptin concen-
trations were measured in 375 persons from a population study
of hypertension and diabetes for whom body-composition data
(bi-
electrical impedance analysis and anthropometry) were available.
Serum leptin concentrations were more than four times higher
in women than in men (18.5 ± 13.9 compared with 3.8 ± 3.6 ng/L,
\(P < 0.0001\)). In individuals with comparable body mass indexes,
these differences persisted after adjustment for either percentage
fat (\(P < 0.05\)) or fat mass (\(P < 0.0001\)) by multivariate-regression
analysis. After fat mass was adjusted for, the serum leptin con-
centration in both men and women was independent of waist
circumference but in women was associated with hip circumference.
Hip circumference is a proxy measure of peripheral fat and
these results suggest that the larger hips of women may contribute
to the sex difference in serum leptin concentration. \textit{Am J Clin

KEY WORDS Leptin, obesity, sex, hip circumference,
body composition

INTRODUCTION

Leptin, the protein product of the \textit{ob} gene (1), is produced
only in adipose tissue (2, 3). In rodents, leptin administration
reduces body weight and adipose tissue mass (4, 5). Receptors
for leptin are present in brain (6, 7) and it has been suggested
that leptin acts as the afferent arm of a feedback loop that
regulates energy stores via receptors in the hypothalamus (8,
9). In obese humans, \textit{OB} mRNA expression in fat cells (3, 10)
and serum leptin concentrations are elevated (11, 12). This
elevation in leptin is associated with increased body mass index
(BMI), fat mass, and percentage body fat (10–12). The high
circulating leptin concentration in obese persons is thought to
indicate leptin resistance (9, 11, 13) and to result in part from
reduced transport of leptin into cerebrospinal fluid (13).

The decrease in serum leptin concentration and expression of
\textit{ob} mRNA with fasting in both mice and humans (11, 12, 14)
is evidence that leptin has a physiologic role in the regulation
of body weight. However, there is great interindividual varia-
tion in leptin concentration for a given BMI (11). Some obese
patients have concentrations similar to those of lean individu-
als, and in obese patients who have lost weight, there are large
fluctuations in serum leptin concentrations with relatively
small changes in body weight (11, 12). These findings suggest
that leptin secretion is influenced by other factors in addition to
the size of the adipose tissue mass. This study was undertaken
to determine how leptin concentrations varied with body
weight and anthropometric estimates of body composition in
a representative population.

SUBJECTS AND METHODS

Subjects

Subjects were recruited as part of a survey being carried out
in Spanish Town, Jamaica, to determine the prevalence of
hypertension and diabetes mellitus in a population of predom-
inantly African origin. This community was identified by the
Statistical Institute of Jamaica as being representative of the
country’s population demographics. The sampling method was
single-stage cluster sampling by probability proportionate to
size. This was facilitated by a predetermined sampling interval
aimed at obtaining a sample of 1600 persons in eight age and
sex categories: men and women aged 25–34, 35–44, 45–54, and
55 y. Clusters were defined by census districts provided by
the Statistical Institute of Jamaica and trained staff can-
vassed each cluster door-to-door. The number of eligible par-
ticipants who were contacted in person was used as the de-
nominator to determine the rate of participation, which was
60%. Households were visited repeatedly to improve partici-
pation rates.

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Anthropometry

Subjects visited a clinic where their height, weight, and waist and hip circumferences were measured. Body weight was measured to the nearest 0.1 kg with lightweight, portable electronic scales. Standing height without shoes was measured with a stadiometer and was recorded to the nearest 0.1 cm. Waist circumference at the narrowest part of the torso as seen from the front and hip circumference at the point of maximum extension of the buttocks were measured twice, to the nearest 0.1 cm. BMI was computed as weight in kilograms divided by height in meters squared (kg/m²).

Impedance in body tissues to the flow of an applied alternating current was estimated by bioelectrical impedance analysis (BIA) and the values obtained used to estimate body composition. All BIA measurements were performed by using a single-frequency (50 kHz), battery-operated, bioimpedance analyzer (model BIA 101Q; RJL Systems, Clinton Township, MI). A tetrapolar placement of electrodes was used (15) and total body water (TBW) was calculated from BIA resistance measurements, height, weight, and sex with use of published equations (16). The use of BIA for the estimation of TBW has been validated in this population against the deuterium dilution method (17). Fat-free mass, fat mass, and percentage fat mass were calculated from TBW estimates (18).

Plasma leptin assay

Leptin concentrations were measured in serum samples from a subset of 375 persons who also had BIA performed. All subjects fasted overnight and blood was taken from an antecubital vein before 0900. Immunoassay leptin concentrations in serum were measured by radioimmunoassay with the human leptin kit (Linco Research Inc, St Charles, MO) by following the manufacturer’s protocol. Plasma leptin concentrations were calculated by using a logistic model. The manufacturer’s stated intra- and interassay CVs were 5.0% and 4.5%, respectively, for serum leptin concentrations ranging from 4.9 to 25.6 µg/L, and the detection limit was 0.5 µg/L. The interassay CVs for the present study were 5.4% at 3.3 µg/L and 7.4% at 14.6 µg/L.

