Familial predisposition for obesity may modify the predictive value of serum leptin concentrations for long-term weight change in obese women1–3

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ABSTRACT  Leptin is believed to play a role in regulating food intake and body weight. The aim of this study was to examine the influence of parental history of obesity on the association between baseline serum leptin concentrations and subsequent 4-y weight changes. Changes in food intake were also considered in the analysis. Middle-aged, obese women with no obese parent (n = 25) or at least one obese parent (n = 24) were included in the analysis. At baseline, women with no parental history of obesity and women with a parental history of obesity did not differ in body mass index (in kg/m²: 41.2 and 40.2, respectively) or median leptin concentrations (40.8 and 38.8 µg/L, respectively). Four-year weight changes varied widely in both groups combined (from −30 to 24 kg). Stratified regression analysis, adjusted for age, weight, and height, revealed that high leptin concentrations predicted less weight gain (or more weight loss) in women with no obese parent (β = −21.2, P = 0.0006) but played no significant role in predicting weight gain in women with at least one obese parent (β = −3.8, P = 0.41). Adding changes in energy and fat intakes to the model reduced the association between leptin and weight change to nonsignificance in the women with no obese parent, indicating that the effect of leptin could be explained largely by dietary changes. In conclusion, serum leptin concentrations predict long-term weight change in obese women with no history of parental obesity, an association largely mediated by changes in food intake.  Am J Clin Nutr 1998;67:1119–23.

KEY WORDS  Leptin, weight change, dietary intake, obesity, genetic predisposition, women, regression analysis

INTRODUCTION

The discovery of the ob gene and the role of its product leptin in mice (1) introduced hope for understanding the regulation of adipose tissue mass in humans (for review see reference 2). It is believed that leptin acts primarily on the hypothalamus to regulate body fat mass in a negative feedback loop. In ob/ob mice, bioinactive leptin leads to hyperphagia and obesity. When recombinant leptin is administered to such mice, food intake is reduced and energy expenditure increased, resulting in weight loss (3–5). A nonfunctional leptin receptor that causes insensitivity to leptin and obesity has also been reported in rodents (6, 7). The role of leptin in humans, however, is still not clear. Defects in the OB gene appear to be a rare cause of obesity (8–10).

Several studies have shown that circulating leptin concentrations are correlated with body mass index (BMI) and body fat mass (11–13). This indicates that some obese individuals may be leptin resistant. The individual variation in leptin concentrations at a given BMI or body fat mass is also large, however (12, 14), suggesting heterogeneity in the leptin system. It was shown previously that relatively low plasma leptin concentrations precede weight gain in Pima Indians (15). In contrast, baseline leptin concentrations of subjects participating in a weight loss program did not predict short-term success in weight loss (16). To better understand the predictive value of leptin for weight change it is therefore of interest to examine subgroups who may differ in response to leptin. It can be speculated that high leptin concentrations suppress appetite and further weight gain in some obese individuals but not all. Because obesity is caused by a complex interaction between genes and environment, a family history of obesity may be one factor modifying the associations between leptin and weight change.

Thus, the aim of this study was to examine the association between serum leptin concentrations at baseline and subsequent 4-y changes in weight and diet in severely obese women included as control subjects in an ongoing intervention study of obesity. The possible modifying role of a family history of obesity was considered in the analysis.

SUBJECTS AND METHODS

Subjects

Subjects in this study were obese women from the control group of an obesity intervention study entitled SOS (Swedish

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3 Address reprint requests to L Lissner, SOS-secretariat, Vita Stråket 15, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden. E mail: lauren.lissner@medfak.gu.se.
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Obese Subjects) (17). Subjects in the SOS intervention group all undergo weight-reducing gastric surgery and are not included in the present study. The SOS control subjects, on whom this study is based, are offered a variety of conventional weight-reducing treatments through the primary health care system and are followed up regularly.

