Fish-Rich Diet, Leptin, and Body Mass

Mikolaj Winnicki, MD, PhD; Virend K. Somers, MD, PhD; Valentina Accurso, MD; Bradley G. Phillips, PharmD; Massimo Puato, MD; Paolo Palatini, MD; Paolo Pauletto, MD

Background—Leptin has been implicated in cardiovascular disease. A diet rich in fish has been associated with decreased cardiac and vascular risk.

Methods and Results—We examined the relationship between diet and leptin in 2 related homogeneous African tribal populations of Tanzania. One tribe consumes freshwater fish as their main diet component (n=279), and the other tribe consumes a primarily vegetarian diet (n=329). In multivariate analysis, plasma leptin levels were associated with type of diet (F=14.3, P<0.001), independent of age, body mass index, body fat, alcohol consumption, or insulin. Both male (2.5±2 [fish diet] versus 11.2±2.4 [vegetarian diet] ng/mL, P=0.017) and female (5.0±1.9 [fish diet] versus 11.8±1.4 [vegetarian diet] ng/mL, P=0.007) fish eaters had lower plasma leptin levels than did their vegetable diet counterparts, even though body mass index values were virtually identical.

Conclusions—A diet rich in fish is associated with lower plasma leptin, independent of body fat. These findings may have implications for understanding the reduced cardiovascular risk in subjects on a high-fish diet. (Circulation. 2002;106: 289-291.)

Key Words: diet ■ fatty acids ■ risk factors

The satiety factor, leptin, a product of the ob gene, is synthesized and secreted mainly from adipose tissue.1 In animals, leptin administration reduces food intake while maintaining energy expenditure and, consequently, induces weight loss.2 In humans, leptin also regulates energy stores and energy balance.1 Farooqi et al3 recently noted low levels of leptin in persons heterozygous for a frameshift mutation in the ob gene and suggested that the body may be highly sensitive to a drop in leptin levels, provoking increases in body fat. They also proposed that in obese subjects with low leptin levels, augmenting leptin may have a therapeutic effect, a decrease in body fat.3 However, common forms of obesity in humans are associated with increased leptin levels.4 In addition, higher leptin levels are independently associated with an adverse cardiovascular risk profile.5-7

The powerful dependence of leptin on total adiposity may mask the influence of several other factors, such as diet or insulin, on leptin concentrations. Fatty acids may regulate the expression of the leptin gene in adipose tissue.5,9 In food-restricted rats fed fish oil, plasma leptin levels were significantly lower than those in safflower oil–fed rats.10

We tested the hypothesis that a fish diet, rich in polyunsaturated fatty acids, may influence leptin levels independent of changes in body mass index (BMI). Therefore, we examined the effects of differential dietary practices on plasma leptin concentrations in a large cohort of subjects from the Lugalawa Study.11 The Lugalawa Study was designed to assess the effect of substantial fish consumption on cardiovascular risk factors in 2 homogeneous African populations of Tanzania. One population consumes freshwater fish as the major dietary component, and the other consumes vegetables as the main component of their diet.

Methods

Subjects

The Lugalawa study was carried out within the populations of 2 villages located near Lake Nyasa in Tanzania. In the population of the village Lupingu (n=622), fish accounted for the major food component (300 to 600 g per day), providing almost 25% of the total daily calorie intake (Table 1), whereas in the population of Madilu (n=686), a nearby village, primarily vegetables/fruits were consumed. Both populations belong to the same tribal group, speak the same dialect, and have similar calorie intake and lifestyles.11

The protocol of the present study was approved by the Ethics Committee of the trial, and the subjects provided informed consent. Details on the subjects’ characteristics and the methods used in the study have been described elsewhere.11

In the present analysis, data were analyzed for all subjects (n=608) for whom serum was available for leptin and insulin measurements. This included 279 subjects living on a fish diet and 329 subjects living on a vegetarian diet. The subjects’ characteristics were not different from those of the rest of population of the Lugalawa Study.

Measurements

Main diet components and anthropometric data, including measurements of body fat, were collected for all subjects. To verify the average calorie and salt intake and the dietary nutrients, detailed questionnaires were collected from a random sample of 53 subjects...
from each population, for whom ω3 fatty acids were also measured. Dietary constituents were calculated from standard food tables. Data were validated by comparison with previous nutrition analyses carried out in Tanzania (Food and Agriculture Organization Food Balance Sheets).11 Body fat was measured as the sum of skinfold thickness at subscapular, biceps, and triceps regions of the nondominant arm.

After an overnight fast, a morning 10-mL sample of blood was obtained. Plasma leptin (Linco Research, Inc; intra-assay coefficient of variation 6.0%, interassay coefficient of variation 6.7%) and plasma insulin (intra-assay coefficient of variation 5.1%, interassay coefficient of variation 6.0%, interassay coefficient of variation 6.7%) were measured by radioimmunoassay.

Statistical Analysis
Because plasma leptin levels differ by sex,1 analyses were performed separately for men and women. Continuous variables were averaged and expressed as mean±SE. A Pearson correlation was used to test the relationship between variables. A multivariate linear regression model was used to examine the relationship between diet, age, BMI, body fat, alcohol consumption, and logarithmically transformed (skewed distribution) insulin and leptin levels (dependent variable). Continuous variables were compared by ANCOVA, with the Tukey post hoc test.