Statistical analysis

Descriptive statistics, including means, SDs, and Pearson correlation coefficients, were calculated. Differences were considered significant at P < 0.05. Multivariate regression was performed with plasma leptin concentration as the dependent variable and fat mass, percentage body fat, sex, waist circumference, and hip circumference as independent variables. All calculations were performed with the SPSS FOR WINDOWS statistical package (SPSS Inc, Chicago).

RESULTS

Anthropometric characteristics were similar between the total sample and the subset in whom leptin measurements were made (Table 1). Serum leptin concentrations were 4.8 times as high in women as in men (Table 2). Corrected for fat mass, leptin was 2.3 times as high in women as in men. BMI, fat mass, percentage body fat, waist circumference, and hip circumference were also higher in women than in men. However, waist-to-hip ratio was larger in men than in women.

In both sexes, bivariate correlation analysis revealed significant associations (P < 0.0001) between leptin and BMI, weight, fat mass, percentage body fat, and waist and hip circumferences. In men, leptin was correlated with waist-to-hip ratio (P < 0.001) and there was no correlation with height. In women, there was no correlation between leptin and waist-to-hip ratio but there was an inverse correlation with height (P < 0.033) (Table 3).

In a multivariate model, after adjustment for percentage body fat, sex was not a significant predictor of leptin concentration (P = 0.1502) (Table 4, equation I). However, sex remained a significant predictor of leptin concentration after adjustment for fat mass (P < 0.0001) (equation 2 in Table 4).

To determine the relation between serum leptin concentration, fat mass, and sex, the mean serum leptin concentration and concentration of leptin corrected for fat mass in each

### Table 1

<table>
<thead>
<tr>
<th>Anthropometric characteristics of the total study population and the subset in whom leptin measurements were made</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong> (n = 144; 42% M, 58% F)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
</tr>
</tbody>
</table>

* SD

### Table 2

<table>
<thead>
<tr>
<th>Leptin concentration and indexes of adiposity in men and women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n = 144)</strong></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
</tr>
<tr>
<td>Leptin (µg/L)</td>
</tr>
<tr>
<td>Leptin/fat mass (µg·L⁻¹·kg⁻¹)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
</tr>
</tbody>
</table>

* SD

* Significantly different from men:
  1. P < 0.0001, 2. P < 0.02.
TABLE 4
Multivariate-regression analysis of leptin, sex, and adiposity

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>SEM (B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation 1: r² = 0.500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>0.721</td>
<td>0.058</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>2.066</td>
<td>1.433</td>
<td>0.1502</td>
</tr>
<tr>
<td>Equation 2: r² = 0.542</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.615</td>
<td>0.044</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>6.202</td>
<td>1.132</td>
<td>0.0001</td>
</tr>
<tr>
<td>Equation 3: r² = 0.521</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>0.572</td>
<td>0.052</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>2.259</td>
<td>0.128</td>
<td>0.0461</td>
</tr>
<tr>
<td>Equation 4: r² = 0.532</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.566</td>
<td>0.049</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>5.413</td>
<td>0.923</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

1 B, slope. In all equations, leptin was the dependent variable. Adjustment was as follows: equation 1, adjusted for percentage body fat; equation 2, adjusted for fat mass; equation 3, adjusted for percentage body fat in a population with BMI < 32.7; equation 4, adjusted for fat mass in a population with BMI < 32.7.

quartile of fat mass were calculated (Figure 1). Most men were in the lowest quartile of fat mass and most women in the two uppermost quartiles. Women in quartiles 1 and 3 had significantly greater fat mass than men (P < 0.01). In both men and women there was a linear increase in the concentration of serum leptin with increase in fat mass (P < 0.0001) but leptin concentration corrected for fat mass did not increase with increased fat mass. Serum leptin concentrations of women were on average 2.6 times as high as those of men, and leptin concentrations corrected for fat mass were 2.3 times as high.

The men and women were dissimilar in distribution according to BMI and fat mass; women predominated in the upper quartiles of BMI and fat mass. To explore the effect of sex on the relation between adiposity and leptin concentration at similar amounts of body fat, a subpopulation of men and women with BMIs less than the 95th percentile of men (32.7) was selected. In this sample, sex was a significant predictor of leptin concentration after percentage body fat or fat mass was adjusted for (P < 0.0001) (equation 3 in Table 4).