In a subgroup of these control subjects, living in Göteborg, fasting serum leptin concentrations at baseline were analyzed in relation to data from the 4-y follow-up examination. The present sample included 49 women with BMIs (in kg/m²) ranging from 28.6 to 52.2 at the time of the inclusion examination. The study was approved by the Ethical Committee of the Medical Faculty, Göteborg University.

**Procedures**

When subjects are included in the SOS Study, anthropometric measurements are taken and blood samples drawn. The subjects also complete extensive questionnaires on their family history of obesity, dietary intake, eating behavior, and psychology. Information on anthropometry and diet is then collected at regular intervals. Baseline and 4-y follow-up data were included in the present analysis.

**Serum leptin concentrations**

Blood was collected from each subject after an overnight fast at the time of the subject’s inclusion in the study. The serum was frozen and stored at –80 °C until analyzed. Serum leptin concentrations were determined in duplicate with a human leptin radioimmunoassay (Linco Research, Inc, St Charles, MO). The limit of sensitivity for the assay was 0.5 μg/L. The intraassay CV was 6.3% at a leptin concentration of 15.6 μg/L. The interassay CVs were 8.8% and 5.2% at serum leptin concentrations of 2.9 and 15.0 μg/L, respectively.

**Family predisposition for obesity**

In one of the questionnaires the women reported the heights and weights of their biological parents at the age of 40 y. They also described their parents with the aid of pictures on a scale from one to nine (18). For women who had reported both of their parents’ heights and weights and described them on the scale from one to nine, the correlations between BMI and the numbers on the scale were \( r = 0.83 (P = 0.0001) \) for mothers and \( r = 0.68 (P = 0.0001) \) for fathers. A BMI of 28 corresponded to the fifth picture in the series for mothers and the sixth for fathers. Because data on parents were incomplete for some of the subjects, parents were classified as obese in one of three ways: 1) for subjects who had reported the heights and weights of their parents, the cutoff of BMI ≥ 28 was used \( (n = 41) \); 2) for subjects who reported their parents’ body shapes by means of pictures only, the figure corresponding to a BMI of 28 was used as the cutoff \( (n = 5) \); and 3) for three women who had not completed either question described above, the criterion of overweight or not overweight at the age of 40 y was used to classify the parents. This division resulted in 25 women who had at least one obese biological parent and 24 who had no obese biological parent.

**Dietary intake**

Dietary intake was reported in a questionnaire that was validated previously and judged to give valid estimates of energy intake by obese as well as normal-weight subjects (19).

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**Statistical analysis**

Data at baseline for the women with no parental history of obesity and those with a parental history of obesity were compared by using Student’s \( t \) test when the variables were normally distributed and the Wilcoxon rank-sum test when the variables were not normally distributed. Paired \( t \) tests were used to test whether the weight change seen within each group was significant. Multiple regression analysis was used to examine the associations between baseline leptin concentrations and subsequent weight changes. The models were controlled for initial weight, height, and age. Leptin concentrations were logarithmically transformed because they were not normally distributed. To examine whether the associations between leptin and weight change differed according to family history of obesity, the cross-product of leptin and parental history of obesity (yes or no) was calculated to test for interaction. In the figure, leptin concentrations were adjusted for weight, height, and age by calculating residuals and adding them to the mean logarithmically transformed leptin value in each group. The adjusted logarithmically transformed leptin values were transformed back to normal values before the data presented in the figure were plotted. The SAS statistical package was used for the calculations (20).

**RESULTS**

**Baseline**

Baseline characteristics of the women are shown in Table 1. Serum leptin concentrations did not differ significantly between the women with no parental history of obesity and those with a parental history of obesity. Median leptin values were 40.8 and 38.8 μg/L, respectively. Neither did the two groups of women differ significantly with respect to age, BMI, waist-to-hip ratio, insulin concentrations, reported energy and fat intakes, age at onset of obesity, number of dieting attempts, highest body weight ever, or menopausal status. Among the women without a parental history of obesity there were two smokers compared with six smokers among the women with a parental history of obesity.