Results
The characteristics of both populations are presented in Tables 1 and 2. Males consuming the fish diet were slightly younger, used less alcohol, and had similar body fat compared with their vegetable diet counterparts. Similar relationships were present in women, except for slightly higher body fat in the fish-eating group. In addition, women on a fish diet had lower insulin levels but similar glucose levels compared with their vegetarian diet counterparts (Table 2).

Total n-3 fatty acids (9.7±2.9% [fish diet] versus 3.5±1.2% [vegetarian diet] of plasma lipids, P<0.001) were higher in fish eaters (n=53) than in vegetable eaters (n=53). The opposite was observed regarding total n-6 fatty acids (25.8±4.8% [fish diet] versus 33.1±5.5% [vegetarian diet] of plasma lipids, P<0.001), as reported previously.11

In univariate analysis, in all men from both subgroups, leptin levels were related to alcohol consumption (r=0.15, P=0.041) and insulin levels (r=0.46, P<0.001) but not to BMI or body fat. In all women, leptin levels were related only to insulin levels (r=0.57, P<0.001). However, in the fish diet subgroup, there was a correlation between plasma leptin levels and both BMI (r=0.22, P=0.009) and body fat (r=0.27, P=0.001).

In multivariate analysis, plasma leptin levels were independently associated with type of diet (F=14.3, P<0.001). Both male (Figure, panel A) and female (Figure, panel B) fish eaters had lower plasma leptin levels than did their vegetable diet counterparts, even though BMIs were virtually identical. Plasma insulin levels were strongly and independently associated with plasma leptin levels for all groups or subgroups studied (P<0.001 for all comparisons). Leptin levels were also independently associated with alcohol consumption in males (P=0.025) and females (P<0.001) consuming vegetable diets. We found no independent association of plasma leptin with BMI in any subgroup and a weak association of plasma leptin with body fat in fish-eating women only (F=2.12, P=0.035).

Discussion
There are several novel findings evident from the present study. Compared with their vegetable diet counterparts, both men and women on a fish diet had markedly lower leptin levels, despite having almost identical BMIs. Although prior studies have consistently reported higher leptin levels in women than in men,12 women on the fish diet had leptin levels less than half those observed in men on a vegetarian diet. The fish-eating men and women had leptin levels even lower than the values observed in persons heterozygous for a frameshift mutation in the ob gene.3 In contrast to other studies,4,12 the present study was unable to demonstrate any independent relationship between plasma leptin and body fat composition, except for a very weak positive association in

### Table 1. Average Daily Calorie Intake and Food Composition in 2 Populations

<table>
<thead>
<tr>
<th></th>
<th>Fish Diet</th>
<th>Vegetarian Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amount</td>
<td>% kcal</td>
</tr>
<tr>
<td>Maize</td>
<td>60–120 g</td>
<td>14</td>
</tr>
<tr>
<td>Beans</td>
<td>40–60 g</td>
<td>7</td>
</tr>
<tr>
<td>Spinach</td>
<td>20–40 g</td>
<td>0.4</td>
</tr>
<tr>
<td>Potatoes</td>
<td>40–60 g</td>
<td>2</td>
</tr>
<tr>
<td>Rice</td>
<td>30–50 g</td>
<td>6</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>650–850 mL</td>
<td>9</td>
</tr>
<tr>
<td>Cassava</td>
<td>150–350 g</td>
<td>38</td>
</tr>
<tr>
<td>Fish</td>
<td>300–600 g</td>
<td>23</td>
</tr>
<tr>
<td>Calories</td>
<td>2196 kcal</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2. Demographic Characteristics of Study Populations

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vegetarian Diet (n=130)</td>
<td>Fish Diet (n=117)</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.6±1.3</td>
<td>41.6±1.4</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>2.8±0.2</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>Body fat,* mm</td>
<td>18.8±0.6</td>
<td>20.2±0.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.6±0.2</td>
<td>20.2±0.2</td>
</tr>
<tr>
<td>Insulin,* U/mL</td>
<td>8.4±0.7</td>
<td>7.6±0.6</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.1±0.1</td>
<td>4.8±0.1</td>
</tr>
</tbody>
</table>

*Adjusted for age and alcohol consumption.
There are several limitations of the present study. First, only lean black Africans were studied. Different relationships between fish diets and leptin may exist in obese subjects and in different races. Second, other unknown dietary or behavioral factors may contribute to the apparent effect of the fish diet on leptin concentrations. However, the food questionnaire used was validated by previous nutrition analyses carried out in Tanzania. Third, underlying genetic factors may contribute to the difference in plasma leptin concentrations. However, both dietary groups belong to the same tribe, speak the same dialect, live near each other, and have similar calorie intakes, lifestyles, and BMI values. The only difference was the type of diet.

In conclusion, we show that a diet rich in fish is associated with lower plasma leptin concentrations, independent of body fat or BMI, suggesting that this kind of diet may improve leptin sensitivity. In subjects on a fish diet, leptin levels are even lower than those documented in persons heterozygous for a frameshift mutation in the ob gene. The low leptin in subjects on a fish diet is not necessarily associated with increases in BMI or body fat. These findings may have implications for understanding the reduced cardiovascular risk in subjects on a fish-rich diet.

Acknowledgments

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References


Compared with their counterparts on vegetable diet, subjects on predominantly fish diet have strikingly lower mean adjusted (for age, alcohol, body fat, BMI, and insulin) leptin levels despite almost identical BMI level. A, Leptin levels in males. B, Leptin levels in females.
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