The influence of fat distribution on the difference in serum leptin concentration between men and women is best determined by direct comparison at similar hip and waist circumferences. However, the significant difference in hip circumference between men and women at a similar waist circumference (data not shown) precluded such an analysis. This comparison was therefore made in a multivariate model that included sex, hip circumference, waist circumference, and fat mass. Hip circumference, sex, and fat mass but not waist circumference were highly significant predictors of leptin concentration (Table 5).

Stepwise-regression analysis was used to evaluate the importance of fat mass and regional fat distribution on leptin concentrations in men and women. In men, leptin was dependent in a first step on fat mass. Additional inclusions did not contribute significantly to the fraction of explained variance. In women, leptin was dependent on hip circumference in a first step and on fat mass and hip circumference in a second step.

FIGURE 1. Serum leptin concentration, fat mass, and leptin concentration corrected for fat mass in men (●) and women (■) in each quartile of fat mass. Fat mass quartiles were as follows (in kg): 1, < 12.6; 2, 12.6–22.2; 3, 22.2–31.5; and 4, > 31.5. *Significantly different from men, P < 0.01.
TABLE 5
Leptin and sex after adjustment for fat mass, waist circumference, or hip circumference in a population with a BMI < 32.7

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>SEM (B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat mass</td>
<td>0.298</td>
<td>0.105</td>
<td>0.005</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.046</td>
<td>0.069</td>
<td>0.500</td>
</tr>
<tr>
<td>Hip circumference</td>
<td>0.326</td>
<td>0.094</td>
<td>0.0006</td>
</tr>
<tr>
<td>Sex</td>
<td>6.344</td>
<td>1.151</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\[ r^2 = 0.567. \text{ B, slope. In all models, leptin was the dependent variable.} \]

Waist circumference was not a significant predictor of leptin concentrations in either men or women (Table 6).

DISCUSSION

The findings in this study of higher leptin concentrations in women and the relation of serum leptin concentration to obesity confirm those in other reports. Sex differences in leptin concentration have been attributed to the greater adiposity of women (11, 12, 19, 20). It has been argued that percentage body fat is not the appropriate adjustment when controlling for body size (A Luke, CN Rotimi, R Durazo-Arvizu, JA Compton, RR Bonshor, RS Cooper, unpublished observations, 1996) because in obese individuals changes in fat mass are underrepresented when expressed as percentage body fat. The relation between body fatness and serum leptin concentration is thought to be best described by absolute fat mass (20). This is illustrated by data from this study in which women made up the majority of the obese subjects. When the sample included persons with BMIs > 32.7 in a multivariate regression model, sex predicted serum leptin concentration when fat mass but not percentage body fat was an independent variable. In subjects with BMIs < 32.7, sex was a significant predictor of leptin concentration when either fat mass or percentage body fat was an independent variable.

When men and women of similar BMIs were compared, leptin concentrations in women were between two and three times as high as those in men. Adjustment for percentage body fat or fat mass did not abolish the sex difference. Female sex therefore appears to have an effect on serum leptin concentration independent of adiposity. In men or women, (n = 7 or 47, respectively) with a BMI greater than the 95th percentile for men, direct measures of adiposity, ie, fat mass or percentage fat, did not correlate with serum leptin concentration. These results suggest that below a certain body size both sex and adiposity influence serum leptin concentrations. Above that threshold, further increases in adiposity did not result in increased serum leptin concentrations.

It has been reported that obese individuals have higher circulating serum leptin concentrations than do lean individuals after adiposity is corrected for (21, 22). We observed a similar increase in serum leptin concentration corrected for BMI or percentage fat (data not shown). However, serum leptin concentration corrected for fat mass was the same in lean and obese individuals. At all values of fat mass, the concentration of leptin corrected for fat mass was higher in women than in men. There is greater expression of OB mRNA in adipose tissue from women (3) and androgens in men are thought to have a suppressive effect on serum leptin concentrations (20). These two factors may be responsible for the greater production of leptin by adipose tissue of women.

Differences in the distribution of adiposity may also contribute to the sex difference in serum leptin concentration. Men have a more central (omental) and women a more peripheral distribution of body fat; waist and hip circumferences are proxy measures for central and peripheral fat, respectively (23). Omental adipocytes are more metabolically active than those in peripheral tissue (24). In multivariate analyses after fat mass was adjusted for, leptin concentration was not predicted by waist circumference in either men or women, suggesting that the greater metabolic activity of omental adipocyte tissue is not associated with greater serum leptin concentrations.

Women in this study had larger hip circumferences and presumably more peripheral adipose tissue than did men. After fat mass was adjusted for in a multivariate model, hip circumference predicted serum leptin concentrations in women but not in men. This finding is in keeping with a report that in humans OB mRNA expression was highest in subcutaneous tissue (2). If high OB mRNA is translated into circulating leptin, the larger hip circumference may contribute to the observed sex difference in serum leptin concentrations.

REFERENCES

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