The correlation in the combined group between serum leptin concentrations and BMI was \( r = 0.50 (P < 0.001) \) and that between leptin concentrations and initial weight was \( r = 0.41 (P < 0.01) \). The correlations between leptin concentrations and BMI and those between leptin concentrations and weight, respectively, were similar in the two groups of women: \( r = 0.53 \) and \( r = 0.42 \) in the women with no parental history of obesity and \( r = 0.49 \) and \( r = 0.42 \) in the women with a parental history of obesity. Age was also significantly associated with leptin concentrations in the combined group, even after BMI was adjusted for \( (\beta = 0.024, P < 0.01) \). Stratification by parental history of obesity revealed that age was significantly and independently associated with leptin concentrations only in the group with a parental history of obesity \( (\beta = 0.028, P < 0.05) \).

**Four-year weight changes**

Weight changes after 4 y varied widely in both groups, with the total weight change in both groups combined ranging from –30 to 24 kg. In the group without a history of parental obesity, the mean weight change was \( 0.9 \pm 11.5 \) kg \( (P = 0.70) \) compared with \( 2.2 \pm 9.0 \) kg \( (P = 0.23) \) in the group with a parental history of obesity. This difference between groups was not significant.
Baseline serum leptin concentrations in relation to weight change

The association between baseline leptin concentrations and 4-y weight change was examined by using multiple regression analysis. Leptin concentrations, controlled for age, initial weight, and height, were significantly associated with 4-y weight change when the two groups of women were combined (β = –12.0, P = 0.001, R² = 26.8%) (Table 2). The interaction between baseline serum leptin concentrations and parental history of obesity in predicting 4-y weight changes was also tested (P = 0.07). A stratified analysis, adjusted for age, weight, and height, revealed that high serum leptin concentrations predicted less weight gain (or more weight loss) in the group with no parental history of obesity, but played no significant role in predicting weight gain in the group with a parental history of obesity. The magnitude of the association was five times as large in the group with no parental history of obesity (β = –3.8, P = 0.41, R² = 14.9%) (model 1 in Table 2). The associations between baseline serum leptin concentrations (adjusted for age, initial weight, and height) and subsequent weight changes are shown in Figure 1.

To investigate dietary mechanisms for the association between leptin concentrations and subsequent 4-y weight change, changes in energy and percentage fat intake were added to the regression model (model 2 in Table 2). Adding changes in energy and percentage fat intake to the model reduced the effect of leptin on weight change to nonsignificance in the women with no parental history of obesity, indicating that the effect of leptin on weight change was explained largely by dietary changes. Note that changes in energy and fat intakes were significantly associated with weight change in the women with no parental history of obesity in a regression model without leptin. In the group with a parental history of obesity, however, changes in diet did not predict 4-y weight changes.

Because weight changes between baseline and 4 y do not necessarily reflect actual weight change over the 4-y period, individual slopes showing change in weight over time were calculated based on measured body weights at 0, 0.5, 1, 2, 3, and 4 y. When 4-y weight changes were replaced with the individual changes, the β values for models 1 and 2 were 57.2%, 21.9%, and 49.7% for the three groups of women, respectively.

### Table 1
Baseline characteristics of women with or without a family predisposition for obesity

<table>
<thead>
<tr>
<th></th>
<th>Nonpredisposed women</th>
<th>Predisposed women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>48 ± 5 (39–58)</td>
<td>49 ± 7 (37–60)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>112.3 ± 10.7 (86.8–137.1)</td>
<td>108.9 ± 17.2 (78.9–152.3)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.65 ± 0.06 (1.55–1.77)</td>
<td>1.64 ± 0.06 (1.52–1.75)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>41.2 ± 3.6 (34.8–52.2)</td>
<td>40.2 ± 5.3 (28.6–49.7)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.95 ± 0.06 (0.82–1.09)</td>
<td>0.95 ± 0.06 (0.84–1.06)</td>
</tr>
<tr>
<td>Leptin (µg/L)</td>
<td>41.9 ± 19.0 (15.9–100.1)</td>
<td>41.4 ± 19.1 (10.8–91.2)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>95.4 ± 51.0 (30.0–233)</td>
<td>119.4 ± 67.8 (42.6–334)</td>
</tr>
<tr>
<td>Energy intake (MJ/d)</td>
<td>10.2 ± 5.0 (2.7–26.7)</td>
<td>10.4 ± 4.5 (4.6–25.9)</td>
</tr>
<tr>
<td>Fat intake (g/d)</td>
<td>99.5 ± 57.2 (24.6–304.6)</td>
<td>99.8 ± 57.0 (35.4–301)</td>
</tr>
<tr>
<td>Fat energy (%)</td>
<td>36.0 ± 4.5 (29.2–43.7)</td>
<td>34.9 ± 4.7 (28.4–45.5)</td>
</tr>
<tr>
<td>Age at onset of obesity (y)</td>
<td>18 ± 9 (6–38)</td>
<td>21 ± 10 (6–50)</td>
</tr>
<tr>
<td>Number of dieting attempts</td>
<td>8.7 ± 7.1 (2–30)</td>
<td>10.6 ± 6.9 (1–25)</td>
</tr>
<tr>
<td>Highest weight ever (kg)</td>
<td>116.9 ± 12.3 (97–146)</td>
<td>113.6 ± 13.2 (92–142)</td>
</tr>
<tr>
<td>Premenopausal (%)</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Number of smokers in group</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 2
Independent predictors of 4-y weight change in obese women with or without a parental history of obesity

<table>
<thead>
<tr>
<th></th>
<th>No parental history of obesity</th>
<th>Parental history of obesity</th>
<th>Combined sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 24)</td>
<td>(n = 25)</td>
<td>(n = 49)</td>
</tr>
<tr>
<td></td>
<td>x Regression coefficient estimate</td>
<td>P</td>
<td>x Regression coefficient estimate</td>
</tr>
<tr>
<td>Model 1</td>
<td>Baseline leptin</td>
<td>–21.2 ± 5.2 ± 6.0</td>
<td>0.0006</td>
</tr>
<tr>
<td>Model 2</td>
<td>Baseline leptin</td>
<td>–11.3 ± 7.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Model 2</td>
<td>Change in energy intake</td>
<td>0.0018 ± 0.0004 ± 0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>Model 2</td>
<td>Change in percentage fat intake</td>
<td>1.33 ± 0.44 ± 0.009</td>
<td>0.009</td>
</tr>
</tbody>
</table>

### Notes
- All models were adjusted for initial weight, height, and age, which explained 0% if the variance in weight change in women with no parental history of obesity, 16.2% in the women with a parental history of obesity, and 8.7% in the combined sample. Model 1 examines the association between baseline serum leptin concentrations (x) and weight change (y). Adjusted R² values for model 1 were 40.8%, 14.9%, and 26.8% in the three groups, respectively. In model 2 changes in energy and fat intake were added to model 1. Model 2 was also adjusted for baseline energy and fat intake. Adjusted R² values for model 2 were 57.2%, 21.9%, and 49.7% for the three groups of women, respectively.
- SEM.

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slopes as the y variable, the results in the multiple regression models were essentially the same (data not shown).

DISCUSSION

This study revealed an inverse association between baseline leptin concentrations and 4-y weight changes in obese women. When the analysis was further stratified by parental history of obesity, the association between leptin and weight change was clear in the group of women with no obese parent, whereas there was no significant association in the women with at least one obese parent.

The results in the combined group of women confirm previous results in Pima Indians, including both men and women, showing that low concentrations of leptin in relation to fat mass are associated with subsequent weight gain (15). The results also concur with results showing that higher leptin concentrations are associated with greater weight loss over 6 mo in postmenopausal women (21), although these results are not directly comparable because of the much longer time period examined in the present study. However, in the present study leptin was associated with weight change only in women with no obese parent. The rationale for dividing the obese women by family history of obesity was because of the well-known differences in susceptibility to obesity as a function of parental history (22–24). A stronger genetic influence was therefore assumed in the women with at least one obese parent.

The present findings underscore the heterogeneous nature of the obese state (25). This may have implications for potential pharmacologic treatment of obesity with leptin, suggesting that leptin may be more efficacious in specific subgroups. The present study included only women and it will be of interest to determine whether the predictive value of leptin is modified by sex, as suggested by other investigators (21, 26). There were also indications in the present study that the association between leptin and weight change was stronger in premenopausal women than in postmenopausal women (not shown). This study did not include enough women to further stratify the analysis by menopausal status, but the numbers of premenopausal and postmenopausal women were similar in both groups of women, indicating that menopausal status could not explain the different associations between leptin and weight change in the two groups.

Consideration of parental history of obesity in the present study led to the identification of a subgroup of women in whom leptin was strongly associated with weight change, suggesting that obese women whose obesity is driven more by environmental influences than genetic ones might be more responsive to leptin than women whose obesity has a stronger genetic origin. Leptin concentrations in the two groups of women were similar and it is therefore unlikely that leptin resistance explains the much weaker association between leptin and weight change in the women with at least one obese parent. Rather, it may be that leptin concentrations play a less dominant role in the development of obesity among women with a stronger genetic influence and in whom other mechanisms may be more important for the development of obesity. In the women with lesser familial influences for obesity, however, leptin concentrations closely predicted weight changes. The association between leptin and weight change in these women was largely explained by changes in dietary intake. Women with no parental history of obesity and with higher leptin concentrations reduced their energy and fat intakes and lost weight whereas women with lower leptin concentrations increased their intakes and gained weight. Because leptin also increases resting energy expenditure, at least in mice (3–5), it is also possible that women with higher leptin concentrations have higher resting energy expenditures. Higher energy expenditure has been shown to be associated with weight loss (27, 28) and lower energy expenditure has been suggested to be a predictor for weight gain (29). Therefore, differences in energy expenditure may also be involved, although there is no information on metabolic rate in the present study.

A possible limitation of this study concerns the stratification by parental history of obesity. The accuracy of reported weights and heights of parents at the age of 40 y can be questioned and the possibility that some of the women were misclassified cannot be excluded. The present stratification, however, identified two groups of obese women whose weight changes differed in response to leptin and reported changes in diet. Furthermore, the agreement between adult offsprings’ recall of parental height and weight and previously measured values has been reported to be good (18).
Another possible limitation concerns the dietary intake measurement. The difficulties in precisely measuring energy intake in obese subjects are well known (30). Despite these problems, our dietary method seemed to capture expected changes in energy and fat intakes, at least in the nonpredisposed women. Baseline leptin concentrations were strongly negatively associated with changes in energy intake (not shown), suggesting that changes in energy intake are the main mechanism behind the strong association between leptin and weight change in the nonpredisposed women. In the women with an identifiable familial predisposition for obesity, changes in diet were not associated with changes in weight. These predisposed women may have been more resistant to dietary changes or the error in measuring dietary intake may have been larger in this group. The fact that changes in fat intake correlated with changes in weight in the women with no parental history of obesity but not in the women with obese parents can be contrasted with previous population-based findings (24) and suggests the presence of gene-nutrient interactions that may be specific to severely obese women.

In conclusion, leptin appears to play a role in the control of food intake leading to weight gain or weight loss in obese women with no parental history of obesity, but not in other obese women. This indicates that the role of leptin in the regulation of appetite and body weight differs between subgroups of women; this finding should be considered when further examining the role of leptin in the regulation of human obesity. In view of the increasing obesity prevalence figures worldwide, this result highlights the complex interactions between genes and the environment in the etiology of obesity.

REFERENCES